Review Article

Precision therapy in metastatic breast cancer: the current landscape of molecular alteration-based therapies

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Abstract: Breast cancer is the most commonly diagnosed cancer in women globally and remains the leading cause of cancer-related death among women. De novo metastatic breast cancer accounts for 5–10% of annual diagnoses, and approximately 30% of women with early-stage disease will eventually experience metastatic recurrence. Median survival varies by tumor subtype: 64–68 months for hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative cancers, 57–60 months for HER2-positive cancers, and around 13 months for triple-negative cancers. While current treatments—including chemotherapy, antibody-drug conjugates, endocrine therapy, HER2-targeted therapies, and immunotherapy—have significantly improved outcomes, resistance and disease progression remain ongoing challenges. Advances in next-generation sequencing (NGS) have enabled the identification of molecular alterations amenable to targeted therapy, underscoring the need for continued research into novel therapeutic targets. As more targeted agents become available and others are in development, staying informed about emerging targetable molecular alterations is increasingly essential. This review aims to summarize current data on targetable molecular alterations in metastatic breast cancer, focusing on available therapeutic options, key clinical trials, and practical insights for oncologists to support informed decision-making.

Keywords: Metastatic breast cancer; targeted therapies; molecular alterations; next-generation sequencing (NGS)

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Introduction

Background

Breast cancer is the most frequently diagnosed cancer in women worldwide, with over 2 million new cases in 2020 (1). In the United States, it accounts for 29% of all new cancers in women. In addition to its high incidence, breast cancer is also the leading cause of cancer-related death among women globally, responsible for 684,996 deaths in 2020, with an age-adjusted mortality rate of 13.6 per 100,000 (1). Breast cancer is a biologically heterogeneous disease, and survival depends on both the stage at diagnosis and the tumor subtype. Clinically, breast cancers are broadly categorized by receptor status into three main subtypes: hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (70% of cases); HER2-positive, which may be HR-positive or negative (15–20% of cases); and HR negative and HER2-negative also known as triple-negative breast cancer (10–15% of cases) (2).

De novo metastatic breast cancer accounts for 5–10% of annual breast cancer diagnoses, while approximately 30% of women with early-stage disease will eventually develop

metastatic recurrence (3,4). The primary goals of systemic treatment for metastatic breast cancer are to prolong survival, alleviate symptoms, and maintain quality of life. The median survival in metastatic breast cancer varies by tumor subtype, sites of metastasis, and disease burden. It is approximately 64–68 months for HR-positive, HER2-negative cancers; 57–60 months for HER2-positive cancers; and 13 months for triple-negative cancers (5-8). Notably, the introduction of newer systemic therapies has led to meaningful survival improvements, particularly in HER2-positive and HR-positive/HER2-negative subtypes.

Rationale and knowledge gap

The selection of treatment for metastatic breast cancer is guided by tumor biology (primarily receptor status) and clinical factors. Current systemic therapies include chemotherapy, antibody-drug conjugates, endocrine therapy, HER2-targeted agents, and immunotherapy for PD-L1-positive triple-negative breast cancer with a combined positive score (CPS) ≥10. While these therapies have significantly improved clinical outcomes, many patients eventually experience disease progression or develop resistance, resulting in limited treatment options.

Advancements in next-generation sequencing (NGS) have enabled the identification of molecular alterations that can be targeted therapeutically, with ongoing research continuing to uncover additional actionable mutations and pathways. Studies in metastatic breast cancer have clearly shown that the use of targeted therapies matched to genomic alterations classified as level I or II according to the European Society for Medical Oncology (ESMO) scale for clinical actionability of molecular targets is associated with significant improvements in outcomes such as progression-free survival (PFS) (9-11). These findings strongly support the notion that genomic/molecular alterations must guide treatment decisions to optimize patient outcomes. Genome-driven precision oncology has led to the approval of targeted therapies based on specific molecular alterations, with some approvals specific to breast cancer and others being tumor-agnostic. However, many patients do not harbor known actionable mutations, highlighting the need for further identification of novel targets and the development of therapies that can benefit a broader patient population.

Objective

This review aims to summarize current molecular alteration-based therapies in metastatic breast cancer, providing practical insights into diagnostics, trial data, and safety profiles to support informed clinical decision-making. It highlights key clinical trials that led to regulatory approvals or support their use in clinical practice. Serving as a practical guide for oncologists, this article provides insights into the current landscape of actionable molecular alterations, their role in cancer growth/progression, available targeted therapies, recommended dosages (summarized in *Table 1*), and associated side effects to support informed decision-making in the management of metastatic breast cancer.

The current landscape of molecular alterations with their associated therapies

PIK3CA/AKT/mTOR pathway

Many HR-positive and HER2-negative metastatic breast cancers harbor mutations in the PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)/AKT (protein kinase B)/mTOR (mammalian target of rapamycin) pathway. This pathway is a key regulator of protein synthesis, cell survival, DNA repair, and angiogenesis. Dysregulation contributes to endocrine resistance, limiting the efficacy of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (12). Hence, targeting these alterations in HR+/HER2– metastatic breast cancer has demonstrated significant efficacy in overcoming therapeutic resistance.

