The Role of Biomarkers in Guiding Clinical Decision-Making in Oncology

DONALD C. MOORE,[1] PharmD, BCPS, BCOP, DPLA, FCCP, and ANDREW S. GUINIGUNDO,[2] MSN, RN, CNP, ANP-BC

From [1]Department of Pharmacy, Levine Cancer Institute, Atrium Health, Charlotte, North Carolina; [2]Cincinnati Cancer Advisors, Cincinnati, Ohio

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Donald C. Moore, PharmD, BCPS, BCOP, DPLA, FCCP, Levine Cancer Institute, 1021 Morehead Medical Drive, Charlotte, NC 28204. E-mail: donald.moore1@atriumhealth.org

https://doi.org/10.6004/jadpro.2023.14.3.17

Abstract

Recent advances in molecular diagnostics have led to the characterization of an increasing number of actionable genomic alterations and immune-based signatures, which have facilitated the development of many highly effective cancer therapies. In addition to their prognostic value, some of these biomarkers have been shown to have predictive value and have had a significant impact on clinical decision-making. The presence of these therapeutic targets can thus aid health-care professionals to select the optimal therapies and avoid use of ineffective, potentially toxic ones. Earlier agents were generally approved for only one or a limited number of malignancies and/or stages, but more recent approvals encompass multiple tumor types that bear a common molecular alteration regardless of tumor type (i.e., tumor-agnostic indications). The expanding use of tumor-agnostic biomarkers has the potential to greatly broaden the use of these therapies to a wider patient population. Yet the rapidly increasing number of tumor-specific and tumor-agnostic biomarkers, and the continually changing treatment guidelines regarding the use of targeted agents and associated testing requirements, present challenges for advanced practitioners to remain current on these topics and their ability to apply these advances to clinical care. Here, we review predictive oncology biomarkers currently in use and their role in clinical decision-making, including those specified in product prescribing information and clinical practice guidelines. Current clinical guidelines regarding recommended targeted therapies for selected malignancies, and when molecular testing should be performed, are discussed.

The discovery of molecular profiles unique to different types of malignancies has greatly improved the treatment of cancer. The identification of biomarkers based on oncogenic driver mutations has led to advancements in diagnosing cancer, predicting response to treatment, and informing prognosis. The characterization of such biomarkers and molecular profiles has brought about an era of targeted therapeutic oncology drug development and precision medicine. Biomarkers may be diagnostic, prognostic, predictive,

J Adv Pract Oncol 2023;14(Suppl 1):15–37

used for monitoring patients, assessing response or susceptibility and risk, and determining drug safety (FDA-NIH Biomarker Working Group, 2016). Given the many advancements in biomarkers and the variability in their therapeutic use, it is important for advanced practitioners to understand the methods used in biomarker assessment and the context for selecting drug therapy in the presence of a given biomarker. Herein, we review common methods and technologies used in the assessment of biomarkers and discuss the current state of biomarker-driven treatments used in the management of solid tumors and hematologic malignancies. Common molecular alterations and corresponding biomarker-driven cancer therapies approved by the US Food and Drug Administration (FDA) are listed in Table 1.

METHODS AND TECHNOLOGIES IN BIOMARKER ASSESSMENT

Biomarker testing in cancer patients involves analyzing DNA, RNA, or proteins obtained by directly sampling the tumor or circulating cell-free tumor DNA (ctDNA) found in the blood. Following sample collection, the necessary technology and methods must be used to identify the specific biomarker. Several different technologies exist for the detection of biomarkers in cancer, each with their own advantages and disadvantages.

Polymerase chain reaction (PCR) is a laboratory technique used to amplify and detect specific sequences of either DNA or RNA (Sokolenko & Imyanitov, 2018; Ulivi, 2020). Polymerase chain reaction testing has the advantages of being highly specific and sensitive, simple to perform, and easy to reproduce. Polymerase chain reaction testing is also relatively inexpensive and only requires a small amount of biological sample. One example of utilizing PCR is in determining the presence of the *BCR-ABL* translocation, i.e., the Philadelphia chromosome, in patients with chronic myeloid leukemia (CML). One disadvantage of PCR is that it is only capable of testing for specific predetermined mutations.

Fluorescence in situ hybridization (FISH) can detect specific sequences of DNA or RNA in tissue samples by utilizing labeled nucleic acid probes. Fluorescence in situ hybridization testing can detect gene amplifications, deletions, fusions, and translocations (Ulivi, 2020). While FISH testing can be reliable and easy to perform, it detects DNA rearrangements and cannot identify sequence mutations. FISH testing is often used when *HER2* amplification is equivocal on initial testing in breast cancer since FISH can distinguish between *HER2*-amplified vs. *HER2*-low status.

Immunohistochemistry (IHC) assesses changes in the amount or expression of specific proteins in tissue samples (El-Deiry et al., 2019). Immunohistochemistry uses antibodies to detect cancer-related proteins, such as tumor-specific antigens, oncogenic proteins involved in cell growth, or markers of cellular proliferation. Immunohistochemistry has the advantage of being able to provide information on where the protein is expressed within the context of the tumor tissue sample. However, this test requires unique antibodies for each of the target proteins of interest, so not all desired targets or antigens may be identifiable. Immunohistochemistry is sometimes utilized for the diagnosis of cancer of unknown primary, where the presence or absence of unique markers can help identify the primary tumor site.

Next-generation sequencing (NGS) is a high-throughput technique for biomarker detection and is often used more frequently than the aforementioned methods (El-Deiry et al., 2019). Next-generation sequencing rapidly examines the genome to assess for changes in DNA, gene fusions, and variations in gene copy number. This methodology has the ability to simultaneously detect multiple gene alterations, either in a limited capacity or across an entire genome, making it an alternative to testing methods that assess only a single gene or that use platforms designed to look for specific mutations. While NGS can offer significant flexibility and can be more comprehensive than other biomarker testing methods, there can be differences in results between the various NGS platforms available. Bioinformatic analysis is also needed to interpret the data derived from some NGS techniques. Some NGS testing involves the evaluation of hundreds of genes, looking for dozens to hundreds of alterations within single genes. Since manual analysis of that much data is simply not possible, bioinformatics (the use of computer systems to assist in analysis) is essential. Next-generation sequencing enables testing of a high number of genes in a reasonable time frame, and it

Table 1. Molecular Alterations and Corresponding Biomarker-Driven FDA-Approved Cancer Therapies[a]

Malignancy	Drug (trade name)	Biomarker	Biomarker alteration(s)
Acute myelogenous leukemia	Midostaurin (Rydapt)	*FLT3*	ITD mutations and TKD mutations D835 and I836
	Gilterinib (Xospata)	*FLT3*	ITD mutations and TKD mutations D835 and I836
	Enasidenib (Idhifa)	*IDH2*	R140Q, R140L, R140G, R140W, R172K, R172M, R172G, R172S, and R172W
	Ivosidenib (Tibsovo)	*IDH1*	R132 mutations (R132C, R132H, R132G, R132S, and R132L)
	Olutasidenib (Rezlidhia)	*IDH1*	R132 mutations (R132C, R132H, R132G, R132S, and R132L)
Breast cancer	Olaparib (Lynparza)	*BRCA1/2*	Mutations
	Talazoparib (Talzenna)	*BRCA1/2*	Mutations
	Ado-trastuzumab emtansine (Kadcyla)	*HER2*	*HER2* amplification or HER-2 protein overexpression
	Trastuzumab (Herceptin)	*HER2*	*HER2* amplification or HER-2 protein overexpression
	Pertuzumab (Perjeta)	*HER2*	*HER2* amplification or HER-2 protein overexpression
	Fam-trastuzumab deruxtecan-nxki (Enhertu)	*HER2*	HER2 protein overexpression
	Abemaciclib (Verzenio)	Ki-67	Ki-67 protein expression
	Alpelisib (Piqray)	*PIK3CA*	C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y
Breast cancer, triple-negative (TNBC)	Pembrolizumab (Keytruda)	PD-L1	PD-L1 protein expression
Cervical cancer	Pembrolizumab (Keytruda)	PD-L1	PD-L1 protein expression
Cholangiocarcinoma	Pemigatinib (Pemazyre)	*FGFR2*	*FGFR2* fusions/rearrangements
	Infigratinib (Truseltiq)	*FGFR2*	*FGFR2* fusions/rearrangements
	Ivosidenib (Tibsovo)	*IDH1*	Single nucleotide variants
Colorectal	Cetuximab (Erbitux)	*KRAS*	EGFR protein expression Mutations in codons 12 and 13 of *KRAS* gene
	Panitumumab (Vectibix)	*KRAS* and *NRAS*	EGFR protein expression *KRAS* wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)
Endometrial carcinoma	Dostarlimab-gxly (Jemperli)	dMMR proteins	MLH1, PMS2, MSH2, and MSH6
	Pembrolizumab (Keytruda) in combination with lenvatinib (Lenvima)	dMMR proteins	MLH1, PMS2, MSH2, and MSH6

Note. dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; TMB-H = tumor mutational burden-high. PD-L1 = programmed cell death ligand 1; FDA = US Food and Drug Administration; HRD = homologous recombination deficiency; HRR = homologous recombination-related; IC = immune cells; Mb = megabase; MET = mesenchymal-epithelial transition; TC = tumor cells. Adapted from FDA (2023).
[a]Updated January 4, 2023.

Table 1. Molecular Alterations and Corresponding Biomarker-driven FDA-Approved Cancer Therapies[a] (cont.)

Malignancy	Drug (trade name)	Biomarker	Biomarker alteration(s)
Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	Mirvetuximab soravtansine-gynx (Elahere)	FOLR1	FOLR1 protein expression
Esophageal squamous cell carcinoma (ESCC)	Pembrolizumab (Keytruda)	PD-L1	PD-L1 protein expression
Follicular lymphoma	Tazemetostat (Tazverik)	*EZH2*	Y646N, Y646F or Y646X (Y646H, Y646S, or Y646C), A682G, and A692V
Gastric and gastroesophageal cancer	Trastuzumab (Herceptin)	HER2	HER-2 protein overexpression
Gastrointestinal stromal tumors (GIST)	Imatinib mesylate (Gleevec)	C-Kit	C-Kit protein expression in CD117 antigen-expressing cells
Melanoma	Trametinib (Mekinist)	*BRAF*	V600E and V600K
	Vemurafenib (Zelboraf)	*BRAF*	V600E
	Cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf)	*BRAF*	V600E or V600K
	Atezolizumab (Tecentriq) in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf)	*BRAF*	*BRAF* V600 mutations
	Encorafenib (Braftovi) in combination with binimetinib (Mektovi)	*BRAF*	V600E or V600K
Melanoma, uveal	Tebentafusp-tebn (Kimmtrak)	*HLA*	HLA-A
Myelodysplastic syndrome/ myeloproliferative disease (MDS/MPD)	Imatinib mesylate (Gleevec)	*PDGFRB*	*PDGFRB* gene rearrangement at 5q31-33
Non–small cell lung cancer	Brigatinib (Alunbrig)	*ALK*	*ALK* gene rearrangements
	Alectinib (Alecensa)	*ALK*	ALK protein expression *ALK* rearrangements
	Crizotinib (Xalkori)	*ALK*	ALK protein expression *ALK* rearrangements
	Ceritinib (Zykadia)	*ALK*	ALK protein expression *ALK* rearrangements
	Lorlatinib (Lorbrena)	ALK	ALK protein expression
	Olaparib (Lynparza)	*BRCA1/2*	Mutations
	Dabrafenib (Tafinlar) in combination with trametinib (Mekinist)	*BRAF*	V600E
	Afatinib (Gilotrif)	*EGFR*	Exon 19 deletion or exon 21 L858R substitution mutation; L861, 719X, and S7681 mutations
	Erlotinib (Tarceva)	*EGFR*	Exon 19 deletion or exon 21 L858R substitution mutation
	Gefitinib (Iressa)	*EGFR*	Exon 19 deletion or exon 21 L858R substitution mutation
	Osimertinib (Tagrisso)	*EGFR*	Exon 19 deletion or exon 21 L858R substitution mutation; T790M mutation
	Amivantamab (Rybrevant)	*EGFR*	*EGFR* exon 20 insertions

Table 1. Molecular Alterations and Corresponding Biomarker-driven FDA-Approved Cancer Therapies[a] (cont.)

