

Evolution of Precision Oncology, Personalized Medicine, and Molecular Tumor Boards



Yu Fujiwara, MD^{a,*}, Shumei Kato, MD^{b,c}, Razelle Kurzrock, MD^{d,e,f}

KEYWORDS

- Histology-agnostic • Personalized medicine • Personalized oncology
- Precision medicine • Tumor-agnostic

KEY POINTS

- Clinicians caring for patients with cancer need to understand the process of precision medicine.
- Precision oncology allows for treatment selection based on molecular profiles of each patient's cancer.
- Precision medicine has been incorporated into definitive and palliative treatments for patients with advanced malignancies regardless of histologic subtype.
- Molecular tumor boards (MTBs) play an important role in the interpretation of genomic profiling tests and recommendations of molecularly matched treatment regimens.
- Many subspecialists take a vital role in the MTB in order to discuss the best personalized treatment for each patient with cancer.

INTRODUCTION

Precision oncology is the concept of providing treatment based on individual patient's tumor mutation profiles. In recent years, new therapeutic options have been approved

This article originally appeared in *Surgical Oncology Clinics*, Volume 33 Issue 2, April 2024.

^a Department of Clinical Oncology, Institute of Science Tokyo, Tokyo, Japan; ^b Center for Personalized Cancer Therapy, University of California San Diego Moores Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093, USA; ^c Division of Hematology and Oncology, Department of Medicine, University of California San Diego Moores Cancer Center, La Jolla, CA, USA; ^d Genomic Sciences and Precision Medicine Center, Medical College of Wisconsin, Froedtert and Medical College of Wisconsin Cancer Center and Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, USA; ^e WIN Consortium, Paris, France; ^f University of Nebraska, Lincoln, NE, USA

* Corresponding author.

E-mail address: Yu.Fujiwara@RoswellPark.org

Hematol Oncol Clin N Am 40 (2026) 685–704

<https://doi.org/10.1016/j.hoc.2026.05.019>

hemonc.theclinics.com

0889-8588/26/© 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en octubre 15, 2026. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2026. Elsevier Inc. Todos los derechos reservados.

for specific cancer patient populations based on corresponding gene alterations and biomarkers.¹ Although biomarker-driven approaches have been developed mainly for patients with advanced cancer, the rapid development of these therapeutics also allows the incorporation of personalized medicine into the adjuvant/neoadjuvant settings along with curative intent surgery and/or radiotherapy. This integration suggests the importance of early molecular profiling testing to determine the best therapy through multidisciplinary discussions for patients with early and advanced-stage cancers.²

Therapeutic options for patients with advanced cancer were historically limited to cytotoxic chemotherapy until the discovery of targetable mutations, which revolutionized the cancer treatment landscape. Early examples of these molecular targeted therapies included imatinib for *BCR-ABL* chronic myeloid leukemia and erlotinib for epidermal growth factor receptor (*EGFR*)-mutant lung adenocarcinoma.^{3–5} Since the development of these agents, the advent of next-generation sequencing (NGS) has allowed clinicians to rapidly identify targetable molecular alterations with novel drugs that may provide better clinical outcomes than classic cytotoxic chemotherapy.^{6,7} These alterations can be observed across cancer types, and molecular targeted therapies may have clinical activity across tumor types.^{8,9} Furthermore, recent developments in immunotherapy, including immune checkpoint inhibitors (ICIs), have dramatically changed the paradigm of cancer treatment by providing durable responses in some cancer patients.¹⁰ Several factors such as high programmed death-ligand 1 (PD-L1) expression and high tumor mutational burden (TMB) have been associated with prolonged survival and could potentially be used as biomarkers to select patients before initiating ICIs.^{11,12} It is through increased understanding of tumor biology that treatment is evolving.

This article summarizes the development of precision oncology, the role of MTBs, and future directions of personalized medicine for patients with cancer including those who are candidates for surgical intervention.

DISCUSSION

History

The evolution of precision oncology dates back to the late 1990s, when imatinib was found to be effective in chronic myeloid leukemia (CML) harboring *BCR-ABL* rearrangement, leading to approval by the US Food and Drug Administration (FDA) in 2001.³ Along with the development of techniques such as fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR), which allowed rapid detection of targetable alterations, several molecular targeted therapies were subsequently developed. One of the first examples of precision medicine for solid tumors was use of a tyrosine kinase inhibitor (TKI), such as erlotinib and gefitinib, for patients with non-small cell lung carcinoma (NSCLC) harboring an *EGFR* mutation. Gefitinib was initially shown to be effective for NSCLC patients, but subgroup analysis suggested that its efficacy was driven by *EGFR*-mutant population, which was subsequently confirmed in a clinical trial limited to patients with an *EGFR* mutation.^{5,13,14} Erlotinib was also developed and initially approved specifically for patients with *EGFR*-mutant NSCLC in 2013.¹⁵ This small molecule inhibitor became the focus of attention, as it inhibits a specific alteration, rendering more efficacy with potentially less toxicity than traditional cytotoxic chemotherapy. Thus, its application was incorporated into the standard of care in patients with malignancy.^{6,7}

The initial development of molecular-targeted agents was achieved by dividing a specific cancer type into subtypes according to genomic mutation patterns such as

EGFR, anaplastic lymphoma kinase (ALK), and c-ros oncogene 1 (ROS1) inhibitors for NSCLC.^{16,17} However, as different types of cancer can share the same genomic alteration, the tumor-agnostic approach has been explored to broaden the application of targeted therapies. In 2019, entrectinib, an neurotrophic tyrosine receptor kinase (NTRK) inhibitor, was approved by the FDA for solid tumors with *NTRK* fusion regardless of cancer type after demonstrating its efficacy (durable overall response rate of 57%).¹⁸ Similarly, pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, was approved by the FDA in patients with DNA mismatch repair-deficiency (dMMR) or microsatellite instability-high (MSI-H) tumors in 2017, and in patients high TMB tumors in 2020, respectively.^{19,20} These strategies have highlighted the importance of performing NGS to expand treatment options without losing the chance of a potentially long-lasting therapeutic opportunity. As personalized medicine evolves, the treatment landscape becomes more complicated, because each cancer possesses a different genetic profile. Currently, multiple agents are approved for specific alterations in 1 tumor type and for the same alteration across cancer types. For example, there are 5 FDA-approved ALK inhibitors for NSCLC, 3 tumor-agnostic indications for the use of pembrolizumab in solid tumors, and 2 NTRK inhibitors for solid tumors harboring *NTRK* fusions.^{18–22} Therefore, discussions in a multidisciplinary fashion at an MTB play a more important role in determining the best treatment for each patient by considering their performance status and comorbidities, the adverse effect profile of the matched agents, and access to clinical trials.²³