PIK3CA activating mutations

Mutations in the PIK3CA gene, which encodes the p110α subunit of PI3K, lead to PI3K hyperactivation and are associated with chemoresistance and poor prognosis. They are found in 28–46% of HR+/HER2– advanced breast cancers (13,14). PIK3CA mutations have been detected in ~45% of primary tumors and up to 53% of matched metastases (15). These mutations can be identified using NGS or real-time polymerase chain reaction (PCR) (14). The Food and Drug Administration (FDA) has approved the therascreen PIK3CA PCR Kit and FoundationOne

Table 1 The current landscape of molecular alteration-based therapies in metastatic breast cancer

Molecular alteration/biomarker	Breast cancer subtype	Targeted therapy	Year of FDA approval	Clinical trial	Recommended standard dose
PIK3CA mutation	HR+, HER2– advanced/metastatic breast cancer	Alpelisib (with fulvestrant)	May 24, 2019	SOLAR-1 trial (NCT02437318). Alpelisib + fulvestrant *vs.* placebo+ fulvestrant. PFS: 11 *vs.* 5.7 months (HR 0.65, P<0.001). ORR: 26.6% *vs.* 12.8%. OS: 39.3 *vs.* 31.4 months (HR 0.86, P=0.15)	Alpelisib: 300 mg orally daily
		Inavolisib (with palbociclib and fulvestrant)	October 10, 2024	INAVO120 trial (NCT04191499). Inavolisib + palbociclib + fulvestrant *vs.* placebo + palbociclib + fulvestrant. PFS: 15 *vs.* 7.3 months (HR 0.43, P<0.0001). ORR: 58% *vs.* 25%	Inavolisib: 9 mg orally daily
PIK3CA or AKT or PTEN alterations	HR+, HER2– advanced/metastatic breast cancer	Capivasertib (with fulvestrant)	November 16, 2023	CAPItello-291 trial (NCT04305496). Capivasertib + fulvestrant *vs.* placebo+ fulvestrant. PFS: 7.3 *vs.* 3.1 months (HR 0.5, P<0.0001). OS at 18 months: 73.2% *vs.* 62.9%	Capivasertib: 400 mg orally twice daily for days 1–4 of each week
ESR1 mutation	HR+, HER2– advanced/metastatic breast cancer	Elacestrant	January 27, 2023	EMERALD trial (NCT03778931). Elacestrant *vs.* fulvestrant or aromatase inhibitor. PFS (in ESR1 mutation): 3.8 *vs.* 1.9 months (HR 0.55, P=0.0005)	Elacestrant: 345 mg orally daily
	HR+, HER2– advanced/metastatic breast cancer	Imlunestrant	Not FDA approved as of March 2025, but approval is anticipated soon	EMBER-3 trial (NCT04975308). Imlunestrant *vs.* standard endocrine therapy: PFS (in all): 5.6 *vs.* 5.5 months (HR 0.87, P=0.12); PFS (in ESR1 mutation: 5.5 *vs.* 3.8 months (P<0.001). Imlunestrant + abemaciclib *vs.* Imlunestrant: PFS (in all): 9.4 *vs.* 5.5 months (HR 0.57, P<0.001)	Imlunestrant: 400 mg orally daily
Germline BRCA 1 or 2 mutation	HR+/–, HER2– advanced/metastatic breast cancer	Olaparib	January 12, 2018	OlympiAD trial (NCT02000622). Olaparib *vs.* chemotherapy. PFS: 7 *vs.* 4.2 months (HR 0.58, P<0.001). OS: 19.3 *vs.* 17.1 months (HR 0.89, 95% CI: 0.67–1.18)	Olaparib: 300 mg orally twice daily
		Talazoparib	October 16, 2018	EMBRACA trial (NCT01945775). Talazoparib *vs.* chemotherapy. PFS: 8.6 *vs.* 5.6 months (HR 0.54, P<0.001). OS: 19.3 *vs.* 19.5 months (HR 0.8, P=0.17)	Talazoparib: 1 mg orally daily
Somatic BRCA 1 or 2 mutation; germline PALB2 mutation	HR+/–, HER2– advanced/metastatic breast cancer	Olaparib	Not FDA approved	TBCRC 048 trial (NCT03344965). Olaparib-single arm. Somatic BRCA1 or 2: PFS 6.3 months, ORR 50%. Germline PALB2: PFS 13.3 months, ORR 82%	Olaparib: 300 mg orally twice daily
HER2/ERBB2 activating mutation	HR+/–, HER2– advanced/metastatic breast cancer	Neratinib (+/– fulvestrant depending on HR status)	Not FDA approved	MutHER trial (NCT01670877). Neratinib + fulvestrant-single arm. CBR: 38% in HR+ve fulvestrant-pretreated; 30% in HR+ve fulvestrant-naïve; 25% in HR-ve	Neratinib: 240 mg orally daily (with dose escalation strategy)
	HR+, HER2– advanced/metastatic breast cancer	Neratinib (+ fulvestrant + trastuzumab)	Not FDA approved	SUMMIT trial (NCT01953926). Neratinib + fulvestrant + trastuzumab-single arm. PFS: 8.3 months, ORR 39%	Neratinib: 240 mg orally daily (with dose escalation strategy)
NTRK fusion	Any advanced/metastatic breast cancer	Larotrectinib	November 26, 2018	LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), NAVIGATE (NCT02576431) trials. Larotrectinib-single arm. PFS: 28.3 months, ORR 79%, OS: 44.4 months	Larotrectinib: 100 mg orally twice daily
		Entrectinib	August 15, 2019	ALKA-372-001, STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267) trials. Entrectinib-single arm. PFS 13.8 months, ORR 61.2%, intra-cranial RR: 63.6%	Entrectinib: 600 mg orally once daily
		Repotrectinib	June 13, 2024	TRIDENT-1 trial (NCT03093116). Repotrectinib-single arm. ORR of 58% (in tyrosine kinase inhibitor naïve), 50% (in tyrosine kinase inhibitor pre-treated)	Repotrectinib: 160 mg orally once daily
RET-fusion	Any advanced/metastatic breast cancer	Selpercatinib	September 21, 2022	LIBRETTO-001 trial (NCT03157128). Selpercatinib-single arm. ORR 44%, PFS 13.2 months, OS 18 months	Selpercatinib: 160 mg orally twice daily for ≥50 kg, 120 mg orally twice daily for <50 kg
FGFR 1–3 fusion/mutation	Any advanced/metastatic breast cancer	Erdafitinib	Not FDA approved	RAGNAR trial (NCT04083976). Erdafitinib-single arm. ORR 30%, DOR 7.1 months	Erdafitinib: 8 mg orally once daily
dMMR/MSI-H	Any advanced/metastatic breast cancer	Pembrolizumab	May 23, 2017	KEYNOTE-158 trial (NCT02628067). Pembrolizumab-single arm. ORR 30.8%, PFS 3.5 months, OS 20.1 months	Pembrolizumab: 200 mg every 3 weeks or 400 mg every 6 weeks intravenously
		Dostarlimab	August 17, 2021	GARNET trial (NCT02715284). Dostarlimab-single arm. PFS 6.9 months	Dostarlimab: 500 mg every 3 weeks for 4 cycles, followed by 1,000 mg every 6 weeks intravenously
TMB-H	Any advanced/metastatic breast cancer	Pembrolizumab	June 16, 2020	KEYNOTE-158 trial (NCT02628067). Pembrolizumab-single arm. ORR 29%, DOR of ≥12 months in 57%, DOR of ≥24 months in 50%	Pembrolizumab: 200 mg every 3 weeks or 400 mg every 6 weeks intravenously