Malignancy	Drug (trade name)	Biomarker	Biomarker alteration(s)
Non–small cell lung cancer (cont.)	Dacomitinib (Vizimpro)	*EGFR*	Exon 19 deletion or exon 21 L858R substitution mutation
	Fam-trastuzumab deruxtecan-nxki (Enhertu)	*HER2*	Activating mutations (SNVs and exon 20 insertions)
	Adagrasib (Krazati)	*KRAS*	KRAS G12C
	Sotorasib (Lumakras)	*KRAS*	G12C
	Capmatinib (Tabrecta)	*MET*	Mutation that leads to MET exon 14 skipping
	Nivolumab (Opdivo) in combination with ipilimumab (Yervoy)	PD-L1	PD-L1 protein expression (TC staining ≥ 1%)
	Atezolizumab (Tecentriq)	PD-L1	PD-L1 protein expression (TC ≥ 50%) or PD-L1–stained tumor-infiltrating IC ≥ 10%
	Entrectinib (Rozlytrek)	*ROS1*	*ROS1* fusions
Ovarian cancer	Rucaparib (Rubraca)	*BRCA1/2*	Mutations
	Niraparib (Zejula)	*BRCA1/2*	Deleterious or suspected deleterious mutations in *BRCA1/2* genes and/or positive Genomic Instability Score
	Olaparib (Lynparza)	HRD	Deleterious or suspected deleterious mutations in *BRCA1/2* genes and/or positive Genomic Instability Score
Pancreatic cancer	Olaparib (Lynparza)	*BRCA1/2*	Mutations
Prostate cancer, metastatic castration resistant	Rucaparib (Rubraca)	*BRCA1/2*	*BRCA1/2* alterations
	Olaparib (Lynparza)	HRR genes	*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* alterations
Solid tumors	Dostarlimab-gxly (Jemperli)	dMMR proteins	MLH1, PMS2, MSH2, and MSH6
	Pembrolizumab (Keytruda)	dMMR proteins	MLH1, PMS2, MSH2, and MSH6
	Entrectinib (Rozlytrek)	*NTRK1*, *NTRK2* and *NTRK3*	*NTRK1*, *NTRK2,* and *NTRK3* fusions
	Pembrolizumab (Keytruda)	MSI-high	Microsatellite instability-high
	Pembrolizumab (Keytruda)	TMB	TMB ≥ 10 mutations per Mb
Thyroid cancer	Selpercatinib (Retevmo)	*RET*	*RET* fusions
Medullary thyroid cancer	Selpercatinib (Retevmo)	*RET*	*RET* mutations (SNVs, MNVs, and deletions)
Urothelial cancer	Erdafitinib (Balversa)	*FGFR3*	Exon 7: R248C (c.742C>T), S249C (c.746C>G); exon 10: G370C (c.1108G>T) and Y373C (c.1118A>G); and fusions (*FGFR3-TACC3v1* and *FGFR3-TACC3v3*)
	Atezolizumab (Tecentriq)	PD-L1	PD-L1 protein expression (PD-L1–stained tumor-infiltrating IC ≥ 5% of tumor area)

Note. dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; TMB-H = tumor mutational burden-high. PD-L1 = programmed cell death ligand 1; FDA = US Food and Drug Administration; HRD = homologous recombination deficiency; HRR = homologous recombination-related; IC = immune cells; Mb = megabase; MET = mesenchymal-epithelial transition; TC = tumor cells. Adapted from FDA (2023).
[a]Updated January 4, 2023.

can detect some alterations that cannot be identified by other available testing methodologies.

Ideally, genetic and genomic results should be easily accessible within the electronic medical record (EMR). The best systems would readily tell us if and when testing had occurred and what testing was completed. Unfortunately, the EMR can serve as a hindrance when trying to find older testing results. The best systems would allow for results to be searchable. On a large scale, when a new targeted agent becomes approved, a search engine should be available to identify patients who previously tested positive for the target. As testing technology improves, the way clinicians house these data also needs to grow.

BIOMARKERS IN SOLID TUMORS

Non–Small Cell Lung Cancer

Approximately 20 years ago, lung cancer was classified as simply either small cell or non–small cell, which were treated with platinum and etoposide or platinum and taxane chemotherapy, respectively. In the ensuing two decades, the importance of histology emerged, immunotherapy revolutionized lung cancer treatment, and the clinical integration of biomarkers made the treatment of some lung cancers more precise.

The first mention of biomarker-driven therapy within treatment guidelines is for stage IB, R0 non–small cell lung cancer (NSCLC; NCCN, 2022a). Stage IB to IIIA, R0 disease can be treated adjuvantly with chemotherapy followed by osimertinib (Tagrisso) in patients with *EGFR* exon 19 deletion or exon 20 L858R mutations (AstraZeneca, 2015). If a patient with stage IIA to IIIA NSCLC has neither of these mutations, atezolizumab (Tecentriq) can be used so long as PD-L1 expression is 1% or greater (Genentech, 2016).

For those with stage IV disease, biomarker testing should be performed following clinical assessment and prior to initiation of treatment. What should be included in testing? For both nonsquamous and squamous NSCLC, at least the following should be tested: mutations in *EGFR*, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*ex14 skipping, *RET*, and *ERBB2* (i.e., HER2), as well as PD-L1 expression. All of these, even the rarer mutations and emerging biomarkers, should be included as part of broad molecular profiling (NCCN, 2022a).

EGFR biomarkers can be further subdivided into the following mutations: exon 19 deletion and 21 L858R, as previously noted for earlier-stage disease. Many targeted agents can be utilized for such patients (seven at the time of this writing). Currently, osimertinib is preferred in the first-line setting. If another medication had been used previously (e.g., erlotinib [Tarceva], afatinib [Gilotrif], gefitinib [Iressa], dacomitinib [Vizimpro]), the patient can further be tested for the *EGFR* T790M mutation (an *EGFR* resistance mutation) upon progression. If positive for this mutation, osimertinib can be used in the second-line setting or for subsequent lines of therapy. Other *EGFR* mutations that can be seen include S769I, L861Q, and G719X. Osimertinib can be used, but afatinib is also a preferred drug in the first-line setting (Boehringer Ingelheim Pharmaceuticals, 2013). The presence of these alterations would be evaluated as part of comprehensive testing of *EGFR* mutations via NGS.

Currently, not all biomarkers dictate the use of targeted agents for first-line therapy, although research is ongoing. For *EGFR* exon 20 insertion mutation, standard-of-care systemic therapy for adenocarcinoma or squamous cell carcinoma should be employed in the first-line setting, while amivantamab-vmjw (Rybrevant) or mobocertinib (Exkivity) can be used as second-line therapy. Another biomarker that directs second-line therapy is *KRAS* G12C, where sotorasib (Lumakras) or adagrasib (Krazati) can be used in the second-line setting. At present, the recommendation is to not switch to the alternate KRAS inhibitor upon progression since these inhibitors have a similar mechanism of action (NCCN, 2022a). HER2-directed therapies such as fam-trastuzumab deruxtecan-nxki (Enhertu) or ado-trastuzumab emtansine (Kadcyla) can also be used after standard first-line therapy in metastatic HER2-mutated NSCLC (Genentech, 2013).

As stated earlier, despite the rarity of some mutations, they should also be included in molecular testing. *ALK* gene rearrangements are present in about 5% of NSCLC tumors (Chia et al., 2014). Such patients can be treated using several medications, including the NCCN Guideline–preferred ALK inhibitors alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena). *ROS1* rearrange-

ment can be targeted with entrectinib (Rozlytrek) or crizotinib (Xalkori). The combination of dabrafenib (Tafinlar) and trametinib (Mekinist) is preferred for the treatment of NSCLC with a *BRAF* V600E mutation. Patients with an *NTRK1/2/3* gene fusion have been successfully treated with larotrectinib (Vitrakvi) or entrectinib. Preferred therapies for NSCLC bearing *MET*ex14 skipping mutations include capmatinib (Tabrecta) or tepotinib (Tepmetko), while patients with a *RET* rearrangement can be treated with selpercatinib (Retevmo) or pralsetinib (Gavreto). These drugs can all be used in lieu of chemotherapy in the first-line setting.

Because delays in reporting molecular testing results to providers continues to be an issue, clinical situations sometimes require the initial use of standard therapy. Guidance is provided if standard chemotherapy was used prior to the discovery of a biomarker (NCCN, 2022a). Often, chemotherapy can be either interrupted, the targeted agent can be used as maintenance therapy after planned chemotherapy, or the targeted agent can be used upon disease progression. The guidelines recommend sending tissue for molecular testing; if the available tissue is inadequate or re-biopsy is not feasible, plasma testing, i.e., liquid biopsy, can be utilized. However, the speed of reporting results is not a factor that is mentioned despite liquid biopsy test results frequently being returned much faster. As the concordance of tissue and liquid biopsy improves, this may be a factor to consider. Further, if the value of simultaneous testing can be established, this too could be a strategy for molecular profiling. The value in this case would be measured both clinically and financially.

Small Cell Lung Cancer

Unlike NSCLC with its multitude of biomarkers, there is very little mention of molecular testing in the NCCN Guidelines for SCLC. In fact, in Version 3.2023, the language regarding testing was slightly revised from the previous version, from "may be considered" to "can be considered in rare cases" (NCCN, 2022b). This type of testing is confined to extensive-stage disease and is recommended for nonsmokers or light smokers. It may also be considered in cases of "pathologic dilemma"; for example, it is unexpected for a nonsmoker to be diagnosed with extensive-stage SCLC, so molecular findings might change the usual management of the disease. No additional guidance is given as to what biomarkers might be found or how to treat them once detected. Some of the tumor-agnostic markers may come into play in this setting. Biomarkers not currently in use that could become important for SCLC include SLFN11 (targeting PARP), MYC (CHK1, AURKA/B), and DLL3 (DLL3; Taniguchi et al., 2020). Tumor mutational burden (TMB) may have some utility in predicting the usefulness of immunotherapy beyond the PD-L1 inhibitors mentioned in the next section.

Immunotherapy is certainly the new standard as an adjunct to standard platinum and etoposide chemotherapy in extensive-stage SCLC. Despite this, SCLC is one of the cancers where specific testing for PD-L1 is not required and is not included in the prescribing information for either atezolizumab or durvalumab (Imfinzi), immune checkpoint inhibitors (ICIs) that are approved for extensive-stage SCLC (Genentech, 2016; AstraZeneca Pharmaceuticals, 2017).