Precision Oncology in Clinic

Historically, precision oncology has been delivered primarily to patients with advanced malignancies after progression on multiple lines of chemotherapy. To explore further therapeutic opportunities such as molecular targeted therapy that are not approved for a specific cancer type and enrollment in clinical trials, genomic profile tests can be performed through NGS. Clinicians need to explain the concept of testing to obtain a genomic profile from tumor tissue or liquid samples, including the benefits and risks of testing to the patients (Table 1). In particular, physicians need to explain the potential risk of detecting a germline mutation, as this would affect the medical care for a patient's relatives, such as an increased risk of developing cancer in siblings and children.²³ In this case, consultation for genetic counseling may be necessary. Additionally, the detection rate of effective treatments for a cancer can be relatively low (approximately 5% to 20%) at present, and patients need to understand what the next process looks like if no therapeutic options are available after performing the genomic profiling test.² Insufficient amount of tissues and remote tissue samples also make it difficult to perform NGS, and in this case, additional biopsy might be needed. Liquid biopsy is another option that may provide up-to-date genomic information in a noninvasive way.^{24,25}

Molecular Tumor Board

Once genomic profiling is obtained from tissues and/or liquid samples, the result and potential treatment options need to be discussed in a multidisciplinary manner to provide the best and most personalized care with the potential for maximum treatment benefit, taking into account factors such as comorbidities and access to care. The MTB plays an integral role in clinical decision making by facilitating discussions with expertise in medical oncology, surgical oncology, bioinformatics, clinical genomics, genetic counseling, and radiation oncology (Fig. 1).²³ Genomic data can provide potential treatment options for targetable alterations and biomarkers to predict the efficacy of available therapies. Through multidisciplinary discussions by obtaining

Table 1 Risk and benefit upon performing genetic profiling testing for precision medicine		
	Benefits	Risks
Therapeutic options	Finding a treatment option available on the market Example: <i>EGFR</i> mutation for EGFR TKI	Treatment corresponding to a detected alteration is not available on the market Example: <i>KRAS G12 V</i> mutation (only <i>KRAS G12 C</i> inhibitors are available).
Predictive marker	Detecting a predictive biomarker for a specific therapy Example: high TMB for immune checkpoint inhibitors	Can potentially find a factor that negatively predicts the therapeutic efficacy Example: low tumor mutational burden that could potentially decrease the efficacy of immune checkpoint inhibitors
Clinical trials	Finding actionable alterations for which many clinical trials are available	Mutations whose molecular structures make them undruggable. Limited options of clinical trials.
Genetic information	Detection of somatic mutations only Counseling of relatives can be omitted in this case	Possibility of detecting germline mutations that predispose to the risk of developing cancer in relatives Genetic counseling may be necessary

Abbreviations: EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; TKI, tyrosine kinase inhibitor.

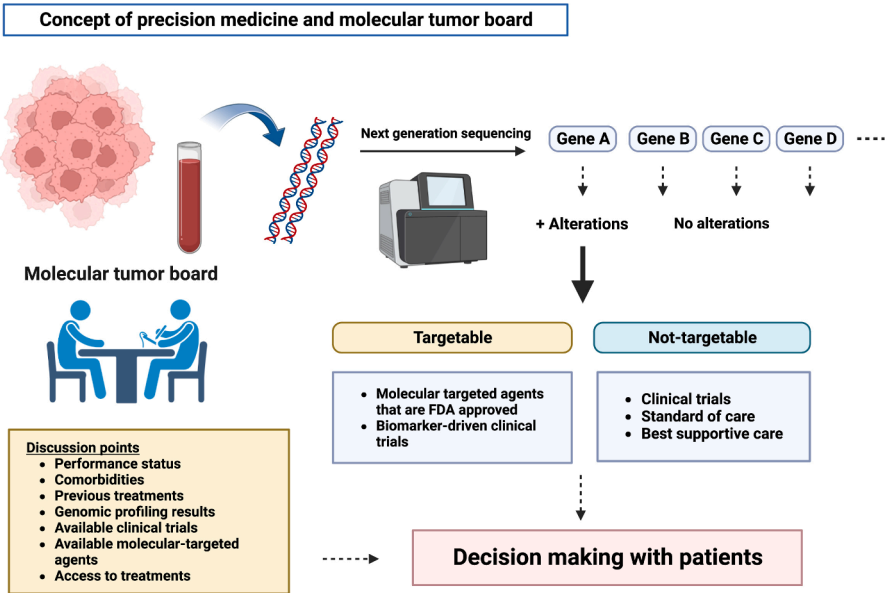


Fig. 1. Concept of precision medicine and role of molecular tumor board. The flowchart to perform precision medicine from specimen sampling, analysis, discussion at molecular tumor board, to treatment suggestions. TMB, Tumor mutational burden. (Used with permission from Yu Fujiwara, MD. Created with BioRender.com.)

perspectives from each specialist, the MTB may suggest consideration of experimental drugs, enrollment in clinical trials, and use of approved agents, based on the available evidence. On top of the genomic profile, information on clinical status such as performance status, active medical issues, and access to health care such as whether patients need to be referred to another institution for clinical trials will be discussed.

The role of MTBs is critical to improve survival outcomes for patients with advanced cancers. Patients with genomic alterations for which targeted therapies are available are more likely to benefit from matched treatments more than those with physician's choice treatment mostly because of the unavailability of agents for their alterations. For example, if patients are matched with agents recommended by the MTB, clinical outcomes such as objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) may be improved more than those treated with physician's choice treatment.²⁶ These approaches have been implemented for patients with advanced malignancies, particularly those with limited treatment options after disease progression on several lines of treatment. However, precision medicine approaches are now rapidly being incorporated into earlier lines of therapy for patients with advanced disease, and the curative setting for patients treated with neoadjuvant or adjuvant therapy. Dating back to the 1970s, the hormonal therapy tamoxifen was shown to delay recurrence in early breast cancer. Tamoxifen and aromatase inhibitors have been used for hormone receptor-positive breast cancer.²⁷ Also in breast cancer, HER2 inhibitors such as trastuzumab and pertuzumab showed survival benefits when used as neoadjuvant and/or adjuvant therapy in those with *ERBB2* amplified tumors.^{28–30} Immunotherapy such as ICLs has also been shown to be effective when used perioperatively by improving relapse-free survival and OS in patients with certain cancers.^{31–36} Therefore, MTBs are becoming increasingly valuable for input and discussion not only from experts providing systemic therapy, but also from experts providing curative treatment such as surgery and radiotherapy.

