Pan-Cancer Tissue

Date of Birth: 00/00/0000
Pan-Cancer Tissue#: OR000000000, PCD00000
Physician: Dr. Smith
Facility: Some Cancer Treatment Center

Case/Specimen ID: AA00-00000 A0
Collection Site: Right axilla mass
Collection Date: 00/00/0000
Received for testing: 00/00/0000

Turnaround: 3 business days
Tumor cells: 95%
Specimen size: 90 mm^2
Requirement met: Optimal

12 NCCN/FDA indications

Therapeutic Option	Indicating biomarkers	Therapeutic Option	Indicating biomarkers
Abemaciclib	ER/PR +, HER2 -	Alpelisib + Fulvestrant	PIK3CA mutation, ER/PR + and HER2 -
Anastrozole	ER + PR +	Eribulin	HER2 -
Exemestane	ER +	Fulvestrant	ER +
Letrozole	ER + PR +	Megestrol	ER + PR +
Palbociclib	ER/PR +, HER2 -	Ribociclib	ER/PR +, HER2 -
Tamoxifen	ER + PR +	Toremifene	ER + PR +

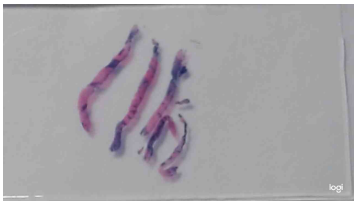
High Interest

Pan cancer	Type specific
TMB: Low (3muts/mb)	ERBB2 CNV: Not Changed
MSI: Stable	ERBB2: Wildtype
NTRK fusion: Negative	ESR1: Wildtype
BRCA1: Wildtype	**PIK3CA: C420R**
BRCA2: Wildtype	PD-L1 (SP142) IHC: Negative
PD-L1 (22C3) Tumor IHC: Negative	
PD-L1 (22C3) TILs IHC: Negative	

7 evidence-based therapy associations

Abiraterone	Bicalutamide	Capecitabine
Enzalutamide	Everolimus	Flutamide
Medroxyprogesterone		

Specimen



Tumor cells: 95%
Specimen size: 90 mm^2
Residual tissue: No

Fibrotic lymph node with metastatic carcinoma having features compatible with breast origin

Gross Description: Xxxxxxxx xxxx XxxxxtXxxxtx Xxxtx Xxxxxxxx xx 0 Xxxxx xxxxxxx xx XX-00-0000 (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx XX-00-0000 (xxx XXXx-00-00000) xxxxtxxxxx xx xxxxxxxxx tx txx xxxxx xxxxx xxtxxxt xxxxx xx txx xxxxxxxxxxxx xxxxxxxx xxtxxxxxx xxxxxt xxtx xxxxxxxx xxxxxxtxxx xxtx xx 00/0/0000. Xxxxx XX-00-0000 xxxx xx xxxxxxxx.

Pathologist has performed a comprehensive review of all records and material submitted.

4 IHCs

AR	2+	70%	Positive
PD-L1 (22C3) TILs	N/A	0%	Negative
PD-L1 (22C3) Tumor	N/A	0%	Negative
PD-L1 (SP142) IC	N/A	0%	Negative
TP	3+	30%	Positive

1 salient genomic finding

Gene	Variant	Quantity
PIK3CA	C420R	31%

Genes with indeterminate findings: RECQL, RB1

3 external results

Biomarker	Type	Value
ER	IHC	Positive High
PR	IHC	Positive
HER2	IHC	Negative

The breast cancer predictive marker (ER, PR, HER2) interpretations in this PCDx test is provided courtesy of an extramural anatomic pathology report and/or provided by the clinical team completing the Exact Sciences tumor analysis requisition/request. The predictive marker data is passed through onto this report and did not arise from ER, PR, HER2 tumor assay performed by Exact Sciences.

26 other genomic findings

Note: this table contains all non-reference alleles found in less than 1% of the population. These may be germline or somatic.

XXXXTX00 x.0000-0X>X
XXXX0 X0000T XXXXX0
X0000X XXX x.0000-0000X>T
XXX0XX X000X
XXXXTX00 X0000
XXX00 Xxxx
XXXXX X0000X
XXX0X0 X0000T
XXX00X x.000+0000X>X
XXX X0000
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XXX0 Xxxx
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XTXX0 x.0000-00000X>X
XTXX X000X
XX000 X000X
XXT T000X XXXX Xxxx
XX X000X XXX0X0
T00 XXT0 X000
XTXX x.0000+00X>X
XXX0 Xxxx
XXX0 X00
XXXX0 X0000X
XXX T000X
XXX0 X000
XXXX0 X00
XXXXXX X00

19 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Abemaciclib	ER/PR +, HER2 -	Yes	I	28,11
Abiraterone	AR +		DTT	13
Alpelisib + Fulvestrant	PIK3CA mutation, ER/PR + and HER2 -	Yes	I	1,22