Melanoma

The first widespread use of immunotherapies such as ICIs was in cutaneous melanoma. Despite this, current guidelines do not recommend specific biomarker testing for PD-L1 as is required for other tumor types. Immunotherapeutics remain a mainstay of therapy for this disease. The biomarkers occurring most commonly in cutaneous melanoma are *BRAF* V600 activating mutations (V600E or V600K). Assessment of *BRAF* V600 activating mutation is recommended for stage IV disease as well as in recurrent and unresectable disease (NCCN, 2022c). Drugs targeting this mutation include three two-drug combinations: dabrafenib/trametinib, vemurafenib (Zelboraf)/cobimetinib (Cotellic), and encorafenib (Braftovi)/binimetinib (Mektovi). Wider testing panels that include more than *BRAF* V600 activating mutations would be helpful, as other actionable markers are sometimes present in this disease. For example, in the presence of *KIT* activating mutations, KIT inhibitor therapy can be considered, including imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), and ripretinib (Qinlock). For *ROS1* fusions, crizotinib or entrectinib could be utilized. For *NTRK* fusions, larotrectinib or entrectinib can be

used. In *BRAF* fusions and non-V600 mutations, trametinib as a single agent is noted. For *NRAS*-mutated tumors and progression following ICI therapy, binimetinib can be used.

More precise prognostic testing for melanoma may be on the horizon. There are several prognostic gene expression profile (GEP) tests available clinically but are being used off-guidelines in melanoma (LeQuang, 2022). Such testing would seek to identify patients with stage I and II melanoma who need more aggressive follow-up and/or treatment, and those with stage III disease who may benefit from less aggressive follow-up and treatment. As this type of testing is not included within the guidelines, it is not yet clear what to do with such results.

Guidelines for the rare condition of uveal melanoma recommend biomarker testing to predict low, medium, or high risk of distant metastasis. Based on the results, the frequency and duration of follow-up imaging differ. The biomarkers disomy 3, gain of chromosome 6, and *EIF1AX* mutations are seen in low-risk patients, while *SF3B1* mutations are noted in those at medium risk. High-risk patients can have monosomy 3, gain of chromosome 8q, *BAP1* mutation, and/or PRAME expression. These biomarkers, along with other characteristics, comprise the risk level for uveal melanoma.

Breast Cancer

Clinicians have been using estrogen receptor (ER) status to determine the usefulness of antiestrogen agents for approximately 40 years (Early Breast Cancer Trialists' Collaborative Group, 2011). The American Society of Clinical Oncology, in conjunction with the College of American Pathologists, reaffirmed its usefulness in 2020 (Hammond et al., 2010). Guidelines suggest ER testing as early as ductal carcinoma in situ (DCIS) through stage IV disease (NCCN, 2023a). Endocrine agents for use in various situations include tamoxifen, anastrozole, letrozole, exemestane, fulvestrant, and others. Also included in the workup for DCIS through stage IV disease is genetic risk assessment, which has treatment as well as hereditary implications. This will be discussed in later sections.

Human epidermal growth factor receptor 2 (HER2) is also a breast cancer biomarker that has been used for decades. While we do not test for HER2 in DCIS, all invasive breast cancers should be tested. Until recently, HER2-directed therapy was confined to patients with an IHC (immunohistochemistry) 3+ score and/or were FISH positive. Recent data support the use of fam-trastuzumab deruxtecan-nxki in unresectable or metastatic adult patients with "HER2-low" tumors, defined as IHC 1+ or 2+/ISH negative (Daiichi Sankyo, 2019). In the adjuvant setting, in patients with tumors < 1 cm, HER2 therapy and chemotherapy can be considered. In those with tumors > 1 cm, trastuzumab (Herceptin) and chemotherapy are recommended. With that same ≥ 1 cm tumor plus a pN1 or greater, the additional HER2-directed agent pertuzumab (Perjeta) can be added. Neoadjuvant chemotherapy plus HER2-directed therapy can be an option in operable disease if it is HER2-positive with a cT1c or cN1 or higher stage, or for inoperable disease. If a pathologic complete response (CR) is obtained, trastuzumab with or without pertuzumab should be continued for a total of 1 year of HER2 therapy. If residual disease is noted, a switch to ado-trastuzumab emtansine can be made for the balance of 1 year of therapy, but could be switched back to trastuzumab with or without pertuzumab if toxicity is excessive.

Additional HER2 agents include lapatinib, which is indicated for use with capecitabine in patients with metastatic disease who had previously received an anthracycline, taxane, and trastuzumab. It can also be used in combination with letrozole in postmenopausal, HER2-positive, and ER-positive metastatic disease. Neratinib (Nerlynx) is an oral HER2 medication that has been used in advanced disease with capecitabine for patients who have received two or more HER2-directed agents previously. A novel use for neratinib was seen in the ExteNET trial in which HER2-positive patients, having completed trastuzumab in the adjuvant setting, were placed on neratinib within 2 years of completing trastuzumab (Chan et al., 2021). The study yielded a hazard ratio of 0.66 for neratinib compared with placebo for invasive disease-free survival (Puma Biotechnology, 2017). Tucatinib (Tukysa) is a kinase inhibitor used in combination with trastuzumab and capecitabine in patients with advanced or metastatic HER2-positive breast cancer who have received one or more prior HER2-

directed therapies (Seagen, 2020). Margetuximab-cmkb (Margenza) is another HER2-directed therapy for use in combination with chemotherapy in patients who have had at least two anti-HER2 therapies, with at least one of those in the metastatic setting (MacroGenics, 2020).

For breast cancers that lack HER2 expression (accounting for ~85% of all cases; Noone et al., 2017) but are still hormone positive, additional therapies exist. CDK4/6 inhibitors such as ribociclib (Kisqali), abemaciclib (Verzenio), and palbociclib (Ibrance) are used in combination with an aromatase inhibitor for first-line treatment of metastatic disease in HER2-negative postmenopausal or premenopausal patients receiving ovarian ablation or suppression. The mTOR inhibitor everolimus combined with anti-estrogen therapy can be used in the second-line setting for HER2-negative disease (Karacin et al., 2023). In *PIK3CA*-mutated disease, alpelisib (Piqray) can be used in the second-line setting and in subsequent lines (Novartis Pharmaceuticals, 2019). In *ESR1*-mutated tumors, elacestrant (Orserdu) is a treatment option as second-line therapy and beyond (Stemline Therapeutics, 2023). For HR-positive, HER2-negative disease in the third-line setting and beyond, biomarker-directed therapy not previously used could be utilized, including drugs for microsatellite instability-high (MSI-H), TMB-high, *NTRK* or *RET* alterations, and others. *PIK3CA*, *ESR1*, TMB, *NTRK*, *RET*, and other traditional hereditary genetic testing are all performed by means of NGS technology.

The complete absence of HR and HER2 expression, i.e., triple-negative breast cancer (TNBC), is significant as well. In the first-line setting, along with a PD-L1 Combined Positive Score (CPS) of 10 or more, pembrolizumab (Keytruda) may be given with chemotherapy. Combined Positive Score is defined as the total number of tumor cells and immune cells (including lymphocytes and macrophages) positively stained with PD-L1 divided by the total number of viable tumor cells, multiplied by 100. For second-line therapy, if no germline *BRCA1/2* mutation is present, the antibody-drug conjugate (ADC) sacituzumab govitecan (Trodelvy) can be used. However, as discussed previously, if the tumor is HER2 1+ or 2+/ISH negative, fam-trastuzumab deruxtecan-nxki is actually preferred in this setting. Within the guidelines, fam-trastuzumab deruxtecan-nxki is listed under systemic regimens for TNBC (NCCN, 2023a), but it could perhaps be argued that the concept of HER2-low could constitute a category unto itself. For TNBC in the third-line setting and beyond, biomarker-directed therapy not previously used could be considered, including drugs for MSI-H, TMB-high, *NTRK* or *RET* fusions, and others.

Some additional biomarkers to consider are pathogenic, e.g., germline (hereditary) *BRCA1* and *BRCA2* mutations (g*BRCA*m). For this reason, all breast cancer patients should be considered for germline genetic testing (NCCN, 2023b). While some diseases allow for the use of mutated somatic (tumor) *BRCA1* and *BRCA2* when utilizing poly(ADP-ribose) polymerase inhibitors (PARPi), in breast cancer g*BRCA*m are the only recognized biomarkers, and only olaparib (Lynparza) is approved in this setting for HER2-negative disease (AstraZeneca Pharmaceuticals, 2014). NCCN Guidelines describe somatic *BRCA* as an "emerging biomarker" along with Ki-67, TMB, and homologous recombination deficiency (HRD). In the adjuvant setting, after chemotherapy and for up to 1 year, olaparib can be administered for as long as a year; such therapy was associated with a hazard ratio of 0.68 for overall survival when olaparib was compared with placebo. In the metastatic setting, in patients who have had prior chemotherapy and had received endocrine therapy (or deemed inappropriate for endocrine therapy), olaparib can be used in patients with g*BRCA*m.

Prostate Cancer

Prostate cancer is another disease where germline and somatic testing go hand in hand. Germline and somatic testing can be considered for any patient who could potentially benefit from mutation-directed therapy. Family history should be obtained due to the hereditary nature of such mutations and for follow-up testing of family members (both males and females) since mutations in these genes raise the risk of cancers other than prostate cancer. The PARPi olaparib is approved for patients with a germline or somatic mutation in any number of homologous recombination repair (HRR) genes, including *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*. Other PARPi can be considered, but each carries nuanced FDA approv-

als (AstraZeneca Pharmaceuticals, 2014; Clovis Oncology, 2016; GlaxoSmithKline, 2017).

Tumor testing should include microsatellite instability (MSI) or mismatch repair (MMR). Additionally, TMB can be considered for metastatic castration-resistant prostate cancers. These three markers can predict the utility of ICIs in this disease, as with others.

There are other considerations regarding germline results. In patients who have tumors that are MSI-H or MMR-deficient, germline Lynch syndrome testing should be performed since both MSI-H and MMR deficiency can occur in the setting of Lynch syndrome (NCCN, 2023b). Additionally, other gene mutations such as *HOXB13* can increase the risk of prostate cancer but do not have an associated targeted therapy. Because such mutations, e.g., Lynch syndrome genes and *HOXB13*, have autosomal dominant hereditary implications, patients with germline mutations in any of these genes should be referred for genetic counseling.

Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

In the case of ovarian/fallopian tube/primary peritoneal cancer (which will be collectively referred to here as ovarian cancer), germline genetic testing is as important for its treatment implications as it is for hereditary cancer assessment. As the name implies, Hereditary Breast and Ovarian Cancer Syndrome mainly refers to disease in which risk is increased by pathogenic mutations in *BRCA1* or *BRCA2*. However, we now know that additional genes increase the risk of ovarian cancer if a mutation exists. According to NCCN Guidelines, mutations in *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *MSH2*, *MLH1*, *MSH6*, *PMS2*, *EPCAM*, *PALB2*, *RAD51C*, and *RAD51D* have all been associated with an increased risk for ovarian cancer, so the presence of a pathogenic variant could lead to interventions ranging from increased screening to risk-reducing salpingo-oophorectomies. Of this list, germline *BRCA1* and *BRCA2* mutations can affect treatment of a current diagnosis of ovarian cancer. In stage II to IV ovarian cancer, PARPi can be utilized as maintenance therapy following CR or partial response (PR) to platinum-based chemotherapy (AstraZeneca Pharmaceuticals, 2014; GlaxoSmithKline, 2017).