Clinical Outcomes by Implementing Precision Medicine and Molecular Tumor Board

Traditionally, clinical trials evaluated patients with a specific cancer, and most did not select patients based on biomarkers that could potentially predict the efficacy of corresponding agents. The era of precision medicine has required novel clinical trial designs that make personalized therapy evaluable and feasible (**Table 2**). Several clinical trial designs have been developed to evaluate the feasibility and efficacy of MTBs and to assess agents selected based on genomic profile information as summarized in a previous review article.³⁷ Compared with these traditional clinical trials, precision medicine requires the evaluation of genomic profiles and the administration of agents matched with genomic alterations. Trials with master protocols allow assessment of more than 1 drug or 1 tumor within a single clinical trial.³⁸ Basket and umbrella trials are the first generation of clinical trials implementing precision medicine. Basket trials evaluate agents against a specific genetic alteration regardless of cancer type, leading to the successful development of pembrolizumab, NTRK inhibitors, BRAF and MEK inhibitors for *BRAF* V600 E mutations, and RET inhibitors for *RET* mutation in a tumor-agnostic manner (**Fig. 2**).^{39–41} In contrast, umbrella trials evaluate multiple molecular alterations within a single cancer type to address heterogeneity within patients with a specific tumor type.³⁷ Umbrella trials are advantageous when evaluating common cancers with multiple alterations such as lung cancer and breast cancer.³⁷ When master protocols evaluate multiple hypotheses in 1 protocol, they are referred to as platform trials. The

Table 2
Clinical trial and research design evaluating precision medicine that includes a molecular tumor board

Design	Design Detail	Pros	Cons	Study References
Master protocol				
Basket trial	Tissue-agnostic, assessing agents targeting a common pan-cancer gene alteration	Can broaden the indication of 1 agent to multiple tumor types	Not all driver alterations are successfully targeted because of heterogeneity across tumor types	TAPUR ^a 82–84
Umbrella trial	Tumor histology-specific, assessing several agents in different genomic subsets	Can address interpatient heterogeneity of a specific tumor type	Difficult to implement clinical trials for rare tumors Hard to determine treatment arms when a patient has multiple actionable alterations	TAPUR ^a 82–84
Platform trial	Trial allowing assessment of several hypothesis in 1 protocol	Can expand or delete treatment arms even when clinical trials are running Can assess multiple biomarkers and targetable alterations in 1 clinical trial Cost-effective	Complicated clinical trial design High burden on trial administration Complexity of statistical analysis	IMPACT1 ^{42,43} IMPACT2 ⁸⁵ TAPUR ^a 82–84
Newer generation				
N-of-1 trial	Patient-centered trial evaluating individualized combination treatments The degree of matching to therapy suggested by the molecular tumor board is assessed Outcomes are compared among patients treated with low vs high degree of molecular matching	Can offer individualized combination treatment approaches for each enrolled patient by considering their molecular features	Complexity of calculating the degree of matching Difficult to generalize the trial outcomes to different populations Patients are treated with customized combination therapies that are unique to each patient	I-PREDICT ^{48,49}

Others				
Real-world data	Analyzing data obtained in electronic medical records and industrial patient data to address unmet needs in real world	Can address unmet needs and clinical questions that arise in daily practice Cost-effective	Patient and treatment selection possess a risk of bias, as real-world data analysis is not a prospective clinical trial	USCD-PREDICT (NCT02478931) ²⁶

Details of each trial listed and other trials not listed here are summarized in previous review articles.^{37,86}

^a Combination of basket and umbrella trial.

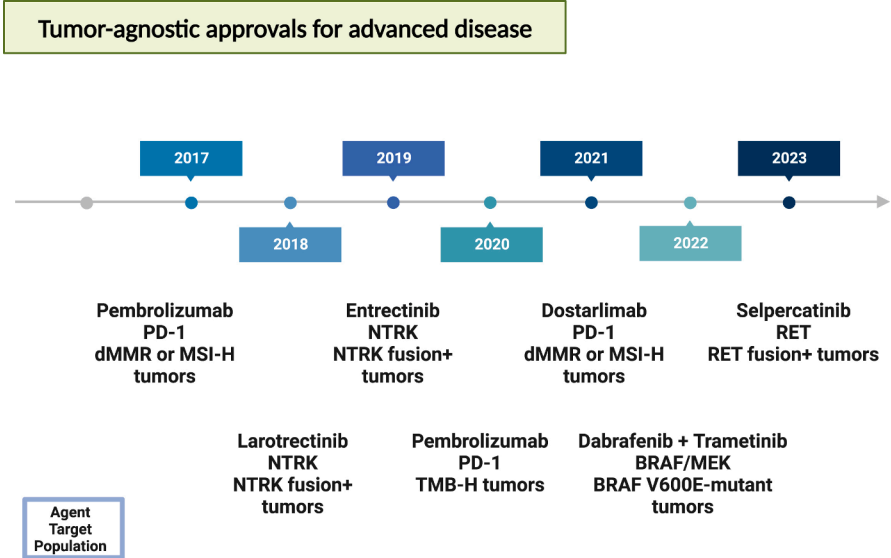


Fig. 2. Evolution of tumor-agnostic precision oncology in the United States. Each column includes: (1) agent name, (2) targeted alterations, and (3) targeted population. BRAF, V-Raf murine sarcoma viral oncogene homolog B; dMMR, DNA mismatch repair-deficiency; MEK, mitogen-activated protein kinase; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; PD-1, programmed cell death protein 1; RET, rearranged during transfection. (Used with permission from Yu Fujiwara, MD. Created with BioRender.com.)