19 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Anastrozole	ER + PR +	Yes Yes	I II-1	12,21 26,8
Bicalutamide	AR +		II-3	19
Capecitabine	TP +		II-3	23
Enzalutamide	AR +		DTT	14
Eribulin	HER2 -	Yes	II-3	17,30
Everolimus	ER + PR +		II-1 II-1	4,2 2
Exemestane	ER +	Yes	I	3,16
Flutamide	AR +		DTT	15
Fulvestrant	ER +	Yes	II-1	10,31
Letrozole	ER + PR +	Yes Yes	I I	27,24 27,24
Medroxyprogesterone	AR + ER +		II-3 DTT	6,5 33
Megestrol	ER + PR +	Yes Yes	I I	7,18 7,18
Palbociclib	ER/PR +, HER2 -	Yes	I	29
Ribociclib	ER/PR +, HER2 -	Yes	I	20
Tamoxifen	ER + PR +	Yes Yes	II-1 II-1	9,32 9,32
Toremifene	ER + PR +	Yes Yes	I I	34,25 34,25

clinical notes

AR expression in Breast cancer: Current understanding of AR expression and AR signaling suggest potential for novel therapeutic targets for breast cancer. Clinical studies are underway, investigating the feasibility of antiandrogen therapy in the treatment of AR+, advanced or metastatic breast carcinoma. Preclinical data suggest complementary effects between enzalutamide and endocrine therapies in estrogen receptor–positive breast cancer xenografts. A phase I/Ib study of enzalutamide alone and in combination with endocrine therapies showed a clinical benefit rate at 24 weeks of 7% and 9% in the enzalutamide monotherapy and combination ET cohorts, respectively. One AR+ patient who received enzalutamide combined with exemestane followed by exemestane experienced stable disease for more than 3 years. As regards the cited evidence for bicalutamide - the referenced study is primarily based on a patient cohort of AR+ HR- breast cancer patients. However, one patient in the published cohort was shown to have weak ER expression measuring 3% and prolonged stable disease for >12 months. This suggests that the potential of targeting AR in both ER(-) and ER(+) breast cancers is not yet fully explored. The efficacy of antiandrogen therapy in rare breast cancer types, such as inflammatory breast cancer, is currently unknown. In ER(+) AR(-) breast cancer, there appears to be a functional loss of the androgen receptor suggesting there is improved therapeutic utility using a SERM rather than an AI. *** According to the referenced literature, at a threshold of ≥ 10% nuclear expression, the androgen receptor is associated with response to AR inhibitors such as enzalutamide or bicalutamide. Although the current AR IHC at a 10% cutoff for total AR nuclear staining can identify responders, it should be noted that this threshold has been associated with only a modest positive predictive value (PPV) of 30% according to Kumar et al. (2017), which may restrict its clinical application. To develop additional information about its utility, please consider enrolling in our Registry Study.

ER expression in Breast cancer: per the current "Recommendation for Estrogen and Progesterone Receptor Testing in Breast Cancer ASCO/CAP Guideline Update" (Allison et al 2018, PMID 31928404), the Expert Panel continues to recommend ER testing of invasive breast cancers by validated immunohistochemistry as the standard for predicting which patients may benefit from endocrine therapy. ER testing in cases of newly diagnosed DCIS (without associated invasion) is also recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer. ER expression of ≥ 1% by IHC remains the current benchmark to identify patients who could potentially benefit from endocrine therapy, with the additional recommendation that a negative quantitative mRNA ER (ESR1) result (eg, on Oncotype DX testing) should not negate an ER IHC-positive result. Per the updated Guideline, a specimen is considered "ER Negative" if <1% or 0% of tumor cell nuclei are immunoreactive. Specimen should be considered "ER Low Positive" with 1% to 10% of cells staining, and specimen with more than 10% staining (and intensity is moderate or strong) are categorically considered "ER Positive". However, the Expert Panel acknowledges that there are limited data on endocrine therapy benefit in patients with Low ER expression, but clinical evidence currently suggests a possible treatment benefit. Therefore, patients are considered eligible for endocrine therapies, although invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER-negative cancers. The treatment of choice in patients with estrogen receptor-positive metastatic breast cancer (ER+ mBC) is classically divided into a variety of endocrine therapies, most commonly including selective estrogen receptor modulators (SERM), aromatase inhibitors (AI), and

clinical notes

selective estrogen receptor degraders (SERD). However, resistance develops in 30-50% of patients due to a sophisticated and at times redundant interference at the molecular level between the ER, growth factors, and downstream cell-signaling pathways. Tumor response may be heightened with adjunctive therapy that includes an mTORC1 inhibitor (everolimus), CDK4/6 inhibitors (palbociclib/ribociclib/abemaciclib), and the PI3K inhibitor alpelisib (Rozeboom et al. 2019 PMID 31911865).

ER +, HER2- Breast Cancer: Palbociclib, ribociclib and abemaciclib are indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or in men, or in combination with fulvestrant in patients with disease progression following endocrine therapy.

HER2- in breast cancer: Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. A negative HER2 test is defined as either an IHC result of 0 or 1+ for cellular membrane protein expression (no staining or weak, incomplete membrane staining in any proportion of tumor cells (Reviewed in Wolff et al 2018 PMID: 29846104). In breast cancer, patients with HER- disease may derive benefit from eribulin, irrespective of hormone receptor status (Ortega et al 2019 PMID: 30679100; Kimura et al 2018 PMID: 29594360).