Tumors should also be tested, although a liquid biopsy for detecting circulating tumor DNA (ctDNA) can be used. Again, the primary aim is to look for somatic *BRCA1* and *BRCA2* mutations, but a wider panel can be useful. The presence of a somatic *BRCA1* or *BRCA2* mutation once again allows for the use of maintenance PARPi following a PR or CR with platinum-based chemotherapy. *BRCA1* and *BRCA2* are what are referred to as tumor suppressor genes, which encode for proteins that repair DNA damage (National Human Genome Research Institute; 2023). When one or the other of these genes is mutated, it is no longer able to function properly, and DNA damage is not repaired as readily as it is in individuals without a mutation. Both loss of heterozygosity (LOH) and HRD indicate a state of deficient DNA repair within a tumor cell. These deficient repair mechanisms can be exploited by use of platinum chemotherapy and PARPi. Any one of these biomarkers could suggest PARPi usage in ovarian cancer, so patients should be tested for such alterations.

As mentioned previously, a genomic panel ranging from a few genes to dozens of genes, in addition to *BRCA*, is useful since other biomarkers are also actionable in ovarian cancer. Dostarlimab (Jemperli) and pembrolizumab can both be used in patients with dMMR and MSI-H tumors. Pembrolizumab can also be used in disease that is TMB-high. *BRAF* V600E-positive tumors can be treated with dabrafenib plus trametinib. *NTRK* mutations are generally rarer, but when present entrectinib or larotrectinib can be utilized. Mirvetuximab soravtansine-gynx (Elahere) in combination with bevacizumab (Avastin) can be given for folate receptor α-expressing tumors. In *RET* gene fusion-positive tumors, selpercatinib can be used.

Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is approached in a very similar way as ovarian cancer, and many of the same genes and associated targeted agents are in play. From a hereditary germline genetics standpoint, any patient with a confirmed diagnosis of pancreatic cancer should be tested utilizing comprehensive panels for hereditary cancer syndromes (NCCN, 2023b). *BRCA1*- and *BRCA2*-related disease perhaps comes to mind initially,

but pancreatic cancer may also be associated with Lynch syndrome. Other hereditary cancer genes for pancreatic cancer include *ATM*, *CDKN2A*, *PALB2*, *STK11*, and *TP53*. The presence of all of these genes has hereditary implications since they are all autosomal dominant in nature. Every first-degree relative of an individual with a mutation in one of these genes has a 50% chance of inheriting the same mutation and, therefore, developing the hereditary syndrome (National Human Genome Research Institute, 2023). Additionally, the presence of germline *BRCA* mutations has targeted therapy implications.

For patients with locally advanced or metastatic disease, somatic tumor testing should be performed if therapy can be administered, keeping in mind that some targets and corresponding therapy are specifically used in patients with poor performance status. Several genomic abnormalities should be evaluated, including fusions involving *ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, *RET*, and other genes. Mutations such as those occurring in *BRAF*, *BRCA1*, *BRCA2*, *KRAS*, and *PALB2* should also be examined, as should gene amplifications such as *HER2*. MSI-H, dMMR, and TMB-high should be tested to assess the potential utility of immunotherapy. Somatic NGS testing can be accomplished by analyzing tumor DNA from a tissue sample or by use of liquid biopsy to evaluate ctDNA.

Prior to the use of biomarker-targeted therapy in pancreatic cancer, the presence of germline or somatic mutations in *BRCA1*, *BRCA2*, or *PALB2* should be assessed since these can impact choice of chemotherapy. For patients with these mutations, platinum-based chemotherapy is preferred for neoadjuvant therapy, i.e., gemcitabine plus cisplatin with or without chemoradiotherapy (cisplatin replaces albumin-bound paclitaxel for these patients). Alternatively, FOLFIRINOX or modified FOLFIRINOX chemotherapy could be used.

In metastatic disease, once again FOLFIRINOX-based regimens can be used in patients with or without *BRCA1*, *BRCA2*, or *PALB2* mutations, but the same gemcitabine-cisplatin regimen can also serve as first-line therapy. As with *BRAF* V600E mutations in other solid tumors, dabrafenib plus trametinib can be used in the first-line setting. Additionally, with any of the immunotherapy markers such as MSI-H, dMMR, and TMB-high, pembrolizumab therapy can be employed. All previous regimens listed here are for individuals with good performance status. For those with poor performance status, single-agent chemotherapy regimens are preferred, but if certain biomarkers are present, targeted therapy can be considered, including larotrectinib or entrectinib for *NTRK* gene fusion-positive patients. With *BRAF* V600E mutations, the same regimen of dabrafenib and trametinib can be used. The same biomarkers listed above for pembrolizumab are also used in poor performance status patients.

Following an initial 4- to 6-month chemotherapy regimen in patients with metastatic pancreatic cancer, those with stable disease may be considered for maintenance therapy. Olaparib can be used only in patients with germline mutated *BRCA1* and *BRCA2* (AstraZeneca Pharmaceuticals, 2014), while rucaparib's (Rubraca) label expands its use to those with germline or somatic *BRCA1*, *BRCA2*, and *PALB2* mutations (Clovis Oncology, 2016).

In subsequent therapy, regimens previously mentioned for *NTRK* and *BRAF* V600E alterations as well as MSI-H, dMMR, and TMB-high are discussed in the guidelines. Additionally, the use of selpercatinib in *RET* gene fusion–positive patients is noted. The prescribing information for erlotinib does not mention biomarkers when utilized in pancreatic cancer in conjunction with gemcitabine (Genentech, 2004). In NSCLC, erlotinib is approved for use with *EGFR* exon 19 deletions or exon 21 substitution mutations. This situation is hinted at in the footnotes of the NCCN Guidelines that state, "Although this combination significantly improved survival, the actual benefit is small, suggesting that only a small subset of patients benefit" (NCCN, 2022d).

Curiously, NCCN Guidelines mention testing for several biomarkers for which there is not a specific FDA approval in pancreatic cancer, nor is there a biomarker-positive approval based simply on the presence of the biomarker as is the case for *NTRK* fusions or MSI-H tumors. Examples of these biomarkers include alterations in *ALK*, *HER2*, and *KRAS*. For these markers, clinical trials or even "compassionate use" are targeted therapy options in this setting.

Colorectal Cancer

Biomarker considerations start early with colon cancer. In the initial workup for nonmetastatic, resectable disease, MMR and MSI analyses should be performed on the tumor. For T4b disease, nivolumab (Opdivo) with or without ipilimumab (Yervoy) or pembrolizumab can be used as an alternative to chemotherapy in the neoadjuvant setting for dMMR or MSI-H tumors. Interestingly, this recommendation has appeared in the medical literature and guidelines (Ludford et al., 2023; Igaue et al., 2022) but not in the FDA-approved prescribing information for these drugs (Merck, 2014; Bristol Myers Squibb, 2014; Bristol Myers Squibb, 2011). However, for unresectable or metastatic colorectal cancer with dMMR or MSI-H, both pembrolizumab as well as nivolumab (with or without ipilimumab) fall within the approved labels for each drug. If tumor tissue is MSI-H or dMMR and the individual has not had germline testing, it should certainly be considered since over 90% of Lynch syndrome tumors are MSI-H (NCCN, 2023b).

In advanced disease, testing for *KRAS*, *NRAS*, and *BRAF* should be performed. With wild-type *RAS* (*wtRAS*), either of the EGFR inhibitors panitumumab (Vectibix) or cetuximab (Erbitux) can be considered as an adjunct to chemotherapy. ("Wild type" indicates that no *RAS* mutation exists.) When mutations do exist, it predicts poor response to these drugs. *BRAF* also needs to be wild-type, or a BRAF inhibitor must be added for EGFR inhibitors to work. With *BRAF* V600E mutations, encorafenib plus an EGFR inhibitor can be used.

In patients with mutated *RAS* (*mRAS*), vascular endothelial growth factor receptor (VEGF) inhibitors can be effective. Bevacizumab is preferred, but the VEGF inhibitors ziv-aflibercept (Zaltrap) or ramucirumab (Cyramza) are options as well. Tumor location also appears to be predictive. In patients with *wtRAS* and right-sided disease, i.e., from the hepatic flexure to the cecum, use of EGFR inhibitors appears to lead to lower progression-free survival, overall survival, and overall response rate (ORR), so VEGF inhibitors can be utilized in this situation (Arnold et al., 2017). With left-sided tumors, from the splenic flexure to the rectum, panitumumab was found to be superior to bevacizumab in the phase III PARADIGM trial (Yoshino et al., 2022).

HER2 expression can be detected in some colorectal cancers. In advanced disease, a regimen of trastuzumab, pertuzumab, lapatinib, and tucatinib can be used. Additionally, fam-trastuzumab deruxtecan-nxki can be utilized. In such cases, tumors should be *HER2* amplified, with *wtRAS* and *wtBRAF* status.

NTRK fusions—but as specifically noted, not *NTRK* point mutations—respond to NTRK-directed medications. These are exceedingly rare in colon cancer (approximately 0.35%). NTRK-positive tumors are all *wtRAS* and *wtBRAF*, and are more commonly dMMR than not. In the LOXO-TRK-14001 trial of larotrectinib, colon cancers comprised 7% of the 55 study subjects with an *NTRK* fusion mutation (Drilon et al., 2018). The ORR was 75%, including 25% complete responses, with a median duration of response of nearly 33 months (Bayer, 2018). Entrectinib is another NTRK-targeted drug for *NTRK* gene fusion-positive advanced colorectal cancer as indicated in treatment guidelines.

RET fusions are also seen in colon cancer. Selpercatinib remains the preferred drug for patients with tumors bearing this alteration, based on NCCN Guidelines. In one study that included 10 colorectal cancer patients, a 20% ORR was seen, and 70% experienced stable disease (Lilly, 2020).

Gastric Cancer

From diagnosis, the initial workup of gastric cancer should include biomarker testing. Guidelines specifically note the need for evaluation of MSI-H status by PCR or NGS (NCCN, 2022e). Alternatively, since dMMR is a surrogate for MSI, it can be tested via IHC. Either marker can predict potential response to the immunotherapeutics pembrolizumab and nivolumab. Further, guidelines indicate that "NGS may be considered." Several reasons are given for this recommendation. As with other malignancies, there are multiple actionable biomarkers in gastric cancer. Additionally, a broad panel utilizing NGS conserves tissue compared to individual gene testing. If tissue quantity is problematic, liquid biopsy utilizing ctDNA is acceptable.

Two biomarkers have previously been noted for the use of PD-1 inhibitors. Additional biomarkers that qualify a patient for use of these drugs include PD-L1 expression by IHC and TMB by NGS. HER2 overexpression should be included in gastric cancer biomarker testing since if positive would allow for use of trastuzumab, as in breast cancer. Finally, TRK inhibitors could be used if a tumor is *NTRK* fusion-positive as determined by NGS.

Bladder Cancer

From the initial workup of suspected bladder cancer, genetic assessment should be considered. While Lynch syndrome is often thought of as "hereditary colorectal cancer" and sometimes "hereditary endometrial cancer" (the two highest-risk cancers associated with Lynch syndrome), other cancers are also associated with mutations in those genes, such as bladder cancer. Unlike other cancers, germline genetic testing in bladder cancer has no guideline-specified treatment impact. Genomic testing of the tumor does not become relevant until late-stage disease (NCCN, 2023c).