IMPACT1 trial, a platform trial, demonstrated the feasibility of the efficacy of precision medicine by showing better survival in patients with matched agents than those without matched therapies.^{42,43} Several platform trials are ongoing such as IMPACT2 and NCI-MATCH across tumor types to evaluate agents matched to unique genomic alterations.^{37,44} In particular, the NCI-MATCH trial comprises 40 treatment arms to evaluate agents matched to alterations of each patient, and demonstrated its feasibility of patient enrollment and performing NGS. Clinical benefit varied across targeted agents; however, approximately 38% of enrolled patients were found to have potential molecular targets, and 18% of patients received matched agents.^{45,46}

The next generation of clinical trials implementing precision medicine includes N-of-1 trials.⁴⁷ In contrast to conventional clinical trials, N-of-1 trials focus on individualized therapy for patients with cancer. This design aims to evaluate the efficacy and safety at the level of an individual patient. Information gathered from N-of-1 trials may provide a tailored therapeutic strategy for individuals by addressing the interpatient heterogeneity of cancer.^{2,47} The Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy (I-PREDICT) trial was the first prospective trial to use the N-of-1 trial design to evaluate personalized treatment suggested by the MTB for patients with advanced cancer. Therapy was suggested based on evaluated biomarkers from tissue NGS, circulating tumor DNA (ctDNA), and immune markers including MSI status, TMB, and PD-L1 expression. Treatment efficacy was assessed by calculating a matching score representing the degree of matched therapies. For example, if a patient had 4 alterations and was given therapy that targets 1 alteration, the matching score was 1/4 (=25% [low]). In contrast, if a patient had 4 alterations and was given therapy that targets 3 alterations, a matching score was calculated as 3/4

(=75% [high]). In this study, higher matching score (>50%) was associated with a statistically better DCR (defined as partial response or stable disease ≥ 6 months) and improved PFS and OS across tumor types when compared to patients who received therapies with a low matching score.^{26,48–50} Overall, the I-PREDICT trial showed the feasibility and safety of N-of-1 trials, customizing personalized treatment approaches provided by the MTB.

The number of studies utilizing MTBs for delivering precision medicine is growing. A recent study by the University of California, San Diego, investigating the utility of MTB showed that a higher matching score in patients with colorectal cancer was associated with longer PFS (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.21–0.81; $P=.01$) with higher clinical benefit rates (41% vs 18%, $P=.058$) than those treated with unmatched therapy. The authors concluded that MTB plays a vital role in treatment decision making and survival improvement in a specific cancer type.⁵¹ Because it is difficult for traditional clinical trials to ensure the feasibility of precision medicine, the authors anticipate that more clinical trials will implement trial designs such as N-of-1 trials. Clinicians involved in the care of patients with cancer need to understand the newer concept of these trials to develop new evidence for patient care through personalized medicine.

PERIOPERATIVE PRECISION ONCOLOGY

Somatic Alterations

Precision oncology through biomarker-based patient selection is now growing in the perioperative setting as neoadjuvant/adjuvant therapy (Table 3). Breast cancer was one of the first cancers to consider patient selection based on biologic characteristics. Endocrine therapy such as tamoxifen and aromatase inhibitors are standard adjuvant therapy in hormone receptor-positive patients, and HER2-targeting agents such as trastuzumab and pertuzumab are now used as a neoadjuvant and adjuvant therapy in locally advanced disease with *ERBB2* amplification.^{29,30} Additionally, a CDK4/6 inhibitor, abemaciclib, has been shown to prolong relapse-free survival in hormone receptor-positive breast cancer with high-risk features in the MonarchE trial, expanding further options in patients with breast cancer as a perioperative strategy.⁵² In lung cancer, the ADAURA trial showed survival improvement with osimertinib, an EGFR TKI, after definitive surgery with or without adjuvant chemotherapy, expanding further personalized options in other cancer types.⁵³

Other than targeted therapy, ICIs are now being incorporated into the standard of care as either neoadjuvant or adjuvant therapy by showing improvement in relapse-free survival and OS in multiple cancer types.^{31–33,35,36} In this setting, an appropriate biomarker for patient selection has not yet been established, but PD-L1 expression may be a positive predictor for relapse-free survival based on subgroup analyses in these trials.^{32,33,36}

Germline Alterations

In addition to a strategy targeting somatic mutation, patients with germline mutation also benefit from precision medicine. For example, poly-ADP ribose polymerase (PARP) inhibitors such as olaparib improve survival in patients with breast cancer harboring *BRCA1/2* mutations.⁵⁴ Subsequently, the maintenance use of PARP inhibitors showed benefit by prolonging relapse-free survival in *BRCA*-mutant ovarian cancer.⁵⁵ Their use has also been expanded to other tumor types such as advanced pancreatic cancer and metastatic castration-resistant prostate cancer harboring *BRCA* mutations.^{56–58} PARP inhibitors are also being used in the perioperative

Table 3
Examples of precision oncology in the perioperative setting

Cancer	Example	Population	Agents	References
Breast cancer	Adjuvant hormonal therapy	Hormone-receptor positive	Tamoxifen Aromatase inhibitors	27,87
	Neoadjuvant/adjuvant HER2 inhibitors	ERBB2 amplification	Trastuzumab Pertuzumab Trastuzumab-emtansine (for residual disease)	29,30,88
	Adjuvant PARP inhibitors	<i>BRCA1/2</i> mutations HRD	Olaparib	59
	Adjuvant CDK4/6 inhibitors	High-risk hormone-receptor positive	Abemaciclib	52
Colorectal cancer	Neoadjuvant immunotherapy	Mismatch repair-deficient rectal cancer	Dostarlimab ^a	89
Lung cancer	Adjuvant EGFR TKI	<i>EGFR</i> mutation	Osimertinib	53
Malignant melanoma	Adjuvant BRAF and MEK inhibitors	<i>BRAF V600 E</i> or <i>V600 K</i> mutations	Dabrafenib plus trametinib	90
Ovarian cancer	PARP inhibitors	<i>BRCA1/2</i> mutations	Olaparib	91

Abbreviations: BRAF, V-Raf murine sarcoma viral oncogene homolog B; BRCA, BReast CANcer gene; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; ERBB2, erythroblastic oncogene B 2; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; MEK, mitogen-activated protein kinase; NSCLC, non-small cell lung cancer; PARP, Poly-ADP ribose polymerase; TKI, tyrosine kinase inhibitor.