Microsatellite Instability Analysis [MSI] Result Stable (MSS): Cancers are classified as either displaying high-frequency microsatellite instability (MSI-H), low-frequency MSI (MSI-L), or microsatellite stability (MSS) depending on the number of microsatellite loci showing errors. Microsatellite stable cancers (MSS) generally show less immune cell infiltration compared with MSI-H cancers. The greatly increased number of mutation-associated neoantigens resulting from mismatch-repair deficiency appears to be a key mechanism in the observed responsiveness to anti–PD-1 agents such as pembrolizumab (Le et al. 2015; PMID: 26028255).

PD-L1 (22C3) TILs: Expression is determined by identifying the percentage of PD-L1 expressing tumor-infiltrating immune cells of any intensity. In breast cancer, Programmed death-ligand 1 (PD-L1) expression on tumor-infiltrating immune cells appears to be the best predictor of response to atezolizumab + nab-paclitaxel in patients with untreated metastatic triple-negative breast cancer whose tumors express PD-L1 stained tumor-infiltrating immune cells [TILs] of any intensity covering ≥ 1% of the tumor area (Schmid et al. 2018). The predictive value of the PD-L1 clone 22C3 for nivolumab, atezolizumab, avelumab or durvalumab is currently unclear. However, an exploratory post-hoc analysis was presented at the European Society of Medical Oncology (ESMO) Annual Meeting 2019 of the IMpassion130 phase III study. The HRs for PFS and OS in favor of atezolizumab plus nab-paclitaxel compared with placebo plus nab-paclitaxel were relatively similar between groups who were PD-L1-positive using Ventana PD-L1 SP142, Dako 22C3, and Ventana PD-L1 SP263 assays.

PD-L1 (22C3) tumor negative: PD-L1 expression is determined by identifying the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. The scoring system divides the results into three groups: those with ≥50% of tumor cells showing any level of positivity (high), those with <50% of tumor cells but ≥1% of tumor cells positive (low), and those with <1% positive (negative). Per the medical literature, there is a strong positive association between PD-L1 expression and response to immune checkpoint inhibitors. However, several studies have revealed that favorable long-term outcomes can be achieved in patients that are PD-L1 negative and this benefit is observable across multiple tumor types and histologies (for example, Patel & Kurzrock 2015, PMID 25695955). A recent meta-analysis (Shen and Zhao 2018, PMID 30201790) that included 2000 patients that were PD-L1 negative, revealed that PD-1 or PD-L1 inhibitors were associated with prolonged overall survival in patients that were PD-L1 negative. The favorable overall survival achieved in this patient group is likely due the biological function of the PD-1 or PD-L1 pathway itself and the complicated interaction between cancer cells and the immune system.

PD-L1 (SP142): PD-L1 (SP142) assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in triple-negative breast carcinoma (TNBC) tissue. Evaluation is based on the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity. Primary or metastatic TNBC tissues may be submitted. Tissues with ≥1% IC are considered positive. On March 8, 2019, the Food and Drug Administration granted accelerated approval to atezolizumab (TECENTRIQ, Genentech Inc.) in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area). Approval was based on IMpassion130 (NCT02425891), a multicenter, international, double-blinded, placebo-controlled, randomized trial that included 902 patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. In patients whose tumors express PD-L1, median progression-free survival (PFS) was 7.4 months (6.6, 9.2) for patients receiving atezolizumab with paclitaxel protein-bound and 4.8 months (3.8, 5.5) for those receiving placebo with paclitaxel protein-bound. The stratified hazard ratio for PFS was 0.60 (95% CI: 0.48, 0.77; p<0.0001) in favor of the atezolizumab plus paclitaxel protein-bound arm. Objective response rate (ORR) in patients with confirmed responses was 53% compared to 33% for the atezolizumab and the placebo-containing arms, respectively. Overall survival data were immature with 43% deaths in the intent to treat (ITT) population. *** Please note that in some cases the PD-L1 SP142 assay may be performed upfront without initial knowledge of HR/HER2 receptor status. If a breast cancer is subsequently identified as non-TNBC, the standard of care regimen of atezolizumab combination will not be reported out regardless of SP142 result. It should be noted that, at present, numerous checkpoint inhibitor trials are actively recruiting breast cancer patients with TNBC, HER2+ or ER+ disease. Some of these trials may include atezolizumab in combination with other agents. Biomarkers (including various PD-L1 clones) are actively being studied to more accurately identify those patients that will or will not respond to checkpoint inhibition. ***

PIK3CA c.1258T>C p.C420R: C420R is a likely pathogenic variant in exon 8 of the PIK3CA gene. The clinical and therapeutic implications of this variant are currently unknown. Based on data from the phase III SOLAR-1 trial, alpelisib (Piqray) has been approved by the FDA for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine therapy. Alpelisib has also demonstrated a tolerable safety profile and encouraging preliminary activity in patients with PIK3CA-altered solid tumors, supporting the rationale for selective PI3Kα inhibition in combination with other agents for the treatment of PIK3CA-mutant tumors. However, the data related to efficacy of alpelisib in PIK3CA-altered cancers is largely based on hotspot mutations such as exon 7: C420R; exon 9: E542K; E545A, E545D, E545G, E545K, Q546E, Q546R; and exon 20: H1047L, H1047R, H1047Y). Additionally, numerous PI3K inhibitors have been developed and are in varying stages of clinical testing, with select trials displayed in the clinical trial appendix of this report.