AKT, protein kinase B; BRCA, breast cancer gene; CBR, clinical benefit rate; CI, confidence interval; dMMR, deficient mismatch repair; DOR, duration of response; ERBB2, Erb-B2 receptor tyrosine kinase 2; ESR1, estrogen receptor 1; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor or hazard ratio; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; OS, overall survival; PALB2, partner and localizer of BRCA2; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RET, rearranged during transfection; TMB-H, tumor mutational burden-high.

CDx—an NGS assay as a companion diagnostic for detecting PIK3CA mutations in tumor tissue or circulating tumor DNA (ctDNA) from plasma. If the plasma test is negative, further testing in tumor tissue is recommended.

Alpelisib

Alpelisib is a selective PI3Kα (p110α subunit) inhibitor that blocks phosphorylation of downstream targets, including Akt, demonstrating anti-tumor activity in PIK3CA-mutant cancers (16). The FDA approved alpelisib in combination with fulvestrant for HR-positive, HER2-negative, PIK3CA-mutated unresectable or metastatic breast cancer following progression on an endocrine-based regimen, based on the SOLAR-1 trial (17). The SOLAR-1, a phase 3 trial in PIK3CA-mutant, HR+/HER2– metastatic breast cancer, showed that alpelisib + fulvestrant significantly when compared to placebo + fulvestrant improved PFS of 11.0 *vs.* 5.7 months [hazard ratio (HR) 0.65, 95% confidence interval (CI): 0.50–0.85, P<0.001], overall response rate (ORR) of 26.6% *vs.* 12.8%, overall survival (OS) of 39.3 *vs.* 31.4 months (HR 0.86, 95% CI: 0.64–1.15, P=0.15). Notably, only 6% of patients in SOLAR-1 had received prior CDK4/6 inhibitor therapy (13,17). In the BYLieve phase 2 trial, alpelisib + fulvestrant demonstrated a 53.8% (95% CI: 44.4–63%) PFS at 6 months in PIK3CA-mutant, HR+/HER2– advanced breast cancer following progression on a CDK4/6 inhibitor + aromatase inhibitor (18).

Dosage considerations: alpelisib is administered at 300 mg once daily, with no dose adjustments required for pre-existing renal or hepatic impairment. Common adverse effects include hyperglycemia (63.7%), diarrhea (57.7%), nausea (44.7%), decreased appetite (35.6%), and rash (35.6%), including maculopapular rash (14.1%). The most frequent grade 3 or 4 adverse events are hyperglycemia (36.6%), rash (9.9%), and diarrhea (6.7%) (17). For patients at risk of hyperglycemia, prophylactic metformin may be considered, and it can significantly reduce the occurrence of grade 3 or 4 hyperglycemia (19).

Inavolisib

Inavolisib is a highly selective PI3Kα inhibitor that also promotes mutant p110α degradation (20). The FDA approved inavolisib with palbociclib and fulvestrant for adults with endocrine-resistant, PIK3CA-mutated, HR+/HER2– locally advanced or metastatic breast cancer who progressed during or within 12 months of adjuvant endocrine therapy and had no prior systemic treatment, based on the phase 3 INAVO120 trial (20). INAVO120 demonstrated that inavolisib + palbociclib + fulvestrant significantly improved PFS of 15.0 *vs.* 7.3 months (HR 0.43, 95% CI: 0.32–0.59; P<0.0001), ORR of 58% *vs.* 25%, and duration of response (DOR) of 18.4 *vs.* 9.6 months compared to placebo + palbociclib + fulvestrant (20).

Dosage considerations: inavolisib is administered at 9 mg orally once daily. For patients with an estimated glomerular filtration rate <60 mL/min, the dose should be reduced to 6 mg daily, while no adjustments are needed for hepatic impairment. The frequent adverse events in the inavolisib + palbociclib + fulvestrant arm included neutropenia (89%), hyperglycemia (58.6%), stomatitis (51.2%), diarrhea (48%), and rash (25%). The frequent grade 3 or higher events were neutropenia (80.2%), stomatitis (5.6%), and diarrhea (3.7%) (20).

PIK3CA or AKT activating mutations or phosphatase and tensin homolog (PTEN) alterations

Alterations in the PIK3CA, AKT, and PTEN pathway contribute to therapy resistance in HR+ve/HER2-ve metastatic breast cancer. AKT, the key component of this pathway, is activated by activating mutations in PIK3CA or AKT1 or by the loss of PTEN function, driving tumor progression (21). These alterations may be present at cancer recurrence or acquired during treatment. One study found that 52.8% of metastatic breast cancers had PI3K/AKT/PTEN alterations, with the most common being PIK3CA mutations (74%), followed by PTEN (22%) and AKT1 (18%) (22). Another study showed mutation frequencies of 36.4% for PIK3CA, 3.2% for AKT1, and 4.8% for PTEN (23). These alterations can be detected using NGS or PCR techniques (22,23). The FDA has approved the FoundationOne CDx NGS assay as a companion diagnostic for detecting PIK3CA/AKT1/PTEN alterations.