^a Not FDA-approved.

setting. Adjuvant use of olaparib for HER2-negative early breast cancer harboring *BRCA1* or *BRCA2* germline mutations with high-risk clinical features showed prolonged invasive disease-free survival (HR, 0.58, 99.5% CI, 0.46–0.74, $P < .0001$) and OS (HR, 0.68, 99.5% CI, 0.50–0.91, $P < .0091$) compared with placebo after neoadjuvant or adjuvant chemotherapy, leading to its FDA approval in 2022.^{59,60} Thus, the authors anticipate an increase in the number of early stage cancer cases requiring genomic profiling tests before or after surgery to guide appropriate perioperative therapy, including the use of PARP inhibitors. As they are now utilized in upfront therapy, all providers need to understand the long-term risks of PARP inhibitors such as a potential increase in the risk of treatment-related myeloid dysplastic syndrome (MDS) or acute myeloid leukemia (AML), as well as the incidental detection of germline mutations in patients' relatives, resulting in an increase in risk of several cancer types.²³

The I-SPY 2 trial, implementing perioperative tailored approach, has a framework of an adaptive phase 2 clinical trial design evaluating neoadjuvant therapy for patients with high-risk breast cancer. The trial categories breast cancer into 10 subtypes according to hormone receptor and HER2 status, and 70-gene assay (MammaPrint) score. For randomization, Bayesian methods are used to achieve a higher probability of efficacy in the use of experimental drugs in addition to standard neoadjuvant chemotherapy.^{61,62} This platform trial is ongoing to identify new agents combined with standard neoadjuvant chemotherapy and ideal strategies for each patients with early stage high-risk breast cancer.

Precision oncology is now rapidly becoming the standard of care even in the early stage setting as part of neoadjuvant/adjuvant therapy (Fig. 3). Performing NGS and molecular profiling tests at the time of cancer diagnosis must be strongly considered

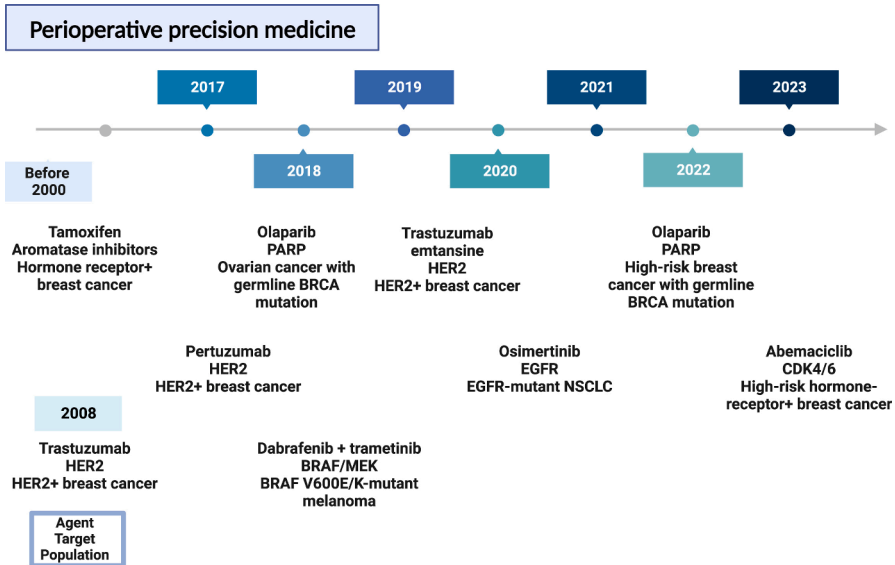


Fig. 3. Development of peri-operative precision oncology. Each column includes: (1) agent name, (2) targeted alterations, and (3) targeted population. BRAF, V-Raf murine sarcoma viral oncogene homolog B; BRCA, BReast Cancer gene; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase; NSCLC, non-small cell lung cancer; PARP, poly-ADP ribose polymerase. (Used with permission from Yu Fujiwara, MD. Created with BioRender.com.)

to gain maximum therapeutic benefit. Details of treatment for each type of cancer are summarized and discussed in other articles.

CHALLENGES OF PRECISION MEDICINE AND MOLECULAR TUMOR BOARD

Expertise

Multidisciplinary discussion facilitates treatment consideration and selection at the MTB. However, availability of experts to conduct the MTB can be challenging, particularly in small institutions, rural areas, and developing countries.^{23,63} Additionally, time constraints may be another issue, as experts may not be available at the same time. In institutions with limited access to individual subspecialists, creating a tumor board team that works remotely both internally and externally can address this issue.⁶⁴ Further, education and lectures created by experienced institutions may also help each clinician improve his or her understanding of the interpretation of genomic test results, resulting in improved feasibility of MTBs in any institution with limited access to experts. Precision oncology using NGS and clinical trials developed primarily in Western countries. Experts in these fields could facilitate the process of holding the MTB in other regions by working remotely, and the feasibility of a virtual MTB has been shown in several studies from Western countries.^{63,65} Clinical trials assessing precision medicine are also being performed in Asian countries, and expansion to other regions is expected in the near future.^{66–68} Broadening the application of precision oncology in these areas would improve survival outcomes in patients with cancer worldwide by addressing racial and ethnic molecular differences.^{69,70} Further global collaborations are needed to address these MTB feasibility issues.

Access to Clinical Trials

However, access to treatment can also be problematic even in larger clinical cancer centers. The MTB suggests tailored therapeutic options for each patient. Oftentimes, clinical trials are the only option that can be suggested as an experimental therapeutic option, which may not be available at the treating physician's institution. Transferring from the original institution could be a burden for patients, and thus, smooth referral to the new clinical site where clinical trials are available is necessary for seamless care. There is a growing demand for collaboration through a clinical trial network to reduce patient burden and ensure access to clinical trials across the country.²³

Unanticipated Germline Findings

The challenging aspect of genetic testing for is the possibility of detecting germline genomic alterations. A pathogenic germline variant can be detected in approximately 4% to 12% of patients using genomic profiling.^{71–74} These findings can lead to prescribing treatments such as PARP inhibitors for *BRCA1/2*-mutant cancers and those with homologous recombination deficiency (HRD), but could also result in family members of these patients being at increased risk of developing cancer in the future because of specific germline mutations. Institutional support such as a genetic counselor must be established at centers where genetic profiling tests are performed. Clinicians should be aware of the psychological burden of detecting germline mutations in patients and their family members. The risk-benefit discussion by providing data such as the detection rate of treatable alterations and germline mutations needs to be carefully conducted with each patient undergoing genomic profiling.