clinical notes

PR (PGR)+ Breast cancer: per the current Recommendation for Estrogen and Progesterone Receptor Testing in Breast Cancer (Allison et al 2018: ASCO/CAP Guideline Update, PMID 31928404), the Expert Panel continues to recommend PR (PGR) testing of invasive breast cancers by validated immunohistochemistry as the standard for predicting which patients may benefit from endocrine therapy. PR (PGR) testing in cases of newly diagnosed DCIS is considered optional. PGR expression of ≥ 1% by IHC remains the current benchmark to identify patients who could benefit from endocrine therapy in breast cancer. PR (PGR) should be interpreted as either positive (if 1%-100% of cells have nuclear staining) or negative (if , 1% or 0% of cells have nuclear staining). There is substantial evidence for higher rates of clinical response to endocrine therapy in PR (PGR)-positive tumors treated neoadjuvantly or in metastatic disease, although randomized trials in the adjuvant setting have revealed no difference in the degree of benefit from adjuvant endocrine treatment according to PR (PGR) status. PR (PGR) negativity appears to be associated with significant reductions in disease-free and overall survival in ER+ breast cancer. Treatment and surveillance strategies in these patients should be tailored accordingly.

TMB: Tumor Mutation Burden [TMB] is defined as the total number of DNA mutations per megabase in a tumor sequence. While thresholds for TMB have not been clearly defined for all immunotherapy drugs, and there is at present no consensus for the optimal quantitative or qualitative threshold by cancer type, TMB appears to have an evolving role as a predictive marker for immunotherapy treatment. Overall, a higher TMB is generally associated with longer survival and higher response rates with ICI therapy. While this effect is seen in the majority of cancer types, indicating that TMB underlies fundamental aspects of immune-mediated tumor rejection, the optimal predictive cut-point may vary by histology (Lee et al. 2019 PMID 31361563, Samstein et al 2019 PMID 30643254). For the purpose of TMB stratification, OncotypeMap has adopted the high (≥ 10 mutations per megabase) and low (< 10 mutations per megabase) dichotomy based on the retrospective analysis of TMB in the CheckMate 227 trial, in which NSCLC patients were treated with nivolumab + ipilimumab combination (Hellmann et al. 2018, PMID: 29658845). This cutoff is also the suggested TMB threshold that underlies the recent tissue-agnostic FDA approval for pembrolizumab to treat adult and pediatric patients with unresectable or metastatic solid tumors, who have progressed following prior treatment and who have no satisfactory alternative treatment options.

TP (TYMP): Thymidine phosphorylase (TP, TYMP), also known as ''platelet-derived endothelial cell growth factor'' (PD-ECGF), is an enzyme, which promotes tumor growth and metastasis by preventing apoptosis and inducing angiogenesis. Elevated levels of TP are associated with tumor aggressiveness and poor prognosis. TP not only serves as an indicator of angiogenic potential and as a prognostic factor but may also play an important role in cancer chemotherapy as a target for antiangiogenic agents. Recent works have demonstrated that a manipulation of intracellular TP levels can affect sensitivity to both 5-FU and 5-FU prodrugs , suggesting an important role for the activation of the extensively used 5-fluorouracil prodrug capecitabine. Clinical trials that combine capecitabine with TP-inducing therapies (such as taxanes or radiotherapy) suggest that increasing TP expression is an adequate strategy to enhance the antitumoral efficacy of capecitabine. Thus, TP plays a dual role in both cancer development as well as therapy. TP inhibitors can abrogate the tumorigenic and metastatic properties of TP and TP activity may be necessary for the activation of several chemotherapeutic drugs. This duality illustrates the complexity of the role of TP in tumor progression and in the clinical response to fluoropyrimidine-based chemotherapy (Bronckaers et al. 2009 PMID 19434693)

clinical trials

in tumor type

AR +	NCT01990209	Orteronel
Orteronel as Monotherapy in Patients With Metastatic Breast Cancer (MBC) That Expresses the Androgen Receptor (AR)		
AR +	NCT02605486	Palbociclib | Bicalutamide
Palbociclib in Combination With Bicalutamide for the Treatment of AR(+) Metastatic Breast Cancer (MBC)		
AR +, ER + and HER2 -	NCT02955394	Enzalutamide | Fulvestrant
Preoperative Fulvestrant With or Without Enzalutamide in ER+/Her2- Breast Cancer		
BRCA1 WT, BRCA2 WT and HER2 -	NCT02401347	PARP Inhibitor BMN-673
Phase II Trial of Talazoparib in BRCA1/2 Wild-type HER2-negative Breast Cancer and Other Solid Tumors		
ER +	NCT01042379	AMG 386 | Ganitumab | MK-2206 | T-DM1 | Ganetespib | ABT-888 | Neratinib | PLX3397 | Pembrolizumab
I-SPY TRIAL: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer		
ER +	NCT02540330	Fulvestrant
A Pre-Surgical PK Study of IM and Intraductally Delivered Fulvestrant		
ER +	NCT02598557	Exemestane
Alternative Dosing of Exemestane Before Surgery in Treating Postmenopausal Patients With Stage 0-II Estrogen Positive Breast Cancer		
ER +	NCT02993159	Afimoxifene | Placebo | Tamoxifen
Testing an Active Form of Tamoxifen (4-hydroxytamoxifen) Delivered Through the Breast Skin to Control Ductal Carcinoma in Situ (DCIS) of the Breast		
ER +	NCT03294694	Ribociclib | PDR001 | Fulvestrant
Ribociclib + PDR001 in Breast Cancer and Ovarian Cancer		