Capivasertib

Capivasertib is a small-molecule inhibitor of AKT1, AKT2, and AKT3 isoforms (24). The FDA approved capivasertib in combination with fulvestrant for locally advanced or metastatic HR+, HER2-negative breast cancer with PIK3CA/AKT1/PTEN alterations, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence within 12 months of adjuvant therapy, based on the phase III CAPItello-291 trial (21). The CAPItello-291 trial showed that in patients with PIK3CA/AKT1/PTEN alterations, capivasertib + fulvestrant improved PFS (7.3 *vs.* 3.1 months; HR 0.5; 95% CI: 0.38–0.65; P<0.0001) and OS at 18 months (73.2% *vs.* 62.9%) compared to placebo + fulvestrant (25). While the benefit was seen in the overall population (PIK3CA/AKT/PTEN-altered + non-altered patients), it was thought that the

benefit was mostly driven because of the PIK3CA/AKT/PTEN altered group, or due to the inclusion of patients with unknown alteration status in the non-altered group who could have had the alterations driving the benefit. As a result, it is currently approved in the U.S. only for patients with PIK3CA/AKT/PTEN alterations.

Dosage considerations: capivasertib is administered at 400 mg twice daily for days 1–4 of each week. No dose adjustments are recommended for pre-existing renal or liver impairment. The most common adverse events were diarrhea (72%), rash (38%), nausea (35%), and hyperglycemia (16.3%). The most common grade 3 or higher adverse events were rash (12%), diarrhea (9.3%), and hyperglycemia (2.3%) (21).

ESR1 mutations

Most HR-positive breast cancers initially respond to endocrine therapy but eventually develop resistance. A key resistance mechanism is a mutation of the ligand-binding domain of estrogen receptor 1 (ESR1), leading to estrogen-independent activation of estrogen receptor α. These mutations confer resistance to aromatase inhibitors but not to estrogen receptor inhibitors such as selective estrogen receptor degraders (SERDs) and modulators (SERMs). ESR1 mutation prevalence varies with prior endocrine therapy exposure: 20–40% in metastatic breast cancer after aromatase inhibitor therapy, 4–5% in recurrent breast cancer following adjuvant aromatase inhibitor, 1.5–7% after neoadjuvant aromatase inhibitor, and <1% in endocrine therapy-naïve metastatic breast cancer (26). Thus, ESR1 mutations predominantly emerge post-aromatase inhibitor in metastatic settings. Elacestrant is FDA-approved for ESR1-mutant, advanced/metastatic HR+, HER2-negative breast cancer, with imlunestrant expected to receive approval soon.

Various technologies detect ESR1 mutations in metastatic breast cancer using solid tissue biopsy, circulating tumor cells (CTCs), or cell-free DNA (cfDNA). Detection methods include NGS and droplet digital PCR (ddPCR), with ddPCR being the most sensitive. Liquid biopsy offers advantages over solid tissue sampling by capturing tumor heterogeneity, but its accuracy can be affected by variations in CTC release and cfDNA shedding. Comparing liquid and solid biopsies remains crucial (26,27). The FDA-approved Guardant360 CDx liquid biopsy assay performs comprehensive genomic profiling of cfDNA and is a companion diagnostic for identifying breast cancer patients eligible for elacestrant.

Elacestrant

Elacestrant is a nonsteroidal, oral, SERD that degrades estrogen receptor alpha in a dose-dependent manner, inhibiting estrogen receptor-directed gene transcription and tumor growth (28). The FDA approved elacestrant for postmenopausal women or adult men with HR-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer after progression on at least one line of endocrine therapy, based on the EMERALD trial, a randomized phase III study (29).

The EMERALD trial enrolled 478 patients who had progressed on 1–2 lines of endocrine therapy (including one with a CDK4/6 inhibitor) and up to one prior chemotherapy line in the advanced/metastatic setting. Patients were randomized 1:1 to elacestrant 345 mg daily (n=239) or investigator's choice of endocrine therapy (fulvestrant or an aromatase inhibitor, n=239). Among ESR1-mutated patients (48%, n=228), median PFS was statistically significantly longer at 3.8 months (95% CI: 2.2–7.3) with elacestrant *vs.* 1.9 months (95% CI: 1.9–2.1) with investigator's choice endocrine therapy (HR =0.55, P=0.0005). No significant PFS difference between the two arms was observed in ESR1 wild-type patients. In ESR1-mutated patients with a durable response (>12 months) to a prior CDK4/6 inhibitor, PFS was significantly longer at 8.6 months with elacestrant versus 1.9 months with the investigator's choice. OS data remains immature, but trends in favour of elacestrant (29).

Dosage considerations: elacestrant is administered orally at 345 mg once daily, with two potential dose reductions for toxicity: 258 mg first, then 172 mg daily. Common adverse effects include musculoskeletal pain and fatigue (41%), nausea (35%), hyperlipidemia (30%), and elevated transaminases (29%) (29). No dose adjustment is needed for renal impairment, but dose reduction is recommended for Child-Pugh B hepatic impairment, and it is contraindicated in Child-Pugh C hepatic impairment.

Imlunestrant

Imlunestrant, an oral next-generation SERD, has shown promise in advanced/metastatic HR+/HER2 breast cancer with ESR1 mutations. The phase 3, EMBER3 trial randomized 874 patients (1:1:1) after progression during or after aromatase inhibitor therapy (administered alone or with a CDK 4/6 inhibitor) to receive imlunestrant, imlunestrant-abemaciclib, or standard endocrine therapy.

In the overall population, the PFS was 5.6 months with imlunestrant *vs.* 5.5 months with standard endocrine therapy (HR 0.87, 95% CI: 0.72–1.04, P=0.12); the PFS was 9.4 months with imlunestrant-abemaciclib *vs.* 5.5 months with imlunestrant (HR 0.57, 95% CI: 0.44–0.73, P<0.001). Among 256 ESR1-mutant patients, imlunestrant alone improved PFS compared to standard endocrine therapy (5.5 *vs.* 3.8 months; P<0.001) but showed no benefit in the overall population. The combination of imlunestrant and abemaciclib significantly improved PFS regardless of ESR1 mutation status (30). Imlunestrant is not yet FDA approved as of March 2025, but approval is anticipated soon.