Tumor Heterogeneity and Evolution

Traditional genomic profiling tests have static characteristics, in which tissue or liquid biopsies are collected and analyzed for clinically meaningful expression or actionable

genetic alterations at a single time. Although some patients can gain useful information from genomic profiling for treatment decisions, it would be difficult for static analyses to account for tumor heterogeneity and evolution within each patient over time. Recently, the concept of functional precision medicine has been proposed, which is an approach based on exposing patient samples to existing or experimental drugs.⁷⁵ In the future, integrating the functional precision medicine approach would allow one to determine which drugs are more potent and effective for each patient. Challenges to functional precision medicine include techniques for handling patient tissues, unclear clinical associations between in vivo analysis and actual patient outcome, and the time from tissue collection, creation of specific models such as cell lines, organoids, and xenograft models, to drug testing.⁷⁶ There are ongoing clinical trials evaluating the feasibility and utility of functional precision medicine. The integration of traditional genomics-driven, static precision medicine and functional precision medicine would provide better rationale for combination treatments and facilitate better discussion in the MTB.⁷⁶

Perioperative Toxicity

In the perioperative setting, the toxicity of agents suggested by the MTB needs to be carefully considered, because severe adverse events from targeted therapies or immunotherapy can delay surgery and affect quality of life in patients whose cancer is potentially curable (see article by Nishizaki and Eskander). To implement the personalized medicine in the early setting, future clinical trials incorporating MTB and precision oncology must assess the safety and the impact of toxicity on the outcome of definitive therapy to optimize outcomes.

FUTURE DIRECTIONS

Clinical trials evaluating precision oncology have demonstrated its feasibility and survival benefits across tumor types leading to the rapid expansion of tailored medicine for patients with solid tumors. Particularly, molecular targeted therapies and immunotherapy are being actively incorporated into neoadjuvant and adjuvant therapy with surgery, suggesting the need for the MTB in the perioperative setting to deliver the best personalized therapeutic strategy to increase the chances of cancer cure.

Current issues and challenges with molecular targeted therapy and ICIs are that most patients receiving these agents eventually acquire resistance and show disease progression while receiving these treatments. Precision medicine trials showed feasibility of patient enrollment and sequencing, but have also shown that therapies targeting a single alteration do not provide significant benefit.⁴⁴ As cancer cells acquire some escape pathways after exposure to these agents, strategies to combine 2 or more agents have been proposed and evaluated to improve treatment outcomes in recent clinical trials.^{77,78} The NCI-ComboMATCH was launched to search for ideal combination therapies based on evidence from preclinical studies.⁷⁹ Results from this type of clinical trial will provide useful information to guide treatment decisions at the MTB.

The development of antibody-drug conjugates (ADCs), bispecific antibodies, cellular therapy, and radionuclide therapy will also expand precision medicine. The use of ADCs for cancer treatment is growing dramatically. ADCs are composed of a cytotoxic payload, an antibody to target antigens expressed on tumor cells, and a linker to connect the payload and antibody. Examples of ADCs in oncology include enfortumab vedotin (payload: MMAE, target antigen: nectin-4), trastuzumab deruxtecan (payload: DXd, target antigen: HER2), and sacituzumab govitecan (payload: SN-38, target

antigen: Trop-2). Because antigen expression patterns differ between tumor types, ADCs have been evaluated for specific tumor types. Recently, trastuzumab deruxtecan demonstrated a promising objective response rate (37.1% in the entire population; 61.3% in patients with IHC 3+ expression) for HER2 overexpressing tumors in the pan-cancer setting (NCT04482309, DESTINY-PanTumor02), suggesting the utility of ADCs as a tumor-agnostic approach.⁸⁰ Additionally, bispecific antibodies and cellular therapy targeting specific tumor-associated antigens on cancer cells also implement the concept of personalized medicine. Radionuclide therapy such as Lutetium-177-PSMA-617 has also been shown to improve PFS in patients with PSMA-positive castration-resistant prostate cancer.⁸¹ All of these treatment modalities have demonstrated clinical benefit by targeting specific antigen expression on tumors, suggesting the importance of dissecting molecular features on tumor cells before determining the treatment plan for each patient.

Addressing challenges such as access to genomic profiling testing and the MTB is also important to resolve health care disparities in the United States and globally. Not all institutions have the capacity to conduct MTBs. Interinstitutional collaboration through the establishment of precision medicine networks, the implementation of virtual meetings at the request of physicians, and education and training in MTBs for health care providers in rural areas may lead to a seamless discussion with patients regardless of the areas in which they live.

MTBs are an integral part of delivering precision medicine to patients with early and advanced cancer. Its presence and role are growing, and multiple clinical trials are underway to evaluate the feasibility of MTB for the implementation of personalized medicine in oncology. The challenges mentioned in this article need to be addressed to eliminate disparities and advance precision oncology, but the future of precision medicine is bright, and MTB will continue to play an important role in offering the best personalized therapy for patients with cancer.

SUMMARY

With multiple molecular targeted therapies available for patients with cancer that correspond to a specific genetic alteration, the selection of the best treatment through discussion is essential to ensure therapeutic efficacy. MTBs play a key role in this decision-making process to deliver personalized medicine to patients with cancer in a multidisciplinary manner. Historically, personalized medicine has been offered to patients with advanced cancer, but the incorporation of molecular targeted therapies and immunotherapy into the perioperative setting requires clinicians, including surgeons, to understand the role of the MTB. Evidence is accumulating to support the feasibility and survival benefit in patients treated with the matched therapy proposed by the MTB, and the MTB will continue to play an integral role in incorporating the growing body of evidence of cancer therapy to provide personalized treatment for each patient with cancer.

CLINICS CARE POINTS

- The MTB is an essential venue for discussing molecular profiling test results and offering personalized therapy including molecular targeted therapy, immunotherapy, and available clinical trials for patients with cancer.
- Precision medicine is being incorporated into the perioperative setting, and, therefore, surgical oncologists should be involved in multidisciplinary MTBs.

DISCLOSURE

Y. Fujiwara reports research expenses from the Conquer Cancer Foundation of the American Society of Clinical Oncology, American Association for Cancer Research, and scholarship fee from Japanese Medical Society of America, outside this study. S. Kato serves as a consultant for Foundation Medicine, receives speaker fees from Roche and research grants from ACT Genomics, Sysmex, Konica Minolta, and Omni-Seq. R. Kurzrock is funded in part by 5U01CA180888-08 and 5UG1CA233198-05. RK has received research funding from Boehringer Ingelheim, Debiopharm, Foundation Medicine, Genentech, Grifols, Guardant, Incyte, Konica Minolta, Medimmune, Merck Serono, Omniseg, Pfizer, Sequenom, Takeda, and TopAlliance and from the NCI; as well as consultant and/or speaker fees and/or advisory board/consultant for Actuate Therapeutics, AstraZeneca, Bicara Therapeutics, Inc., Biological Dynamics, Caris, Datar Cancer Genetics, Daiichi, Eisai, EOM Pharmaceuticals, Iylen, Labcorp, Merck, NeoGenomics, Neomed, Pfizer, Precirix, Prosperdtx, Regeneron, Roche, TD2/Volastra, Tempus, Turning Point Therapeutics, X-Biotech; has an equity interest in CureMatch Inc; serves on the Board of CureMatch and CureMetrix, and is a co-founder of CureMatch.