clinical trials

ER +	NCT03330405	Avelumab | Talazoparib | Avelumab | Talazoparib

Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors

ER +	NCT03332797	GDC-9545 | Palbociclib | LHRH agonist

A Study of GDC-9545 Alone or in Combination With Palbociclib and/or Luteinizing Hormone-Releasing Hormone (LHRH) Agonist in Locally Advanced or Metastatic Estrogen Receptor-Positive Breast Cancer

ER +	NCT03573648	Avelumab | Tamoxifen | Palbociclib

Neoadjuvant Tamoxifen, Palbociclib, Avelumab in Estrogen Receptor Positive Breast Cancer

ER + and HER2 -	NCT02204098	Mammaglobin-A DNA Vaccine | Anastrozole | Letrozole | Tamoxifen | Exemestane | Goserelin

Safety and Immune Response to a Mammaglobin-A DNA Vaccine In Breast Cancer Patients Undergoing Neoadjuvant Endocrine Therapy

ER + and HER2 -	NCT02619669	TAK-228 (MLN0128) | Letrozole

Neoadjuvant Run-In Study With TAK-228 Followed by Letrozole/TAK-228 in Women With High-Risk ER+/HER2- Breast Cancer

ER + and HER2 -	NCT02626507	Gedatolisib | Faslodex | Palbociclib | Zoladex

Phase I Study of Combination of Gedatolisib With Palbociclib and Faslodex in Patients With ER+/HER2- Breast Cancer

ER + and HER2 -	NCT02632045	LEE011 | Fulvestrant | Placebo

Study of Efficacy of Ribociclib After Progression on CDK4/6 Inhibition in Patients With HR+ HER2- Advanced Breast Cancer

ER + and HER2 -	NCT02632045	LEE011 | Fulvestrant | Placebo

Study of Efficacy of Ribociclib After Progression on CDK4/6 Inhibition in Patients With HR+ HER2- Advanced Breast Cancer

ER + and HER2 -	NCT02668666	Palbociclib | Tamoxifen

Palbociclib in Combination With Tamoxifen as First Line Therapy for Metastatic Hormone Receptor Positive Breast Cancer

ER + and HER2 -	NCT02668666	Palbociclib | Tamoxifen

Palbociclib in Combination With Tamoxifen as First Line Therapy for Metastatic Hormone Receptor Positive Breast Cancer

ER + and HER2 -	NCT02684032	Gedatolisib | Palbociclib | Letrozole | Fulvestrant

A Study To Assess The Tolerability And Clinical Activity Of Gedatolisib In Combination With Palbociclib/Letrozole Or Palbociclib/Fulvestrant In Women With Metastatic Breast Cancer

ER + and HER2 -	NCT02738866	Palbociclib | Fulvestrant

Palbociclib With Fulvestrant for Metastatic Breast Cancer After Treatment With Palbociclib and an Aromatase Inhibitor

ER + and HER2 -	NCT02752685	Pembrolizumab | Nab-Paclitaxel

Phase II Study of Pembrolizumab and Nab-paclitaxel in HER-2 Negative Metastatic Breast Cancer

ER + and HER2 -	NCT02764541	Letrozole | Tamoxifen | Palbociclib | Endocrine Therapy

Palbociclib and Endocrine Therapy for LObular Breast Cancer Preoperative Study (PELOPS)

ER + and HER2 -	NCT02778685	Letrozole | Palbociclib | Pembrolizumab

Pembrolizumab, Letrozole, and Palbociclib in Treating Postmenopausal Patients With Newly Diagnosed Metastatic Stage IV Estrogen Receptor Positive Breast Cancer

ER + and HER2 -	NCT02953860	Fulvestrant with Enzalutamide

Fulvestrant Plus Enzalutamide in ER+/Her2- Advanced Breast Cancer

ER + and HER2 -	NCT03250676	H3B-6545

Trial of H3B-6545, in Women With Locally Advanced or Metastatic Estrogen Receptor-positive, HER2 Negative Breast Cancer

ER + and HER2 -	NCT03366844	Pembrolizumab | Radiation

Breast Cancer Study of Preoperative Pembrolizumab + Radiation

ER + and HER2 -	NCT03439735	Aromatase Inhibitor and Palbociclib

Determinants of Resistance to First-line Therapy With an AI and Palbociclib for HR+ MBC

ER + and HER2 -	NCT03455270	G1T48

G1T48, an Oral SERD, Alone and in Combination With Palbociclib in ER-Positive, HER2-Negative Advanced Breast Cancer