Dosage considerations: imlunestrant is administered orally at a dose of 400 mg once daily. Common adverse events, mostly grade 1, include fatigue (22.6% *vs.* 13.3%), diarrhea (21.4% *vs.* 11.7%), and nausea (17.1% *vs.* 13.0%) compared to standard endocrine therapy (30).

Germline BRCA1 or BRCA2 mutation

Germline BRCA (breast cancer gene)1/2 mutations are found in approximately 5% of metastatic breast cancer patients and are more common in those diagnosed at a younger age, with a strong family history, or with bilateral breast or ovarian cancer (31,32). BRCA1 mutations are associated with triple-negative breast cancer, while BRCA2 mutations are linked to HR-positive and HER2-negative breast cancer. BRCA1/2-deficient cancer cells have a defect in homologous recombination and lack an effective DNA double-strand break repair mechanism, making them highly dependent on poly ADP ribose polymerase (PARP)-mediated single-strand break repair. PARP inhibitors disrupt this process, leading to DNA damage accumulation and tumor cell death while sparing normal cells (32). PARP inhibitors have demonstrated efficacy in multiple BRCA1/2-mutated tumors. Germline BRCA mutations are detected via germline sequencing assays. The FDA-approved BRACAnalysis CDx test (Myriad Genetic Laboratories) is a companion diagnostic for identifying pathogenic or suspected pathogenic BRCA1/2 mutations. In HER2-negative breast cancer, including HR+ cases previously treated with chemotherapy (≤2 prior regimens for olaparib, ≤3 for talazoparib) and at least one line of endocrine therapy if HR+, PARP inhibitors are approved.

Olaparib

Olaparib is a potent oral PARP1/2/3 inhibitor that induces lethality in BRCA1/2-deficient tumors by promoting irreparable double-stranded DNA breaks, leading to cell death (33). Olaparib was the first FDA-approved drug for germline BRCA1/2-mutated breast cancer and is also approved for ovarian, pancreatic, and prostate cancers with associated BRCA1/2 mutations. The FDA approval for advanced or metastatic HER2-negative breast cancer with pathogenic or suspected pathogenic germline BRCA1/2 mutations was based on the phase III OlympiAD trial (32). The OlympiAD trial showed that Olaparib improved PFS over chemotherapy (7.0 *vs.* 4.2 months; HR 0.58, 95% CI: 0.43–0.80, P<0.001) and had a higher ORR (59.9% *vs.* 28.8%). However, OS was not significantly different (19.3 *vs.* 17.1 months; HR 0.89, 95% CI: 0.67–1.18) (32,34).

Dosage considerations: olaparib is administered at 300 mg orally twice daily. For pre-existing renal impairment, reductions to 200 mg twice daily [creatinine clearance (CrCl) 31–50 mL/min] or 100–150 mg twice daily (CrCl ≤30 mL/min) are recommended. No adjustments are needed for pre-existing hepatic impairment. The common adverse events with olaparib were anemia, nausea, vomiting, fatigue, cough, and headache. The common grade ≥3 adverse events included anemia (16.1%), neutropenia (9.3%), leukopenia (3.4%), fatigue (2.9%), and elevated aspartate aminotransferase (AST) (2.4%) and alanine aminotransferase (ALT) (1.5%) (32).

Talazoparib

Talazoparib is a potent PARP1/2 inhibitor with strong catalytic suppression and superior DNA-PARP complex trapping compared to other PARP inhibitors, leading to irreparable DNA damage and cell death (35). It is FDA-approved for advanced or metastatic HER2-negative breast cancer with pathogenic or suspected pathogenic germline BRCA1/2 mutations based on the phase III EMBRACA trial (35). The EMBRACA trial demonstrated a PFS benefit with talazoparib over standard chemotherapy (median 8.6 *vs.* 5.6 months; HR 0.54, 95% CI: 0.41–0.71, P<0.001) and a higher ORR (62.6% *vs.* 27.2%; OR 5.0, 95% CI: 2.9–8.8; P<0.001). However, OS was not significantly different (19.3 *vs.* 19.5 months; HR 0.8, 95% CI: 0.67–1.07; P=0.17) (35,36).

Dosage and considerations: talazoparib is administered orally at 1 mg once daily. Dose reductions are recommended for pre-existing renal impairment: 0.75 mg daily for CrCl 30–59 mL/min and 0.5 mg daily for CrCl <30 mL/min. No adjustments are required for pre-existing hepatic impairment. The common adverse events with talazoparib were anemia, fatigue, and nausea. Grade 3–4

hematologic adverse events, primarily anemia, occurred in 55% of the talazoparib group. Anemia, neutropenia, and thrombocytopenia were the most frequent causes of talazoparib modifications (35).

Somatic BRCA1 or BRCA2 mutations; *germline PALB2 mutations*

Somatic BRCA1/2 mutations are less common than germline mutations but have shown PARP inhibitor efficacy in solid cancers like ovarian and prostate (37,38). A study of breast cancer patients found germline BRCA1/2 mutations in 7% and somatic BRCA1/2 mutations in only 3% of the patients (39). In addition to BRCA1/2, other homologous recombination pathway genes, such as PALB2 (partner and localizer of BRCA2), also contribute to DNA repair and cancer susceptibility, with patients carrying germline PALB2 mutations potentially responding to PARP inhibitors. Germline PALB2 mutations occur in about 1% of breast cancer cases (40). Somatic BRCA mutations can be identified through NGS of tumor tissue or ctDNA, while germline PALB2 mutations are detected via germline sequencing.