Genomic testing can be considered for stage IIIB tumors. When this disease advances to or presents as stage IV disease, genomic testing should be performed. NCCN Guidelines note that testing should be performed early to help with treatment decision-making and to avoid delays at progression. This is true of any tumor type. Patients with bladder cancer should be tested for *FGFR2* and *FGFR3* mutations. The kinase inhibitor erdafitinib (Balversa) is specifically directed at those mutations (Janssen Oncology, 2019). Bladder cancer is the third most mutated cancer, with a staggering 93% of patients having at least one clinically significant mutation and an average of 2.6 mutations per patient. Understanding that most genomic testing will occur via large-panel testing, some of the more prevalent mutations in bladder cancer include *CDKN2A*, *FGFR3*, *PIK3CA*, and *Her2/neu*.

For many uses of ICIs, specific biomarker testing is not required. For use of atezolizumab in cisplatin-ineligible patients, however, tumors must express PD-L1, with PD-L1–stained tumor-infiltrating immune cells covering 5% or more of the tumor surface.

Uterine Cancer

Initial evaluation of uterine/endometrial cancer should include both assessment of tumor genomics and hereditary risk assessment. From a hereditary perspective, Lynch syndrome is thought of as a hereditary colon cancer syndrome. Indeed, in one study, Møller and colleagues (2017) found that the incidence of colon cancer was as high as 46%. The risk for uterine cancer is even higher (up to 51%), depending on which Lynch syndrome gene is mutated. However, unlike g*BRCA*m in breast cancer, the finding of a mutated Lynch syndrome gene does not have an immediate impact on the treatment of uterine cancer.

In evaluating endometrial carcinoma molecularly, the first marker discussed is the *POLE* hotspot mutation. The presence of this mutation constitutes an endometrial carcinoma subtype. These mutations, present in up to 12% of endometrial carcinomas, are a good prognostic indicator (Veneris et al., 2019). On the opposite end of the spectrum, *p53* copy number-high (CNH) tumors are associated with the worst prognosis (López-Reig et al., 2019). Prognostically, MSI-H falls between *POLE* hotspot mutations and *p53* CNH. Of course, MSI and other similar markers like dMMR and TMB-high are actionable biomarkers, and such tumors can be treated with ICIs. With dMMR in advanced disease, the anti-VEGF kinase inhibitor lenvatinib (Lenvima) can be combined with pembrolizumab (Eisai, 2015).

In stage III or IV uterine cancer, primary or adjuvant treatment can include trastuzumab if tumors are HER2 positive (both in uterine carcinoma or carcinosarcoma of the uterus). Additionally, as with other tumor types, the rare *NTRK* fusion mutation can be treated with larotrectinib or entrectinib. Although seemingly similar to pathologic assessment of breast cancer, endometrial carcinoma can also express ERs. This biomarker therefore should be evaluated in patients with stage III, IV, or recurrent disease. Preferred regimens for ER-positive disease are megestrol acetate alternating with tamoxifen or everolimus with letrozole (NCCN, 2022f). Aromatase inhibitors, tamoxifen, and fulvestrant can all be used as single agents. In uterine-limited disease, progestational agents or even a levonorgestrel intrauterine device can be used in patients not suitable for surgery.

Uterine sarcoma presents some additional biomarkers. For example, inflammatory myofibroblastic tumors (IMT) sometimes are associated with *ALK* rearrangements. Five different ALK inhibitors can be used for *ALK* translocations. In perivascular epithelioid cell tumor (PEComa), mTOR inhibitors including albumin-bound sirolimus are indicated as first-line therapy, while sirolimus (Rapamune), everolimus, and temsirolimus (Torisel) can be used in the second-line setting and subsequent lines of therapy. In *BRCA2*-altered leiomyosarcoma, the PARPi olaparib, niraparib (Zejula), and rucaparib can all be used in the second-line setting and subsequently.

BIOMARKERS IN HEMATOLOGIC MALIGNANCIES

Leukemias

One of the landmark discoveries in targeted oncology therapeutics was the identification of the *BCR-ABL* gene in CML and the advent of BCR-ABL tyrosine kinase inhibitors (TKIs; O'Brien et al., 2003). The t(9;22) translocation in CML led to the identification of the Philadelphia chromosome (Ph), which involves the *BCR-ABL* fusion gene. This gene encodes for the p210 BCR-ABL protein and leads to dysregulated tyrosine kinase activity, thereby causing the development of leukemogenesis. Over 90% of cases of CML harbor t(9;22). The BCR-ABL TKI imatinib specifically targets the tyrosine kinase present in the vast majority of CML cases, and this paved the way for the development of other targeted therapeutics in oncology. Several other TKIs directed at BCR-ABL have since been approved for CML including bosutinib (Bosulif), dasatinib, nilotinib, and ponatinib (Iclusig; Pfizer, 2012; Bristol Myers Squibb, 2006; Novartis Pharmaceuticals, 2007; Takeda Pharmaceuticals, 2012).

Several new targeted therapeutic agents have been approved for acute myeloid leukemia (AML) in the past several years. Use of these therapies is based on the presence of specific biomarkers, including isocitrate dehydrogenase 1 and 2 (*IDH1/2*), fms-like tyrosine kinase 3 (*FLT3*), and CD33. *IDH* mutations are present in approximately 20% of patients with AML (Stein et al., 2021). Ivosidenib and olutasidenib (Rezlidhia) are IDH1 inhibitors, while enasidenib (Idhifa) is an IDH2 inhibitor (Montesinos et al., 2022; Watts et al., 2023; Stein et al., 2017). These therapies may be used as monotherapy in patients with actionable *IDH* mutations. Ivosidenib may also be used in combination with azacitidine in patients with newly diagnosed *IDH1*-mutant AML (Montesinos et al., 2022).

FLT3 is another actionable mutation present in approximately 30% of AML cases (Ravandi et al., 2010). Several therapeutic agents that target *FLT3* are available including midostaurin (Rydapt), gilteritinib (Xospata) , and sorafenib (Nexavar). Midostaurin may be combined with 7+3 intensive induction remission chemotherapy for patients with newly diagnosed *FLT3*-positive AML (Stone et al., 2017). Gilteritinib is an oral *FLT3* inhibitor that can be considered in the setting of relapsed/refractory *FLT3*-positive AML (Perl et al., 2019). For patients with CD33-positive disease, the anti-CD33 ADC gemtuzumab ozogamicin (Mylotarg) may be used in various settings, including in combination with intensive remission induction chemotherapy and as monotherapy in patients who are not considered candidates for intensive remission induction chemotherapy, both in the newly diagnosed and relapsed/refractory settings (Pfizer, 2000).

In acute lymphoblastic leukemia (ALL), the Ph is the most common genetic abnormality observed. It has an increasing prevalence with age, affecting > 50% of patients with ALL over the age of 60 (Foà et al., 2011). Treatment modalities in adult ALL are often stratified by Ph+ and Ph– disease, with BCR-ABL TKIs incorporated into the treatment paradigm as targeted therapies when the Ph+ biomarker is present (NCCN, 2022g). Depending on a host of factors, BCR-ABL TKIs may be combined with corticosteroids, multiagent chemotherapy, or blinatumomab (Blincyto) for the treatment of adult Ph+ ALL.

Lymphomas

Diffuse large B-cell lymphoma (DLBCL) is broadly characterized into two molecular subtypes: germinal center B-cell (GCB) and activated B-cell (ABC; also referred to as non-GCB type). Ibrutinib and lenalidomide (Revlimid)-based therapies have demonstrated clinical activity in the setting of relapsed/refractory DLBCL, ABC type. Ibrutinib monotherapy has demonstrated an ORR of 37% and 5% in ABC and GCB subtypes, respec-

tively (Wilson et al., 2015). In the setting of DLBCL, lenalidomide is clinically more active in non-GCB DLBCL than the GCB subtype. In a phase II/III clinical trial of lenalidomide vs. investigator's choice of chemotherapy in relapsed/refractory DLBCL, median progression-free survival was increased with lenalidomide regardless of molecular subtype, but the magnitude of benefit was greater in non-GCB patients than GCB (15.1 vs. 10.1 weeks; Czuczman et al., 2017).

Myeloid differentiation primary response 88 (MYD88) is a protein encoded by the *MYD88* gene that functions as an adaptor protein regulating the interleukin-1 and Toll-like receptor signaling complex involved in immune system regulation. Mutations in this gene, specifically the *MYD88*^{L265P} mutation, can be expressed in several different lymphomas including DLBCL, marginal zone lymphoma, and most commonly Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL; Lee et al., 2017; Hunter et al., 2014). *MYD88* is present in up to 90% of patients with WM/LPL, and the presence of this mutation may confer benefit with Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib, while response rates tend to be lower with BTK inhibitors in the setting of *MYD88* wild-type disease (Moore, 2021).

Anaplastic lymphoma kinase (*ALK*) can be expressed in some non-Hodgkin lymphomas, specifically *ALK*-positive DLBCL and *ALK*-positive anaplastic large cell lymphoma. *ALK* positivity in the setting of DLBCL represents a very rare lymphoma subtype that responds poorly to chemotherapy and typically does not express CD20, ruling out a therapeutic role for rituximab (Li et al., 2015). Responses to ALK inhibitors have been observed in this setting, so alectinib or lorlatinib can be considered as therapeutic options in patients with relapsed/refractory disease (Li et al., 2015; NCCN, 2023d).

CD30 is an extracellular membrane protein that can be expressed in a variety of non-Hodgkin lymphomas. In DLBCL, CD30 is expressed in 14% to 25% of patients (van der Weyden et al., 2017; Jacobsen, 2015). The anti-CD30 ADC brentuximab vedotin (Adcetris) may be considered for single-agent therapy in relapsed/refractory CD30+ DLBCL (NCCN Guidelines, 2023d). Several subtypes of T-cell lymphomas commonly express CD30, and brentuximab vedotin may be considered in the setting of CD30 positivity, either as a single agent or in combination with other chemotherapeutic agents, depending on the clinical scenario (NCCN, 2023e).

Multiple Myeloma

In patients with multiple myeloma and other plasma cell disorders, the presence of t(11;14) has shown to be a predictive marker of efficacy of the oral B-cell lymphoma 2 (BCL-2) inhibitor venetoclax (Venclexta; Kumar et al., 2020; Chakraborty et al., 2022). In the setting of multiple myeloma, t(11;14) can be found in approximately 20% of newly diagnosed patients (Paner et al., 2020). Multiple myeloma cells bearing this translocation have a high dependency on the BCL-2 protein for survival and therefore are very sensitive to the anti–BCL-2 activity induced by venetoclax, resulting in cellular apoptosis (Touzeau et al., 2014). In the phase III BELLINI trial, the subgroup of patients with relapsed/refractory multiple myeloma and t(11;14) who received venetoclax, bortezomib (Velcade), and dexamethasone experienced improved response rates compared with those treated with placebo, bortezomib, and dexamethasone (90% vs. 47%, $p = .0038$; Kumar et al., 2020).

Systemic light chain (AL) amyloidosis is another plasma cell disorder in which t(11;14) can be present. This translocation is observed in approximately 50% of patients, and venetoclax has demonstrated efficacy in a small cohort of patients with relapsed/refractory AL amyloidosis who harbor t(11;14) (Sidiqi et al., 2020).

Myelodysplastic Syndromes

A common cytogenetic abnormality observed in patients with myelodysplastic syndromes (MDS) are deletions in the long arm of chromosome 5 (del5q), occurring in 16% to 28% of cases (Giagounidis et al., 2004). Patients with del5q MDS demonstrate unique clinical features, including anemia, dysplastic megakaryocytes in the bone marrow, elevated erythropoietin production, and red blood cell (RBC)-transfusion dependence. The presence of del5q has also been shown to serve as a biomarker that can predict the efficacy of lenalidomide in MDS (List et al., 2006). A randomized, double-blind, phase III trial of patients with low/intermediate-1 risk del5q MDS had a higher

proportion of patients achieving RBC-transfusion independence following treatment with lenalidomide 5 mg once daily compared to placebo (42.6% vs. 5.9%; $p < .001$; Fenaux et al., 2011).