ER + and HER2 -	NCT03471663	D-0502 | palbociclib

A First-in-Human Study of D-0502 Alone and in Combination With Palbociclib in Women With Advanced or Metastatic ER-Positive and HER2-Negative Breast Cancer

ER + and HER2 -	NCT03560531	ZN-c5 | Palbociclib

A Study of ZN-c5 in Subjects With Breast Cancer

Continued

clinical trials

ER + and HER2 -	NCT03566485	Atezolizumab | Cobimetinib | Idasanutlin

Atezolizumab and Cobimetinib or Idasanutlin in Participants With Stage IV or Unresectable Recurrent Estrogen Receptor Positive Breast Cancer

ER + and HER2 -	NCT03584009	Venetoclax | Fulvestrant

A Phase II Study Comparing The Efficacy Of Venetoclax + Fulvestrant Vs. Fulvestrant In Women With Estrogen Receptor-Positive, Her2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy

ER + and HER2 -	NCT03628066	Letrozole | Palbociclib | Goserelin

Biological and Clinical Effects of Palbociclib With Ovarian Suppression and Letrozole in the Neoadjuvant Treatment of Breast Cancer

ER + and HER2 -	NCT03659136	Xentuzumab | Placebo | Everolimus | Exemestane

The XENERA™ 1 Study Tests Xentuzumab in Combination With Everolimus and Exemestane in Women With Hormone Receptor Positive and HER2-negative Breast Cancer That Has Spread

ER + and HER2 -	NCT03691493	Anastrozole | Exemestane | Fulvestrant | Letrozole | Palbociclib | Tamoxifen

Radiation Therapy, Palbociclib, and Hormone Therapy in Treating Breast Cancer Patients With Bone Metastasis

ER + and HER2 -	NCT03701334	Ribociclib | Endocrine Therapy

A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer

ER + and HER2 -	NCT03725059	Pembrolizumab | Placebo | Paclitaxel | Doxorubicin | Epirubicin | Cyclophosphamide | Endocrine therapy

Study of Pembrolizumab (MK-3475) Versus Placebo in Combination With Neoadjuvant Chemotherapy & Adjuvant Endocrine Therapy in the Treatment of Early-Stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2-) Breast Cancer (MK-3475-756/KEYNOTE-756)

ER + and HER2 -	NCT03742986	Nivolumab | Doxorubicin +Cyclophosphamide | Nivolumab + Docetaxel +Trastuzumab +Pertuzumab | Doxorubicin+Cyclophosphamide

Trial of Nivolumab With Chemotherapy as Neoadjuvant Treatment in Inflammatory Breast Cancer (IBC)

ER + and HER2 -	NCT03747042	Letrozole

Letrozole in Post-Menopausal Patients With Operable Hormone-Sensitive Breast Cancer

ER + and HER2 -	NCT03803761	Copanlisib | Fulvestrant

A Study of a New Drug Combination, Copanlisib and Fulvestrant, in Advanced Breast Cancer

ER + and HER2 -	NCT03822468	Ribociclib | Letrozole or Anastrozole | Goserelin

Study of 2 Ribociclib Doses in Combination With Aromatase Inhibitors in Women With HR+, HER2- Advanced Breast Cancer

ER + and HER2 -	NCT03854903	Palbociclib | Bosutinib | Fulvestrant

WI231696: Bosutinib, Palbocicilib and Fulvestrant for HR+HER2- Advanced Breast Cancer Refractory to a CDK4/6 Inhibitor

ER + and HER2 -	NCT03874325	DurvalumablAnastrozolelLetrozole lExemestane

Aromatase Inhibitor and Durvalumab in Postmenopausal Breast Cancer

ER + and HER2 -	NCT03901339	SacituzumabGovitecanlEribulinlCapecitabinelGemcitabinelVinorelbine

Study of IMMU-132 in HR+/HER2- MBC (TROPICS-02)

ER + and HER2 -	NCT03906669	LetrozolelLetrozole and PrometriumlTamoxifen and Prometrium

A Window of Opportunity Study of Pre-operative Endocrine Therapy With and Without Prometrium in Postmenopausal Women With Early Stage Breast Hormone Receptor Positive (HR+) Human Epidermal Receptor 2 Negative (HER2-) Breast Cancer.

ER + and HER2 -	NCT03939897	AbemacicliblCopanlisiblFulvestrant

Testing the Addition of Copanlisib to Usual Treatment (Fulvestrant and Abemaciclib) in Metastatic Breast Cancer

ER +, HER2 - and PIK3CA mutation	NCT01723774	PD0332991 | Anastrozole

PD 0332991 and Anastrozole for Stage 2 or 3 Estrogen Receptor Positive and HER2 Negative Breast Cancer

ER +, PR + and HER2 -	NCT03326674	Tesetaxel + Capecitabine | Capecitabine

Tesetaxel Plus Reduced Dose of Capecitabine vs. Capecitabine in HER2 Negative, HR Positive, LA/MBC

ER +, PR + and HER2 -	NCT03519178	PF-06873600

A Safety, Pharmacokinetic, Pharmacodynamic and Anti-Tumor Study of PF-06873600 as a Single Agent and in Combination With Endocrine Therapy