Olaparib

Olaparib may be considered for advanced or metastatic HER2-negative breast cancer with somatic BRCA1/2 mutations or germline PALB2 mutations based on a phase II trial, though it is not FDA-approved for this indication (38). The trial reported an ORR of 50% and a PFS of 6.3 months (90% CI: 4.4–not reached) in somatic BRCA1/2 mutations, while germline PALB2 mutations showed an ORR of 82% and a median PFS of 13.3 months (90% CI: 12–not reached). No responses were observed in germline ATM or CHEK2 mutations (38).

Dosage considerations: the dosage and side-effect profile are consistent with prior studies. Grade 2 nausea occurred in 9% (none ≥ grade 3), anemia in 26% (13% ≥ grade 3), and grade 2 alopecia in 4% (38).

HER-2/ERRB2 activating mutations

Cancers with HER2 overexpression or amplification are defined as HER2-positive breast cancer. However, somatic activating mutations in the HER2 also known as Erb-B2 receptor tyrosine kinase 2 (ERBB2) gene can occur without HER2 amplification or overexpression, found in nearly 2% of primary breast cancers, 3–5% of HR-positive metastatic breast cancer cases, and further enriched in those with lobular histology (5–8%) (41). These mutations drive resistance to endocrine therapy in ER-positive patients through crosstalk between HER2 and estrogen receptor signaling, making them viable therapeutic targets. HER2-activating mutations are detected using NGS assays.

Neratinib

Neratinib is an oral, irreversible pan-HER tyrosine kinase inhibitor with activity in HER2-mutant tumors (41). While not FDA-approved for this indication, it can be used with fulvestrant or fulvestrant + trastuzumab in HER2-mutant, HER2 non-amplified, HR-positive breast cancer when no alternative therapies are available.

In the MutHER phase 2 study, neratinib + fulvestrant in 35 patients with HER2 mutant, HER2 non-amplified breast cancer showed a clinical benefit rate (CBR) of 38% (18–62%) in HR+, fulvestrant-pretreated patients; 30% (7–65%) in HR+, fulvestrant-naïve patients; and 25% (1–81%) in HR– patients. Adding trastuzumab at progression (in 5 patients) led to three partial responses and one stable disease ≥24 weeks. ctDNA analysis identified secondary HER2 mutations or amplification as mechanisms of neratinib resistance, suggesting that a subset of HER2-mutant metastatic breast cancer requires stronger HER2 inhibition for sustained response (42).

In the SUMMIT phase 2 trial, neratinib + fulvestrant + trastuzumab in 57 patients with HR+ positive, HER2-mutant, HER2 non-amplified metastatic breast cancer post-CDK4/6 inhibitor progression achieved an ORR of 39% (95% CI: 26–52%) and median PFS of 8.3 months (95% CI: 6.0–15.1). No responses were observed in patients treated with fulvestrant ± trastuzumab, reinforcing the necessity of neratinib in the triplet regimen (41).

Dosage considerations: neratinib is administered at a dose of 240 mg once daily. To improve neratinib tolerability and reduce the severity and duration of neratinib-induced diarrhea, a dose-escalation strategy can be used: 120 mg once daily (week 1), 160 mg once daily (week 2), and 240 mg once daily (week 3 and beyond) (43). If not using the dose escalation strategy, antidiarrheal prophylaxis is recommended for the first 56 days: loperamide 4 mg three times daily (days 1–14), then 4 mg twice daily (days 15–56), followed by titration to maintain 1–2 bowel movements per day. No dose adjustment is needed for renal impairment, but for Child-Pugh class C hepatic impairment, reduce the initial dose of neratinib to 80 mg daily. The common adverse effects are diarrhea (93%), nausea (72%), fatigue

(40%), constipation (39%), decreased appetite (39%), abdominal pain (30%), anemia (18%), muscle spasms (18%), rash (18%) (41).

Neurotrophic tyrosine receptor kinase (NTRK) fusion

NTRK genes encode tropomyosin receptor kinases (TRKs), transmembrane proteins involved in neuronal signaling. These receptors play a crucial role in neuronal development during embryogenesis and are primarily expressed in neuronal tissue later in life. There are three NTRK genes—*NTRK1*, *NTRK2*, and *NTRK3*—and their fusion can result in a chimeric TRK oncogene, leading to constitutive activation and overexpression of this tyrosine kinase, driving downstream signaling and oncogenesis (44). NTRK fusions were among the first targetable oncogenic mutations identified. Their prevalence is relatively low in solid malignancies, with as low as 0.13% in breast cancer patients (45). Detection methods include PCR, fluorescent *in situ* hybridization (FISH), and NGS. Immunohistochemistry (IHC) can also help identify tumors with high TRK protein expression; however, as TRK proteins may be expressed in non-NTRK fusion tumors, confirmation with NGS is recommended (45). The FDA has approved FoundationOne CDx and TruSight Oncology Comprehensive, both NGS assays, as companion diagnostic tests for detecting NTRK fusions in solid tumors.

Larotrectinib

Larotrectinib is a highly selective and potent small-molecule inhibitor of the three TRK proteins—TRKA, TRKB, and TRKC, which are encoded by NTRK genes *NTRK1*, *NTRK2*, and *NTRK3*, respectively (44). The FDA approved Larotrectinib for unresectable or metastatic solid tumors (tumor agnostic) harboring NTRK gene fusions without known resistance mutations with no alternative treatment options. This approval was based on pooled data from three single-arm trials—LOXO-TRK-14001, SCOUT, and NAVIGATE—analyzing the first 55 patients (44). A subsequent larger analysis of 159 patients, of which 5 (3%) had breast cancer (including the initial 55) reported an ORR of 79% (95% CI: 72–85%), a median PFS of 28.3 months (95% CI: 22–not reached), and a median OS of 44.4 months (95% CI: 36.5–not reached) (46).