BIOMARKERS IN TUMOR-AGNOSTIC THERAPEUTICS

In recent years there has been a growing interest in targeting specific biomarkers that may be present across multiple tumor types, and advancing drug development toward a tumor-agnostic approach rather than approvals being based on tumor site of origin. The first tumor-agnostic approval in the United States occurred in 2017 when pembrolizumab was approved for the treatment of pediatric and adult patients with unresectable or metastatic MSI-H or mismatch repair–deficient (dMMR) solid tumors (Merck, 2014). Since this landmark approval, several other cancer therapies have gained tumor-agnostic approvals including larotrectinib, entrectinib, dostarlimab, dabrafenib/trametinib, and selpercatinib (Table 2).

MSI-H/dMMR

Genetic variations related to DNA damage response pathways, such as MSI-H and dMMR, have emerged as biomarkers that may be predictive of response to immune checkpoint inhibition (Bai et al., 2020). Approximately 2% to 4% of solid tumors will have dMMR, often arising sporadically, with varying prevalence across different malignancies; alternatively, they may arise from hereditary genetic conditions such as Lynch syndrome (Cortes-Ciriano et al., 2017; Bonneville et al., 2017; Marabelle et al., 2020). Among the most common malignancies with dMMR include endometrial cancer (17%–33%), gastric cancer (9%–22%), and colorectal cancer (6%–13%; Marabelle et al., 2020). Tumors with dMMR harbor many more mutations than those that are mismatch repair-proficient and are therefore much more susceptible to developing mutations in short, repeated sequences of DNA known as microsatellites. High levels of microsatellite instability (MSI-H) can occur when mistakes in DNA mismatch do not get corrected and repaired.

Tumor cells with dMMR/MSI-H can express high levels of immune checkpoint proteins such as PD-L1 and have high levels of tumor-infiltrating lymphocytes. With the immunogenic cellular infiltration caused by the presence of dMMR/MSI-H, such tumors are especially susceptible to the antitumor activity elicited by ICIs. Immune checkpoint inhibition has generated ORRs of up to 55% in patients with treatment-refractory or metastatic disease across all tumor types (Marabelle et al., 2020; André et al., 2020; André, et al., 2022). In a recent phase II trial of neoadjuvant dostarlimab for the treatment of locally advanced dMMR rectal cancer, for example, a CR was observed in 100% of patients ($N = 12$; Cercek et al., 2022). Although this was a small trial that warrants further investigation in a larger patient population and replication of results, this finding highlights the highly sensitive nature of dMMR tumors to immune checkpoint inhibition. Both pembrolizumab and dostarlimab currently carry tumor-agnostic approvals for the treatment of patients with dMMR solid tumors.

Tumor Mutational Burden

Another emerging tumor-agnostic biomarker in cancer therapeutics is tumor mutational burden (TMB), which is tested by NGS. This biomarker indicates the number of somatic mutations present in tumor cells as expressed by the number of mutations per megabase (mut/Mb; Chalmers et al., 2017). Tumors that are TMB-high may be more sensitive to the effects of ICIs. The biological basis for this is that tumors that are TMB-high produce high levels of immunogenic antigens that get recognized by host cytotoxic T lymphocytes. The immune checkpoint inhibition and subsequent T-cell upregulation induced by PD-1 inhibitors may make TMB-high cancers sensitive to such immunotherapeutic activity (Samstein et al., 2019). It has been purported that the more mutations present, the higher the potential for immune system recognition induced by immune checkpoint inhibition (Lawlor et al., 2021). While different thresholds for what constitutes TMB-high have been proposed and reported in the literature, a threshold of ≥ 10 mut/Mb is commonly accepted as defining TMB-high (Lawlor et al., 2021; Marcus et al., 2021). The TMB scale used should be noted by the reporting lab.

In 2020, pembrolizumab gained an additional tumor-agnostic FDA approval when it was granted

Table 2. FDA-Approved Tumor-Agnostic Oncologic Agents

Drug	Biomarker	Tumor-agnostic indication[a,b]	FDA approval date for tumor-agnostic indication
Pembrolizumab (Keytruda)	MSI-H/ dMMR	Treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.	May 2017
Larotrectinib (Vitrakvi)	*NTRK* gene fusion	Treatment of adult and pediatric patients with solid tumors that: • Have an *NTRK* gene fusion without a known acquired resistance mutation, • Are metastatic or where surgical resection is likely to result in severe morbidity, and • Have no satisfactory alternative treatments or that have progressed following treatment.	November 2018
Entrectinib (Rozlytrek)	*NTRK* gene fusion	Treatment of adult and pediatric patients ≥ 12 years of age with solid tumors that: • Have an *NTRK* gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, • Are metastatic or where surgical resection is likely to result in severe morbidity, and • Have either progressed following treatment or have no satisfactory alternative therapy.	August 2019
Pembrolizumab (Keytruda)	TMB-H	Treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥ 10 mutations/ Mb) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.	June 2020
Dostarlimab-gxly (Jemperli)	dMMR	Treatment of adult patients with dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.	August 2021
Dabrafenib (Tafinlar)/ Trametinib (Mekinist)[c]	*BRAF* V600E mutation	Treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.	June 2022
Selpercatinib (Retevmo)	*RET* gene fusion	Treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.	September 2022

Note. dMMR = mismatch repair deficient; FDA = US Food and Drug Administration; MSI-H = microsatellite instability-high; NTRK = neurotrophic tyrosine receptor kinase; TMB-H = tumor mutational burden-high.
[a]All require use of an FDA-approved test to confirm presence of relevant biomarker.
[b]All agents are also approved for other tumor-specific indications; see relevant prescribing information for details.
[c]Dabrafenib and trametinib are approved as a combination regimen for this indication.

accelerated approval for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high (≥ 10 mut/mB) solid tumors that have progressed following a prior treatment and who have no satisfactory alternative treatment options (Marcus et al., 2021). This approval was based on the ORR observed in the multicenter, nonrandomized, open-label KEYNOTE-158 trial in which there was a prospectively planned retrospective analysis of 10 patient cohorts. This evaluation included 102 patients with TMB ≥ 10 mut/Mb. The ORR was 29.4%, with 4 patients (3.9%) achieving a CR. Responses were observed across 8 tumor types. Most patients (57%) who achieved a response maintained the response ≥ 12 months, and 50% of responders maintained it at 24 months.

NTRK

The neurotrophic receptor tyrosine kinase (*NTRK*) gene family is composed of three members: *NTRK1*, *NTRK2*, and *NTRK3,* which encode for TRKA, TRKB, and TRKC proteins, respectively (Drilon et al., 2018). TRK proteins play a vital role in the development of the central and peripheral nervous system (Chao, 2003). Chromosomal fusion events involving the *NTRK* gene have been identified in various malignancies in both adult and pediatric patients. These gene fusions result in overexpression of the chimeric fusion protein, thereby leading to constitutively active signaling (Stransky et al., 2014). Such alterations have been shown to act as oncogenic drivers in several solid tumors, at high frequencies in rare cancers such as secretory breast carcinoma and lower frequencies in common cancers such as colorectal cancer, NSCLC, salivary cancer, and thyroid cancers (Marchetti, 2022). Overall, *NTRK* gene fusions may be present in up to 1% of all solid tumors.

Larotrectinib and entrectinib are oral, selective, potent TKIs that target *NTRK* gene fusion proteins. Larotrectinib was approved in 2018 for the treatment of adults and children with locally advanced or metastatic solid tumors harboring an *NTR*K gene fusion without a known acquired resistance mutation (Bayer, 2018). Entrectinib was approved in 2019 for the treatment of adults with locally advanced or metastatic solid tumors, including central nervous system tumors, harboring an *NTRK* gene fusion (Genentech, 2019). In a combined analysis of three clinical trials (a phase I trial for adults, phase I/II trial for children, and phase II trial in adolescents and adults), larotrectinib therapy resulted in a 75% ORR across 17 different tumor types in patients ranging from age 4 months to 76 years (Drilon et al., 2018). In a composite evaluation of three phase I/II clinical trials of adults with *NTRK*-positive metastatic solid tumors that encompassed 10 tumor types and 19 different histologies, entrectinib therapy was associated with a 54% ORR, including a 7% CR rate (Doebele et al., 2020).

RET

Rearranged during transfection (RET) is a proto-oncogene that encodes for a transmembrane tyrosine kinase domain, and alterations in *RET* can lead to a number of different solid tumor malignancies (Takahashi, 2022). *RET* gene fusions are found most commonly in 5% to 10% of thyroid cancers and 1% to 2% of NSCLC cases. Fusions in *RET* have also been observed at a low frequency (< 1%) in a number of other cancers including breast, colon, esophageal, ovarian, prostate, gastric, pancreatic, salivary gland, sarcomas, and histiocytic neoplasms (Subbiah et al., 2022). Selpercatinib is an oral, highly selective RET kinase inhibitor that received accelerated approval in 2022 for the treatment of adults with locally advanced or metastatic solid tumors with a *RET* gene fusion whose disease has progressed on or following prior systemic treatment or who have no satisfactory alternative therapeutic options (Lilly, 2020). The efficacy of selpercatinib was evaluated in patients with *RET* fusion–positive cancers in the multicenter, open-label, multicohort phase I/II LIBRETTO-001 basket trial (Subbiah et al., 2022). The tumor-agnostic approval for selpercatinib was based on an ORR of 44%, with a duration of response of 24.5 months. Efficacy was seen across a wide spectrum of tumor types including breast, cholangiocarcinoma, colorectal, pancreatic, salivary, soft tissue sarcoma, and unknown primary.

BRAF

Mutations in *BRAF* at codon 600, leading to constitutive activation of the MAPK pathway, are found in approximately 50% of all melanomas and, to a lesser extent, in 1% to 3% of cancers overall (Salama et al., 2020). Non-melanoma cancers in which *BRAF* mutations may be present include colorectal cancer, hairy cell leukemia, NSCLC, and thyroid cancers. In 2022, the FDA granted accelerated approval to the combination of dabrafenib and trametinib for the treatment of adult and pediatric patients 6 years of age or older with unresectable or metastatic solid tumors bearing a *BRAF* V600E mutation who have progressed following a prior treatment and have no satisfactory alternative therapeutic options. This tumor-agnostic approval was supported by the composite outcomes of several open-label, multi-cohort basket trials including BRF117017, CTMT212X2101, and NCI-MATCH (Novartis Pharmaceuticals, 2013a;

Novartis Pharmaceuticals, 2013b). These three basket trials involved 24 different tumor types including, but not limited to, gliomas, anaplastic thyroid cancer, gastrointestinal stromal tumor, and biliary tract cancer. Across these trials, the ORR was 41% among the 131 adult patients and 25% in the 36 pediatric patients.

CONCLUSION

Biomarkers and their associated therapies have been rapidly integrated into oncology and hematology standards of care for many malignancies in recent years. While from the clinician's point of view care protocols have become more complex, care for the patient has become more precise. This precision care has often resulted in better outcomes than would have been realized with older treatment regimens. Now, and moving into the future, it will be incumbent upon advanced providers to know the optimal tests to order, to correctly interpret the results, and to be able to select the best therapies directed at biomarkers present or absent. Most of all, advanced practitioners will need to continue to keep up with inevitable, unceasing changes of the standards of care.