HER2 -	NCT01042379	AMG 386 | Ganitumab | MK-2206 | T-DM1 | Ganetespib | ABT-888 | Neratinib | PLX3397 | Pembrolizumab

I-SPY TRIAL: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer

Continued

clinical trials

HER2 -	NCT01750073	Paclitaxel | Cyclophosphamide | Trastuzumab | Doxorubicin
Paclitaxel and Cyclophosphamide With or Without Trastuzumab Before Surgery in Treating Patients With Previously Untreated Breast Cancer		
HER2 -	NCT02157051	CD105/Yb-1/SOX2/CDH3/MDM2 multiplasmid vaccine
Vaccine Therapy in Treating Patients With HER2-Negative Stage III-IV Breast Cancer		
HER2 -	NCT02957968	Doxorubicin | Cyclophosphamide | Paclitaxel | Carboplatin
Neoadjuvant Pembrolizumab + Decitabine Followed by Std Neoadj Chemo for Locally Advanced HER2- Breast Ca		
HER2 -	NCT03294694	Ribociclib | PDR001 | Fulvestrant
Ribociclib + PDR001 in Breast Cancer and Ovarian Cancer		
HER2 -	NCT03554044	Anastrozole | Exemestane | Fulvestrant | Letrozole | Paclitaxel | Talimogene Laherparepvec | Tamoxifen
Talimogene Laherparepvec With Chemotherapy or Endocrine Therapy in Treating Participants With Metastatic, Unresectable, or Recurrent HER2- Negative Breast Cancer		
HER2 -	NCT03734029	Trastuzumab deruxtecan (DS-8201a) | Capecitabine | Eribulin | Gemcitabine | Paclitaxel | Nab-paclitaxel
Trastuzumab Deruxtecan (DS-8201a) Versus Investigator's Choice for HER2-low Breast Cancer That Has Spread or Cannot be Surgically Removed [DESTINY-Breast04]		
HER2 -, ER + and PR +	NCT02520063	Letrozole | Everolimus | TRC105
Preoperative Combination of Letrozole, Everolimus, and TRC105 in Postmenopausal Hormone-Receptor Positive and Her2 Negative Breast Cancer		
PIK3CA mutation	NCT03337724	Ipatasertib | Paclitaxel | Placebo
A Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Participants With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor-Positive, HER2-Negative Breast Cancer		
PIK3CA mutation, ER + and HER2 -	NCT02738866	Palbociclib | Fulvestrant
Palbociclib With Fulvestrant for Metastatic Breast Cancer After Treatment With Palbociclib and an Aromatase Inhibitor		
PR +	NCT01042379	AMG 386 | Ganitumab | MK-2206 | T-DM1 | Ganetespib | ABT-888 | Neratinib | PLX3397 | Pembrolizumab
I-SPY TRIAL: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer		
PR +	NCT03330405	Avelumab | Talazoparib | Avelumab | Talazoparib
Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors		
PR + and HER2 -	NCT02738866	Palbociclib | Fulvestrant
Palbociclib With Fulvestrant for Metastatic Breast Cancer After Treatment With Palbociclib and an Aromatase Inhibitor		
PR + and HER2 -	NCT02752685	Pembrolizumab | Nab-Paclitaxel
Phase II Study of Pembrolizumab and Nab-paclitaxel in HER-2 Negative Metastatic Breast Cancer		
PR + and HER2 -	NCT02764541	Letrozole | Tamoxifen | Palbociclib | Endocrine Therapy
Palbociclib and Endocrine Therapy for LObular Breast Cancer Preoperative Study (PELOPS)		
PR + and HER2 -	NCT03439735	Aromatase Inhibitor and Palbociclib
Determinants of Resistance to First-line Therapy With an AI and Palbociclib for HR+ MBC		
PR + and HER2 -	NCT03659136	Xentuzumab | Placebo | Everolimus | Exemestane
The XENERA™ 1 Study Tests Xentuzumab in Combination With Everolimus and Exemestane in Women With Hormone Receptor Positive and HER2-negative Breast Cancer That Has Spread		
PR + and HER2 -	NCT03659136	Xentuzumab | Placebo | Everolimus | Exemestane
The XENERA™ 1 Study Tests Xentuzumab in Combination With Everolimus and Exemestane in Women With Hormone Receptor Positive and HER2-negative Breast Cancer That Has Spread		
PR + and HER2 -	NCT03691493	Anastrozole | Exemestane | Fulvestrant | Letrozole | Palbociclib | Tamoxifen
Radiation Therapy, Palbociclib, and Hormone Therapy in Treating Breast Cancer Patients With Bone Metastasis		
PR + and HER2 -	NCT03701334	Ribociclib | Endocrine Therapy
A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer		
PR + and HER2 -	NCT03742986	Nivolumab | Doxorubicin +Cyclophosphamide | Nivolumab + Docetaxel +Trastuzumab +Pertuzumab | Doxorubicin+Cyclophosphamide
Trial of Nivolumab With Chemotherapy as Neoadjuvant Treatment in Inflammatory Breast Cancer (IBC)		