Dosage considerations: larotrectinib is administered orally at 100 mg twice daily. No dose adjustment is required for renal impairment, but a 50% dose reduction is recommended for patients with moderate to severe hepatic impairment (Child-Pugh B and C). The most common adverse reactions (≥20%) include fatigue, nausea, dizziness, vomiting, elevated AST, cough, elevated ALT, constipation, and diarrhea. Grade 3 or 4 treatment-related adverse events include elevated ALT (3%), anemia (2%), and decreased neutrophil count (2%) (44,46).

Entrectinib

Entrectinib, like larotrectinib, is an inhibitor of the three TRK proteins—TRKA, TRKB, and TRKC (47). The FDA approved Entrectinib for unresectable or metastatic solid tumors (tumor agnostic) with NTRK gene fusions, without known resistance mutations, and no alternative treatment options, based on combined data from the ALKA-372-001, STARTRK-1, and STARTRK-2 trials. An updated analysis of 121 patients, including 7 (5.8%) with breast cancer, reported an ORR of 61.2%, a median DOR of 20 months (95% CI: 13–38.2), and a median PFS of 13.8 months (95% CI: 10.1–19.9). Among 11 patients with measurable central nervous system disease, the intracranial ORR was 63.6% (95% CI: 30.8–89.1%), with a median intracranial DOR of 22.1 months (95% CI 7.4–not reached) (47).

Dosage considerations: entrectinib is administered orally at 600 mg orally once daily, with no recommended dose adjustments for pre-existing renal or hepatic impairment. Serious adverse reactions include congestive heart failure, central nervous system effects, skeletal fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, and vision disorders (47).

Repotrectinib

Repotrectinib is a multikinase inhibitor targeting the proto-oncogene ROS1 and the three TRK proteins—TRKA, TRKB, and TRKC (48). The FDA approved Repotrectinib for unresectable or metastatic solid tumors with NTRK gene fusions and no alternative treatment options based on the TRIDENT-1 trial, a multi-cohort, phase 1–2 study (49). The trial included two cohorts of adults with locally advanced or metastatic NTRK fusion-positive solid tumors: 48 patients who had received a prior TRK tyrosine kinase inhibitor (TKI) and 40 who were TKI-naïve. The ORR was 58% (95% CI: 41–73%) in the TKI-naïve group and 50% (95% CI: 35–65%) in the TKI-pretreated group. Data on PFS, OS, and median DOR are not yet mature (49).

Dosage considerations: repotrectinib is administered orally at 160 mg orally once daily for 14 days, then increased to 160 mg twice daily. No dose adjustments are recommended for those with pre-existing renal or hepatic

impairment. The most common (>20%) adverse reactions include dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea (49).

RET fusion

RET is a proto-oncogene linked to multiple endocrine neoplasia and various cancers, most commonly thyroid, salivary gland, and non-small cell lung cancer (NSCLC). RET fusions drive constitutive, ligand-independent RET pathway activation, occurring in 1–2% of NSCLC and 5–10% of thyroid cancers (papillary or poorly differentiated), where hyperactive RET is a key driver in oncogenesis. While NSCLC and thyroid cancers account for most RET fusion-positive cases, fusions also appear in <1% of breast, colon, esophageal, ovarian, prostate, stomach, pancreatic, salivary gland, connective tissue, and histiocytic cancers (50). In breast cancer, RET signaling influences tumorigenesis, metastasis, and therapeutic resistance, with RET fusions occurring at similar frequencies in primary and metastatic tumor samples (51). The preferred detection method for RET fusion is NGS testing (52).

Selpercatinib

Selpercatinib is an oral, highly selective RET kinase inhibitor with intracranial activity. The FDA approved Selpercatinib for adults with advanced or metastatic RET fusion-positive solid tumors (tumor-agnostic) who have progressed on prior therapies with no alternative options, based on the LIBRETTO-001 trial, a phase 1/2 multi-cohort, basket trial (50). The LIBRETTO-001 trial evaluated 41 patients with RET fusion-positive solid tumors (excluding NSCLC and thyroid cancer, where selpercatinib is already approved). The ORR was 44% (95% CI: 28–60%), with a median DOR of 24.5 months (95% CI: 9.2–not estimable), median PFS of 13.2 months (95% CI: 7.4–26.2), and median OS of 18 months (95% CI: 10.7–not estimable). In the breast cancer cohort (2 patients out of the 41 in this study), the ORR was 100% (95% CI: 15.8–100%), with a median DOR of 17.3 months (95% CI: 17.3–17.3) (50).

Dosage considerations: selpercatinib is administered orally at 160 mg twice daily for patients ≥50 kg and at 120 mg twice daily for those ≤50 kg, with dose reduction recommended for hepatic impairment. Common grade ≥3 adverse events include hypertension (22%), elevated ALT (16%), and AST (13%). Other significant events include QT prolongation, pneumonitis, cytopenias, and hemorrhage (including cerebral hemorrhage and hemoptysis) (50).

FGFR 1-3 fusions/mutations

The fibroblast growth factor receptor (FGFR) family regulates cell proliferation, migration, differentiation, and survival, while FGFR mutations or fusions can drive oncogenesis through constitutive activation of downstream signaling (53). FGFR aberrations are found in approximately 18–32% of breast cancer patients, with amplifications being the most common, followed by mutations and fusions (53,54). These aberrations are detected using PCR or NGS. The FDA has approved the FoundationOne CDx and TheraScreen FGFR RGQ RT-PCR assays as companion diagnostic tests for identifying solid tumors treatable with FGFR inhibitors.

Erdafitinib

Erdafitinib is a pan-FGFR inhibitor that blocks FGFR1–4, reducing FGFR-driven signaling and cancer cell viability in FGFR-altered cancers (55). Erdafitinib can be used as a tumor-agnostic therapy for advanced solid tumors with FGFR alterations in patients who have exhausted other treatment options, based on the phase 2, RAGNAR trial (56). However, erdafitinib currently does not have an FDA approval for this indication and is FDA-approved currently for advanced or metastatic FGFR3-mutant urothelial carcinoma. The RAGNAR trial enrolled 217 patients with various solid tumors (non-urothelial cancers), of whom 66% had FGFR fusions and 34% had FGFR1–3 mutations; no patients had FGFR4 mutations due to its low incidence in adults. Sixteen patients (7%) had breast cancer. The trial reported ORR of 30% (95% CI: 24–36%) with a median DOR of 7.1 months (95% CI: 5.5–9.3) (56).