REFERENCES

1. Wu Q, Qian W, Sun X, et al. Small-molecule inhibitors, immune checkpoint inhibitors, and more: FDA-approved novel therapeutic drugs for solid tumors from 1991 to 2021. *J Hematol Oncol* 2022;15(1):143.
2. Tsimberidou AM, Fountzilas E, Nikanjam M, et al. Review of precision cancer medicine: evolution of the treatment paradigm. *Cancer Treat Rev* 2020;86:102019.
3. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344(14):1031–7.
4. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350(21):2129–39.
5. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361(10):947–57.
6. Schwaederle M, Zhao M, Lee JJ, et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. *J Clin Oncol* 2015;33(32):3817–25.
7. Horak P, Fröhling S, Glimm H. Integrating next-generation sequencing into clinical oncology: strategies, promises and pitfalls. *ESMO Open* 2016;1(5):e000094.
8. Subbiah V, Puzanov I, Blay JY, et al. Pan-cancer efficacy of vemurafenib in BRAF (V600)-mutant non-melanoma cancers. *Cancer Discov* 2020;10(5):657–63.
9. Gouda MA, Nelson BE, Buschhorn L, et al. Tumor-agnostic precision medicine from the AACR GENIE database: clinical implications. *Clin Cancer Res* 2023;29(15):2753–60.
10. Kiyotani K, Toyoshima Y, Nakamura Y. Personalized immunotherapy in cancer precision medicine. *Cancer Biol Med* 2021;18(4):955–65.
11. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther* 2017;16(11):2598–608.
12. Doroshow DB, Bhalla S, Beasley MB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 2021;18(6):345–62.

13. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase ii trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003;21(12):2237–46.
14. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362(25):2380–8.
15. Khosin S, Blumenthal GM, Jiang X, et al. U.S. Food and Drug Administration approval summary: erlotinib for the first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations. *Oncol* 2014;19(7):774–9.
16. Kazandjian D, Blumenthal GM, Chen HY, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. *Oncol* 2014;19(10):e5–11.
17. Pegram MD, Lipton A, Hayes DF, et al. Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. *J Clin Oncol* 1998;16(8):2659–71.
18. Marcus L, Donoghue M, Aungst S, et al. FDA approval summary: entrectinib for the treatment of NTRK gene fusion solid tumors. *Clin Cancer Res* 2021;27(4):928–32.
19. Marcus L, Lemery SJ, Keegan P, et al. FDA approval summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. *Clin Cancer Res* 2019;25(13):3753–8.
20. Marcus L, Fashoyin-Aje LA, Donoghue M, et al. FDA approval summary: pembrolizumab for the treatment of tumor mutational burden-high solid tumors. *Clin Cancer Res* 2021;27(17):4685–9.
21. Rijavec E, Biello F, Indini A, et al. Current Insights on the treatment of anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer: focus on brigatinib. *Clin Pharmacol* 2022;14:1–9.
22. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* 2020;21(4):531–40.
23. Mateo J, Steuten L, Aftimos P, et al. Delivering precision oncology to patients with cancer. *Nat Med* 2022;28(4):658–65.
24. Parikh AR, Leshchiner I, Elagina L, et al. Liquid versus tissue biopsy for detecting acquired resistance and tumor heterogeneity in gastrointestinal cancers. *Nat Med* 2019;25(9):1415–21.
25. Kinugasa H, Nouse K, Miyahara K, et al. Detection of K-ras gene mutation by liquid biopsy in patients with pancreatic cancer. *Cancer* 2015;121(13):2271–80.
26. Kato S, Kim KH, Lim HJ, et al. Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. *Nat Commun* 2020;11(1):4965.
27. Jordan VC. Tamoxifen: a most unlikely pioneering medicine. *Nat Rev Drug Discov* 2003;2(3):205–13.
28. Baselga J, Perez EA, Pienkowski T, et al. Adjuvant trastuzumab: a milestone in the treatment of HER-2-positive early breast cancer. *Oncol* 2006;11(Suppl 1):4–12.
29. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353(16):1659–72.
30. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early her2-positive breast cancer. *N Engl J Med* 2017;377(2):122–31.

31. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med* 2022;386(6):556–67.
32. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med* 2021;385(8):683–94.
33. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med* 2021;384(22):2102–14.
34. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 2022;23(10):1274–86.
35. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 2022;386(21):1973–85.
36. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet* 2021;398(10308):1344–57.
37. Fountzilias E, Tsimberidou AM, Vo HH, et al. Clinical trial design in the era of precision medicine. *Genome Med* 2022;14(1):101.
38. Park JJH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019;20(1):572.
39. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selipercatinib 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(10):1261–73.
40. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAFV600E mutations: results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol* 2020;38(33):3895–904.
41. Wen PY, Stein A, van den Bent M, 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(1):53–64.
42. Tsimberidou AM, Iskander NG, Hong DS, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res* 2012;18(22):6373–83.
43. Tsimberidou AM, Hong DS, Wheler JJ, et al. Long-term overall survival and prognostic score predicting survival: the IMPACT study in precision medicine. *J Hematol Oncol* 2019;12(1):145.
44. O'Dwyer PJ, Gray RJ, Flaherty KT, et al. The NCI-MATCH trial: lessons for precision oncology. *Nat Med* 2023;29(6):1349–57.
45. Flaherty KT, Gray RJ, Chen AP, et al. Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: national cancer institute molecular analysis for therapy choice (NCI-MATCH). *J Clin Oncol* 2020;38(33):3883–94.
46. NCI-MATCH Sets. Benchmark of actionability. *Cancer Discov* 2021;11(1):6–7.
47. Gouda MA, Buschhorn L, Schneeweiss A, et al. N-of-1 trials in cancer drug development. *Cancer Discov* 2023;13(6):1301–9.
48. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. *Nat Med* 2019;25(5):744–50.
49. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of advanced malignancies guides first-line N-of-1 treatments in the I-PREDICT treatment-naïve study. *Genome Med* 2021;13(1):155.