Acknowledgment

Writing assistance was provided by Larry Rosenberg, PhD. Funding and support provided by Pfizer.

Disclosure

Dr. Moore has served on advisory boards for AstraZeneca, Janssen, Pfizer, and Oncopeptides. Mr. Guinigundo has served as a consultant for Amgen, Jazz Pharmaceuticals, and Pharmacosmos, and on speakers bureaus for Amgen, Astellas, GSK, and Pfizer.

References

André, T., Lonardi, S., Wong, K. Y. M., Lenz, H. J., Gelsomino, F., Aglietta, M.,...Overman, M. J. (2022). Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. *Annals of Oncology, 33*(10), 1052–1060. https://doi.org/10.1016/j.annonc.2022.06.008

André, T., Shiu, K. K., Kim, T. W., Jensen, B. V., Jensen, L. H., Punt, C.,...Diaz, L. A. Jr; KEYNOTE-177 Investigators. (2020). Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *New England Journal of Medicine, 383*(23), 2207–2218. https://doi.org/10.1056/NEJMoa2017699

Arnold, D., Lueza, B., Douillard, J. Y., Peeters, M., Lenz, H. J., Venook, A.,...Ciardiello F. (2017). Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Annal of Oncology, 28*(8), 1713–1729. https://doi.org/10.1093/annonc/mdx175

AstraZeneca. (2015). Tagrisso (osimertinib) package insert. https://www.tagrissohcp.com/

AstraZeneca Pharmaceuticals. (2014). Lynparza (olaparib) package insert. https://www.lynparza.com/

AstraZeneca Pharmaceuticals. (2017). Imfinzi (durvalumab) package insert. https://www.imfinzihcp.com/

Bai, R., Lv, Z., Xu, D., & Cui, J. (2020). Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. *Biomarker Research, 8*, 34. https://doi.org/10.1186/s40364-020-00209-0

Bayer. (2018). Vitrakvi (larotrectinib) package insert. https://labeling.bayerhealthcare.com/

Boehringer Ingelheim Pharmaceuticals. (2013). Gilotrif (afatinib) package insert. https://www.gilotrifhcp.com/

Bonneville, R., Krook, M. A., Kautto, E. A., Miya, J., Wing, M. R., Chen, H. Z.,...Roychowdhury, S. (2017). Landscape of microsatellite instability across 39 cancer types. *JCO Precision Oncology, 2017*. https://doi.org/10.1200/PO.17.00073

Bristol Myers Squibb. (2006). Sprycel (dasatinib) package insert. https://www.sprycel-hcp.com/

Bristol Myers Squibb. (2011). Yervoy (ipilimumab) package insert. https://www.hcp.yervoy.com/

Bristol Myers Squibb. (2014). Opdivo (nivolumab) package insert. https://www.opdivo.com/

Cercek, A., Lumish, M., Sinopoli, J., Weiss, J., Shia, J., Lamendola-Essel, M.,...Diaz, L. A. Jr. (2022). PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *New England Journal of Medicine, 386*(25), 2363–2376. https://doi.org/10.1056/NEJMoa2201445

Chakraborty, R., Bhutani, D., & Lentzsch, S. (2022). How do we manage t(11;14) plasma cell disorders with venetoclax? *British Journal of Haematology, 199*(1), 31–39. https://doi.org/10.1111/bjh.18243

Chalmers, Z. R., Connelly, C. F., Fabrizio, D., Gay, L., Ali, S. M., Ennis, R.,...Frampton, G. M. (2017). Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Medicine, 9*(1), 34. https://doi.org/10.1186/s13073-017-0424-2

Chan, A., Moy, B., Mansi, J., Ejlertsen, B., Holmes, F. A., Chia, S.,...ExteNET Study Group. (2021). Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. *Clinical Breast Cancer, 21*(1), 80–91.e7. https://doi.org/10.1016/j.clbc.2020.09.01

Chao, M. V. (2003). Neurotrophins and their receptors: A convergence point for many signalling pathways. *Nature Reviews Neuroscience, 4*(4), 299–309. https://doi.org/10.1038/nrn1078

Chia, P. L., Mitchell, P., Dobrovic, A., & John, T. (2014). Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. *Clinical Epidemiology, 6*, 423–432. https://doi.org/10.2147/CLEP.S69718

Clovis Oncology. (2016). Rubraca (rucaparib) package insert.

https://www.rubraca.com
Cortes-Ciriano, I., Lee, S., Park, W. Y., Kim, T. M., & Park, P. J. (2017). A molecular portrait of microsatellite instability across multiple cancers. *Nature Communications, 8*, 15180. https://doi.org/10.1038/ncomms15180
Czuczman, M. S., Trněný, M., Davies, A., Rule, S., Linton, K. M., Wagner-Johnston, N.,...Lewis, I. D. (2017). A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. *Clinical Cancer Research, 23*(15), 4127–4137. https://doi.org/10.1158/1078-0432.CCR-16-2818
Daiichi Sankyo. (2019). Enhertu (fam-trastuzumab deruxtecan-nxki) package insert. https://www.enhertuhcp.com/
Doebele, R. C., Drilon, A., Paz-Ares, L., Siena, S., Shaw, A. T., Farago, A. F.,...Demetri, G. D.; trial investigators. (2020). Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. *Lancet Oncology, 21*(2), 271–282. https://doi.org/10.1016/S1470-2045(19)30691-6
Drilon, A., Laetsch, T. W., Kummar, S., DuBois, S. G., Lassen, U. N., Demetri, G. D.,...Hyman, D. M. (2018). Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *New England Journal of Medicine, 378*(8), 731–739. https://doi.org/10.1056/NEJMoa1714448
Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Davies, C., Godwin, J., Gray, R., Clarke, M., Cutter, D.,...Peto, R. (2011). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet, 378*(9793), 771–784. https://doi.org/10.1016/S0140-6736(11)60993-8
Eisai. (2015). Lenvima (lenvatinib) package insert. https://www.lenvima.com/hcp
El-Deiry, W. S., Goldberg, R. M., Lenz, H. J.,...Marshall, J. L. (2019). The current state of molecular testing in the treatment of patients with solid tumors, 2019. *CA: A Cancer Journal for Clinicians, 69*(4), 305–343. https://doi.org/10.3322/caac.21560
FDA-NIH Biomarker Working Group. (2016). BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD), FDA. https://www.ncbi.nlm.nih.gov/books/NBK326791/
Fenaux, P., Giagounidis, A., Selleslag, D., Beyne-Rauzy, O., Mufti, G., Mittelman, M.,...Hellström-Lindberg, E.; MDS-004 Lenalidomide del5q Study Group. (2011). A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del5q. *Blood, 118*(14), 3765–3776. https://doi.org/10.1182/blood-2011-01-330126
Foà, R., Vitale, A., Vignetti, M., Meloni, G., Guarini, A., De Propris, M. S.,...Baccarani, M.; GIMEMA Acute Leukemia Working Party. (2011). Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood, 118*(25), 6521–6528. https://doi.org/10.1182/blood-2011-05-351403
Genentech. (2004). Tarceva (erlotinib) package insert. https://www.gene.com/
Genentech. (2013). Kadcyla (ado-trastuzumab emtansine) package insert. https://www.kadcyla.com/
Genentech. (2016). Tecentriq (atezolizumab) package insert. https://www.tecentriq-hcp.com/
Genentech. (2019). Rozlytrek (entrectinib) package insert. https://www.rozlytrek-hcp.com/
Giagounidis, A. A., Germing, U., Haase, S., Hildebrandt, B., Schlegelberger, B., Schoch, C.,...Aul, C. (2004). Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. *Leukemia, 18*(1), 113–119. https://doi.org/10.1038/sj.leu.2403189
GlaxoSmithKline. (2017). Zejula (niraparib) package insert. https://zejula.com/
Hammond, M. E., Hayes, D. F., Dowsett, M., Allred, D. C., Hagerty, K. L., Badve, S.,...Wolff, A. C. (2010). American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Archives of Pathology & Laboratory Medicine, 134*(6), 907–922. https://doi.org/10.5858/134.6.907
Hunter, Z. R., Xu, L., Yang, G., Zhou, Y., Liu, X., Cao, Y.,...Treon. S. P. (2014). The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood, 123*(11), 1637–1646. https://doi.org/10.1182/blood-2013-09-525808
Igaue, S., Okuno, T., Ishibashi, H., Nemoto, M., Hiyoshi, M., Kawasaki, H.,...Yamamoto, J. (2022). A pathological complete response after nivolumab plus ipilimumab therapy for DNA mismatch repair-deficient/microsatellite instability-high metastatic colon cancer: A case report. *Oncology Letters, 24*(1), 211. https://doi.org/10.3892/ol.2022.13332
Jacobsen, E. D., Sharman, J. P., Oki, Y., Advani, R. H., Winter, J. N., Bello, C. M.,...Bartlett, N. L. (2015). Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. *Blood, 125*(9), 1394–1402. https://doi.org/10.1182/blood-2014-09-598763
Janssen Oncology. (2019). Balversa (erdafitinib) package insert. https://www.balversahcp.com/
Karacin, C., Oksuzoglu, B., Demirci, A., Keskinkılıç, M., Baytemür, N. K., Yılmaz, F.,...Hacıbekiroğlu, İ. (2023). Efficacy of subsequent treatments in patients with hormone-positive advanced breast cancer who had disease progression under CDK 4/6 inhibitor therapy. *BMC Cancer, 23*(1), 136. https://doi.org/10.1186/s12885-023-10609-8
Kumar, S. K., Harrison, S. J., Cavo, M., de la Rubia, J., Popat, R., Gasparetto, C.,...Moreau, P. (2020). Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): A randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncology, 21*(12), 1630–1642. https://doi.org/10.1016/S1470-2045(20)30525-8
Lawlor, R. T., Mattiolo, P., Mafficini, A., Hong, S. M., Piredda, M. L., Taormina, S. V.,...Luchini, C. (2021). Tumor mutational burden as a potential biomarker for immunotherapy in pancreatic cancer: Systematic review and still-open questions. *Cancers (Basel), 13*(13), 3119. https://doi.org/10.3390/cancers13133119
Lee, J. H., Jeong, H., Choi, J. W., Oh, H., & Kim, Y. S. (2017). Clinicopathologic significance of MYD88 L265P mutation in diffuse large B-cell lymphoma: a meta-analysis.

Science Reports, 7(1), 1785. https://doi.org/10.1038/s41598-017-01998-5

LeQuang, J. A. (2022). Using gene expression profiling to personalize skin cancer management. *Journal of Clinical Aesthetic Dermatology, 15*(Suppl 1), S3–S15

Li, J., Ouyang, J., Zhou, R., Chen, B., & Xu, Y. (2015). Promising response of anaplastic lymphoma kinase-positive large B-cell lymphoma to crizotinib salvage treatment: Case report and review of literature. *International Journal of Clinical and Experimental Medicine, 8*(5), 6977–6985.