Dosage considerations: erdafitinib is administered orally at 8 mg/day on a continuous 21-day cycle, with the option to increase to 9 mg/day based on tolerability. No dose adjustments are recommended for pre-existing renal or hepatic impairment. The most common treatment-emergent adverse events (≥30%) were hyperphosphatemia (71%), stomatitis (54%), diarrhea (50%), dry mouth (48%), dry skin (35%), and palmar-plantar erythrodysesthesia syndrome (34%). The most common grade 3 or higher treatment-emergent adverse events were stomatitis (12%), anemia (8%), and palmar-plantar erythrodysesthesia syndrome (6%) (56).

Deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H)

dMMR cancers exhibit defective mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), due to inherited or sporadic mutations, leading to impaired DNA repair during replication. These DNA repair defects are particularly evident in microsatellite regions, resulting in MSI-H (57). dMMR/MSI-H occurs in approximately 2% of breast cancers (57-59). Detection methods include PCR and NGS for microsatellite markers, as well as IHC for the four MMR proteins (59).

The FDA approved the VENTANA MMR RxDx panel, a qualitative IHC test, as the companion diagnostic test for the identification of solid tumors with dMMR status (60).

Pembrolizumab

Pembrolizumab is a selective anti-programmed cell death-1 (PD-1) monoclonal antibody that prevents PD-1 ligands (PD-L1 and PD-L2) from binding to PD-1 receptors on T-cells, thereby reversing T-cell suppression and inducing an antitumor response (61). It was the first immunotherapy to receive FDA approval for tumor-agnostic indications. It is approved for unresectable or metastatic dMMR/MSI-H solid tumors that have progressed on prior treatments with no alternative treatment options. This approval was partly based on the Keynote-158 trial, a phase 2, basket trial evaluating dMMR/MSI-H non-colorectal cancers across 27 cancer types. In cohort K, which included breast cancer patients (3.7%, 13 of 351 patients), the ORR was 30.8% (95% CI: 25.8–36.2%), median PFS was 3.5 months (95% CI: 2.3–4.2 months), and median OS was 20.1 months (95% CI: 14.1–27.1 months) (58).

Dosage considerations: pembrolizumab is administered intravenously at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks, with no dose adjustments recommended for pre-existing renal or hepatic impairment. The most common treatment-related adverse events of any grade were pruritus (14.5%), fatigue (12.3%), and diarrhea (11.7%). Grade 3–5 treatment-related adverse events included elevated ALT, AST, and gamma-glutamyl transferase levels, as well as hyperglycemia and pneumonitis (58).

Dostarlimab

Dostarlimab, like pembrolizumab, is an anti-PD-1 monoclonal antibody that blocks PD-1 ligand binding to the PD-1 receptor on T-cells, inhibiting negative immune regulation and inducing an antitumor response (62). Based on the GARNET trial, the FDA approved Dostarlimab for metastatic or unresectable dMMR/MSI-H solid tumors (tumor agnostic) that have progressed on prior treatment with no alternative options (62). GARNET trial is a phase 1, basket trial that included 327 patients with dMMR/MSI-H tumors, with breast cancer comprising <1% of cases. The trial reported an ORR of 44.0% (95% CI: 38.6–49.6%), a median PFS of 6.9 months (95% CI: 4.2–13.6 months), and a median OS that was not reached (95% CI: 31.6 months–not reached) (62).

Dosage and safety: dostarlimab is administered intravenously at 500 mg every 3 weeks for four cycles, followed by 1,000 mg every 6 weeks from cycle five onward, with no dose adjustments recommended for pre-existing renal or hepatic impairment. The most common adverse events (≥20%) were fatigue, anemia, diarrhea, and nausea. The most frequent immune-related adverse events included hypothyroidism (6.9%), elevated ALT (5.8%), and arthralgia (4.7%) (62).

Tumor mutational burden-high (TMB-H)

TMB quantifies somatic mutations per megabase of the tumor genome and is linked to enhanced T-cell reactivity and response to immune checkpoint blockade (63,64). TMB-H is defined as ≥10 mutations/megabase, occurring in approximately 5% of breast cancers, with higher prevalence in metastatic (8.4%) than primary tumors (2.9%) (64). TMB is detected through NGS (63). The FDA-approved FoundationOneCDx assay as the companion diagnostic test for assessing TMB status.

Pembrolizumab

The FDA approved pembrolizumab for unresectable or metastatic TMB-H (≥10 mutations/megabase) solid tumors (tumor agnostic) that have progressed on prior treatments with no alternative options, based on a prospective retrospective analysis of 10 cohorts in the phase 2 Keynote-158 trial. Of 102 TMB-H patients (none of whom had breast cancer), the ORR was 29% (95% CI: 21–39%), with a median DOR not reached; 57% of patients had a DOR ≥12 months, and 50% had a DOR ≥24 months (65).

Dosage considerations: pembrolizumab is administered intravenously at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks, with no dose adjustments recommended for pre-existing renal or hepatic impairment. The most frequent adverse events were fatigue, hypothyroidism, decreased appetite, and pruritus. The most frequent

immune-related adverse events were hypothyroidism, hyperthyroidism, colitis, and pneumonitis (65).

Conclusions

In conclusion, the field of molecular alteration-based therapy in metastatic breast cancer is rapidly evolving. Identifying actionable molecular alterations through tissue or liquid biopsy is crucial as it enables more personalized treatment, expands therapeutic options, and improves outcomes. With more targeted agents now available and many others in development, staying informed about emerging targetable molecular alterations is increasingly important. Clinicians should be familiar with these therapies, including their indications, side effects, and monitoring requirements, to provide the best possible care to patients with cancer.

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Footnote

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