50. Schwaederle M, Parker BA, Schwab RB, et al. Precision oncology: the UC San Diego Moores Cancer Center PREDICT experience. *Mol Cancer Ther* 2016;15(4):743–52.
51. Louie BH, Kato S, Kim KH, et al. Precision medicine-based therapies in advanced colorectal cancer: The University of California San Diego Molecular Tumor Board experience. *Mol Oncol* 2022;16(13):2575–84.
52. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of hr+, her2-node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol* 2020;38(34):3987–98.
53. Tsuboi M, Herbst RS, John T, et al. Overall Survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med* 2023;389(2):137–47.
54. Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 2017;377(6):523–33.
55. Arora S, Balasubramaniam S, Zhang H, et al. FDA approval summary: olaparib monotherapy or in combination with bevacizumab for the maintenance treatment of patients with advanced ovarian cancer. *Oncol* 2021;26(1):e164–72.
56. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med* 2019;381(4):317–27.
57. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020;382(22):2091–102.
58. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol* 2020;38(32):3763–72.
59. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med* 2021;384(25):2394–405.
60. Geyer CE Jr, Garber JE, Gelber RD, 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(12):1250–68.
61. Nanda R, Liu MC, Yau C, et al. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 Trial. *JAMA Oncol* 2020;6(5):676–84.
62. Barker A, Sigman C, Kelloff G, et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clinical Pharmacology & Therapeutics* 2009;86(1):97–100.
63. Irwin KE, Ko N, Walsh EP, et al. Developing a virtual equity hub: adapting the tumor board model for equity in cancer care. *Oncol* 2022;27(7):518–24.
64. Pishvaian MJ, Blais EM, Bender RJ, et al. A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology to physicians and their patients. *JAMIA Open* 2019;2(4):505–15.
65. Michele B, Alice B, Gaia G, et al. A fully virtual and nationwide molecular tumor board for gynecologic cancer patients: the virtual experience of the MITO cooperative group. *Int J Gynecol Cancer* 2022;32(9):1205.
66. Park KH, Choi JY, Lim AR, et al. Genomic landscape and clinical utility in Korean advanced pan-cancer patients from prospective clinical sequencing: K-MASTER program. *Cancer Discov* 2022;12(4):938–48.
67. Heong V, Syn NL, Lee XW, et al. Value of a molecular screening program to support clinical trial enrollment in Asian cancer patients: The Integrated Molecular Analysis of Cancer (IMAC) Study. *Int J Cancer* 2018;142(9):1890–900.

68. Nakamura Y, Taniguchi H, Ikeda M, et al. Clinical utility of circulating tumor DNA sequencing in advanced gastrointestinal cancer: SCRUM-Japan GI-SCREEN and GOZILA studies. *Nat Med* 2020;26(12):1859–64.
69. Moyers JT, Subbiah V. Think globally, act locally: globalizing precision oncology. *Cancer Discov* 2022;12(4):886–8.
70. Drake TM, Knight SR, Harrison EM, et al. Global Inequities in precision medicine and molecular cancer research. *Front Oncol* 2018;8:346.
71. Meric-Bernstam F, Brusco L, Daniels M, et al. Incidental germline variants in 1000 advanced cancers on a prospective somatic genomic profiling protocol. *Ann Oncol* 2016;27(5):795–800.
72. Seifert BA, O'Daniel JM, Amin K, et al. Germline analysis from tumor-germline sequencing dyads to identify clinically actionable secondary findings. *Clin Cancer Res* 2016;22(16):4087–94.
73. Schrader KA, Cheng DT, Joseph V, et al. Germline variants in targeted tumor sequencing using matched normal DNA. *JAMA Oncol* 2016;2(1):104–11.
74. DeLeonardis K, Hogan L, Cannistra SA, et al. When should tumor genomic profiling prompt consideration of germline testing? *Journal of Oncology Practice* 2019;15(9):465–73.
75. Letai A. Functional precision cancer medicine-moving beyond pure genomics. *Nat Med* 2017;23(9):1028–35.
76. Letai A, Bhola P, Welm AL. Functional precision oncology: testing tumors with drugs to identify vulnerabilities and novel combinations. *Cancer Cell* 2022;40(1):26–35.
77. Jin H, Wang L, Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. *Nat Rev Drug Discov* 2023;22(3):213–34.
78. Fujiwara Y, Mitra A, Naqash AR, et al. A review of mechanisms of resistance to immune checkpoint inhibitors and potential strategies for therapy. *Cancer Drug Resist* 2020;3(3):252–75.
79. Meric-Bernstam F, Ford JM, O'Dwyer PJ, et al. National cancer institute combination therapy platform trial with molecular analysis for therapy choice (Combo-MATCH). *Clin Cancer Res* 2023;29(8):1412–22.
80. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results. *J Clin Oncol* 2023;41(17_suppl):LBA3000.
81. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 2021;385(12):1091–103.
82. Mangat PK, Halabi S, Bruinooge SS, et al. Rationale and design of the targeted agent and profiling utilization registry (TAPUR) study. *JCO Precis Oncol* 2018;2018.
83. Alva AS, Mangat PK, Garrett-Mayer E, et al. Pembrolizumab in patients with metastatic breast cancer with high tumor mutational burden: results from the targeted agent and profiling utilization registry (TAPUR) Study. *J Clin Oncol* 2021;39(22):2443–51.
84. Ahn ER, Rothe M, Mangat PK, et al. Pertuzumab plus trastuzumab in patients with endometrial cancer with ERBB2/3 amplification, overexpression, or mutation: results from the TAPUR study. *JCO Precis Oncol* 2023;7:e2200609.
85. Tsimberidou AM, Hong DS, Fu S, et al. Precision medicine: preliminary results from the Initiative for Molecular Profiling and Advanced Cancer Therapy 2 (IMPACT2) study. *NPJ Precis Oncol* 2021;5(1):21.
86. Adashek JJ, Subbiah V, Kurzrock R. From tissue-agnostic to N-of-one therapies: (R)evolution of the precision paradigm. *Trends Cancer* 2021;7(1):15–28.

87. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365(9453):60–2.
88. von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2018;380(7):617–28.
89. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *N Engl J Med* 2022;386(25):2363–76.
90. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-MUTATED MELAnoma. *N Engl J Med* 2017;377(19):1813–23.
91. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018;379(26):2495–505.