Lilly. (2020). Retevmo (selpercatinib) package insert. https://www.retevmo.com/

List, A., Dewald, G., Bennett, J., Giagounidis, A., Raza, A., Feldman, E.,...Knight, R.; Myelodysplastic Syndrome-003 Study Investigators. (2006). Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *New England Journal of Medicine, 355*(14), 1456–1465. https://doi.org/10.1056/NEJMoa061292

López-Reig, R., Fernández-Serra, A., Romero, I., Zorrero, C., Illueca, C., García-Casado, Z.,...López-Guerrero, J. A. (2019). Prognostic classification of endometrial cancer using a molecular approach based on a twelve-gene NGS panel. *Scientific Reports, 9*(1), 18093. https://doi.org/10.1038/s41598-019-54624-x

Ludford, K., Ho, W. J., Thomas, J. V., Raghav, K. P. S., Murphy, M. B., Fleming, N. D.,...Overman, M. J. (2023). Neoadjuvant pembrolizumab in localized microsatellite instability high/deficient mismatch repair solid tumors. *Journal of Clinical Oncology,* 2023 Jan 9:JCO2201351. https://doi.org/10.1200/JCO.22.01351

MacroGenics. (2020). Margenza (margetuximab-cmkb) package insert. https://www.margenza.com/

Marabelle, A., Le, D. T., Ascierto, P. A., Di Giacomo, A. M., De Jesus-Acosta, A., Delord, J. P.,...Diaz, L. A. Jr. (2020). Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. *Journal of Clinical Oncology, 38*(1), 1–10. https://doi.org/10.1200/JCO.19.02105

Marchetti, A., Ferro, B., Pasciuto, M. P., Zampacorta, C., Buttitta, F., & D'Angelo, E. (2022). NTRK gene fusions in solid tumors: Agnostic relevance, prevalence and diagnostic strategies. *Pathologica, 114*(3), 199–216. https://doi.org/10.32074/1591-951X-787

Marcus, L., Fashoyin-Aje, L. A., Donoghue, M., Yuan, M., Rodriguez, L., Gallagher, P. S.,...Lemery. S. J. (2021). FDA approval summary: Pembrolizumab for the treatment of tumor mutational burden-high solid tumors. *Clinical Cancer Research, 27*(17), 4685–4689. https://doi.org/10.1158/1078-0432.CCR-21-0327

Merck. (2014). Keytruda (pembrolizumab) package insert. https://www.keytrudahcp.com/

Møller, P., Seppälä, T., Bernstein, I., Holinski-Feder, E., Sala, P., Evans, D. G.,...Mallorca Group (http://mallorca-group.eu). (2017). Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: First report from the prospective Lynch syndrome database. *Gut, 66*(3), 464–472. https://doi.org/10.1136/gutjnl-2015-309675

Montesinos, P., Recher, C., Vives, S., Zarzycka, E., Wang, J., Bertani, G.,...Döhner, H. (2022). Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *New England Journal of Medicine, 386*(16), 1519–1531. https://doi.org/10.1056/NEJMoa2117344

Moore, D. C. (2021). Bruton tyrosine kinase inhibitors for Waldenström macroglobulinemia: A review. *Journal of Oncology Pharmacy Practice, 27*(8), 1993–1999. https://doi.org/10.1177/10781552211038309

National Comprehensive Cancer Network. (2023d). NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. V2.2023. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

National Comprehensive Cancer Network. (2023c). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. V1.2023. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

National Comprehensive Cancer Network. (2023a). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V2.2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network. (2023b). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V3.2023. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

National Comprehensive Cancer Network. (2023e). NCCN Clinical Practice Guidelines in Oncology: T-Cell Lymphomas. V1.2023. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf

National Comprehensive Cancer Network. (2022g). NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. V1.2022. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

National Comprehensive Cancer Network. (2022e). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. V2.2022. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network. (2022c). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous. V1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network. (2022a). NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer. V1.2023. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network. (2022d). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. V2.2022. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network. (2022b). NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer. V3.2023. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf

National Comprehensive Cancer Network. (2022f). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. V1.2023. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

National Human Genome Research Institute. (2023). Talking Glossary of Genetic Terms. https://www.genome.gov/genetics-glossary/

Noone, A. M., Cronin, K. A., Altekruse, S. F., Howlader, N., Lewis, D. R., Petkov, V. I.,...Penberthy, L. (2017). Cancer incidence and survival trends by subtype using data from the Surveillance Epidemiology and End Results Program, 1992-2013. *Cancer Epidemiology, Biomarkers & Prevention, 26*(4), 632–641. https://doi.org/10.1158/1055-

9965.EPI-16-0520
Novartis Pharmaceuticals. (2007). Tasigna (nilotinib) package insert. https://www.us.tasigna.com/
Novartis Pharmaceuticals. (2013a). Mekinist (trametinib) package insert. https://www.novartis.com/
Novartis Pharmaceuticals. (2013b). Tafinlar (dabrafenib) package insert. https://www.novartis.com/
Novartis Pharmaceuticals. (2019). Piqray (alpelisib) package insert. https://www.hcp.novartis.com/
O'Brien, S. G., Guilhot, F., Larson, R. A., Gathmann, I., Baccarani, M., Cervantes, F.,...Druker, B. J.; IRIS Investigators. (2003). Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *New England Journal of Medicine, 348*(11), 994–1004. https://doi.org/10.1056/NEJMoa022457
Paner, A., Patel, P., & Dhakal, B. (2020). The evolving role of translocation t(11;14) in the biology, prognosis, and management of multiple myeloma. *Blood Reviews, 41*, 100643. https://doi.org/10.1016/j.blre.2019.100643
Perl, A. E., Martinelli, G., Cortes, J. E., Neubauer, A., Berman, E., Paolini, S.,...Levis, M. J. (2019). Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. *New England Journal of Medicine, 381*(18), 1728–1740. https://doi.org/10.1056/NEJMoa1902688
Pfizer. (2000). Mylotarg (gemtuzumab ozogamicin) package insert. https://mylotarg.pfizerpro.com/
Pfizer. (2012). Bosulif (bosutinib) package insert. https://labeling.pfizer.com
Puma Biotechnology. (2017). Nerlynx (neratinib) package insert. https://nerlynxhcp.com/
Ravandi, F., Kantarjian, H., Faderl, S., Garcia-Manero, G., O'Brien, S., Koller, C.,...Beran, M. (2010). Outcome of patients with FLT3-mutated acute myeloid leukemia in first relapse. *Leukemia Research, 34*(6), 752–756. https://doi.org/10.1016/j.leukres.2009
Salama, A. K. S., Li, S., Macrae, E. R., Park, J. I., Mitchell, E. P., Zwiebel, J. A.,...Flaherty, K. T. (2020). Dabrafenib and trametinib in patients with tumors with BRAFV600E mutations: Results of the NCI-MATCH trial subprotocol H. *Journal of Clinical Oncology, 38*(33), 3895–3904. https://doi.org/10.1200/JCO.20.00762
Samstein, R. M., Lee, C. H., Shoushtari, A. N., Hellmann, M. D., Shen, R., Janjigian, Y. Y.,...Morris, L. G. T. (2019). Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nature Genetics, 51*(2), 202–206. https://doi.org/10.1038/s41588-018-0312-8
Seagen. (2020). Tukysa (tucatinib) package insert. https://www.tukysahcp.com/
Sidiqi, M. H., Al Saleh, A. S., Leung, N., Jevremovic, D., Aljama, M. A., Gonsalves, W. I.,...Kapoor, P. (2020). Venetoclax for the treatment of translocation (11;14) AL amyloidosis. *Blood Cancer Journal, 10*(5), 55. https://doi.org/10.1038/s41408-020-0321-6
Sokolenko, A. P., & Imyanitov, E. N. (2018). Molecular diagnostics in clinical oncology. *Frontiers in Molecular Biosciences, 5*:76. https://doi.org/10.3389/fmolb.2018.00076
Stein, E. M., DiNardo, C. D., Fathi, A. T., Mims, A. S., Pratz, K. W., Savona, M. R.,...Tallman, M. S. (2021). Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: A phase 1 study. *Blood, 137*(13), 1792–1803. https://doi.org/10.1182/blood.2020007233
Stein, E. M., DiNardo, C. D., Pollyea, D. A., Fathi, A. T., Roboz, G. J., Altman, J. K.,...Tallman, M. S. (2017). Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood, 130*(6), 722–731. https://doi.org/10.1182/blood-2017-04-779405
Stemline Therapeutics. (2023). Orserdu (elacestrant) package insert. https://www.orserdu.com/
Stone, R. M., Mandrekar, S. J., Sanford, B. L., Laumann, K., Geyer, S., Bloomfield, C. D.,...Döhner, H. (2017). Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *New England Journal of Medicine, 377*(5), 454–464. https://doi.org/10.1056/NEJMoa1614359
Stransky, N., Cerami, E., Schalm, S., Kim, J. L., & Lengauer, C. (2014). The landscape of kinase fusions in cancer. *Nature Communications, 5*, 4846. https://doi.org/10.1038/ncomms5846
Subbiah, V., Wolf, J., Konda, B., Kang, H., Spira, A., Weiss, J.,... Drilon, A. (2022). 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 Oncology, 23*(10), 1261–1273. https://doi.org/10.1016/S1470-2045(22)00541-1
Takahashi, M. (2022). RET receptor signaling: Function in development, metabolic disease, and cancer. *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences, 98*(3), 112–125. https://doi.org/10.2183/pjab.98.008
Takeda Pharmaceuticals. (2012). Iclusig (ponatinib) package insert. https://www.iclusig.com/
Taniguchi, H., Sen, T., & Rudin, C. M. (2020). Targeted therapies and biomarkers in small cell lung cancer. *Frontiers in Oncology, 10*, 741. https://doi.org/10.3389/fonc.2020.00741
Touzeau, C., Dousset, C., Le Gouill, S., Sampath, D., Leverson, J. D., Souers, A. J.,...Amiot, M. (2014). The Bcl-2 specific BH3 mimetic ABT-199: A promising targeted therapy for t(11;14) multiple myeloma. *Leukemia, 28*(1), 210–212. https://doi.org/10.1038/leu.2013.216
Ulivi, P. (2020). Predictive biomarkers in clinical practice: State of the art and perspectives in solid tumors. *International Journal of Biological Markers, 35*(1_suppl), 16–19. https://doi.org/10.1177/1724600820904964
US Food and Drug Administration. (2023). List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools
van der Weyden, C. A., Pileri, S. A., Feldman, A. L., Whisstock, J., & Prince, H. M. (2017). Understanding CD30 biology and therapeutic targeting: a historical perspective providing insight into future directions. *Blood Cancer Journal, 7*(9), e603. https://doi.org/10.1038/bcj.2017.85
Veneris, J. T., Lee, E. K., Goebel, E. A., Nucci, M. R., Lindeman, N., Horowitz, N. S.,...Campos, S. (2019). Diagnosis and management of a recurrent polymerase-epsilon (POLE)-mutated endometrial cancer. *Gynecologic Oncology, 153*(3), 471–478. https://doi.org/10.1016/j.ygyno.2019.03.247
Watts, J. M., Baer, M. R., Yang, J., Prebet, T., Lee, S., Schiller, G. J.,...Cortes, J. E. (2023). Olutasidenib alone or with azacitidine in IDH1-mutated acute myeloid leukaemia and myelodysplastic syndrome: Phase 1 results of a phase

1/2 trial. *Lancet Haematolology, 10*(1), e46–e58. https://doi.org/10.1016/S2352-3026(22)00292-7

Wilson, W. H., Young, R. M., Schmitz, R., Yang, Y., Pittaluga, S., Wright, G.,...Staudt, L. M. (2015). Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nature Medicine, 21*(8), 922–926. https://doi.org/10.1038/nm.3884

Yoshino, T., Watanabe, J., Shitara, K., Yasui, H., Ohori, H., Shiozawa, M.,...Muro, K. (2022). Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. *Journal of Clinical Oncology, 40* (suppl 17; abstr LBA1)