Continued

clinical trials

PR + and HER2 -	NCT03822468	Ribociclib | Letrozole or Anastrozole | Goserelin

Study of 2 Ribociclib Doses in Combination With Aromatase Inhibitors in Women With HR+, HER2- Advanced Breast Cancer

PR + and HER2 -	NCT03854903	Palbociclib | Bosutinib | Fulvestrant

WI231696: Bosutinib, Palbocicilib and Fulvestrant for HR+HER2- Advanced Breast Cancer Refractory to a CDK4/6 Inhibitor

PR + and HER2 -	NCT03901339	SacituzumabGovitecanlEribulinlCapecitabinelGemcitabinelVinorelbine

Study of IMMU-132 in HR+/HER2- MBC (TROPICS-02)

PR + and HER2 -	NCT03906669	LetrozolelLetrozole and PrometriumlTamoxifen and Prometrium

A Window of Opportunity Study of Pre-operative Endocrine Therapy With and Without Prometrium in Postmenopausal Women With Early Stage Breast Hormone Receptor Positive (HR+) Human Epidermal Receptor 2 Negative (HER2-) Breast Cancer.

PR + and HER2 -	NCT03939897	AbemacicliblCopanlisiblFulvestrant

Testing the Addition of Copanlisib to Usual Treatment (Fulvestrant and Abemaciclib) in Metastatic Breast Cancer

multi-indication trials

ER + and HER2 -	NCT03959891	Ipatasertib;Fulvestrant;Aromatase Inhibitor;Palbociclib;

AKT Inhibitor, Ipatasertib, With Endocrine and CDK 4/6 Inhibitor for Patients With Metastatic Breast Cancer (TAKTIC)

ER + and HER2 -	NCT04109066	paclitaxel (PTX);anthracycline;cyclophosphamide;Endocrine Therapy;

Study of Nivolumab Versus Placebo in Combination With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in Participants With High-risk, Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Primary Breast Cancer

ER + and HER2 -	NCT04305496	Fulvestrant;Capivasertib;Placebo;

Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2- Breast Cancer

ER + and HER2 -	NCT04305236	Abemaciclib;Fulvestrant;

Neo-Adjuvant Abemaciclib With Fulvestrant in Patients With ER/PR +HER Negative Breast Cancer

ER + and HER2 -	NCT04294225	Anastrozole;Letrozole;

Anastrozole and Letrozole After Surgery for the Treatment of Stage I-III Breast Cancer

ER + and HER2 -	NCT04352777	Abemaciclib;Fulvestrant;Aromatase Inhibitors;

Impact of Endocrine Therapy and Abemaciclib on Host and Tumor Immune Cell Repertoire/Function in Advanced ER+/HER2- Breast Cancer

ER + and HER2 -	NCT04443348	Pembrolizumab;Paclitaxel;Carboplatin;Cyclophosphamide;Doxorubicin;Capecitabine;

Pre-op Pembro + Radiation Therapy in Breast Cancer

ER + and HER2 -	NCT04514159	ZN-c5;Abemaciclib;

A Study of ZN-c5 and Abemaciclib in Participants With Breast Cancer

ER +, PR + and HER2 -	NCT04052555	Berzosertib;

Testing the Addition of an Anti-cancer Drug, M6620, to the Usual Treatment (Radiation Therapy) for Chemotherapy-Resistant Triple-Negative and Estrogen and/or Progesterone Receptor Positive, HER2 Negative Breast Cancer

ER +, PR + and HER2 -	NCT04215146	Paclitaxel;Avelumab;

A Study to Assess Overall Response Rate by Inducing an Inflammatory Phenotype in Metastatic BReast cAnCEr With the Oncolytic Reovirus PeLareorEp in CombinaTion With Anti-PD-L1 Avelumab and Paclitaxel - BRACELET-1 Study

ER +, PR + and HER2 -	NCT04134884	Talazoparib;ASTX727;

Study of ASTX727 Plus Talazoparib in Patients With Triple Negative or Hormone Resistant/HER2-negative Metastatic Breast Cancer

ER +, PR + and HER2 -	NCT03147287	Palbociclib;Fulvestrant;Avelumab;

Palbociclib After CDK and Endocrine Therapy (PACE)

HER2 -	NCT03952325	Tesetaxel;Tesetaxel;Tesetaxel;Nivolumab;Pembrolizumab;Atezolizumab;Tesetaxel;

Tesetaxel Plus 3 Different PD-(L)1 Inhibitors in Patients With Metastatic TNBC and Tesetaxel Monotherapy in Patients With HER2 Negative MBC

HER2 -	NCT04042480	SGN-CD228A;

A Study of SGN-CD228A in Advanced Solid Tumors

HER2 -	NCT04333706	Capecitabine;

A Dose Finding Phase 1 of Sarilumab Plus Capecitabine in HER2/Neu-Negative Metastatic Breast Cancer and a Single-arm, Historically-controlled Phase 2 Study of Sarilumab Plus Capecitabine in Stage I-III Triple Negative Breast Cancer With High-Risk Residual Disease (EMPOWER)

HER2 - and ER +	NCT04494425	Trastuzumab deruxtecan;Capecitabine;Paclitaxel;Nab-Paclitaxel;

Study of Trastuzumab Deruxtecan (T-DXd) vs Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer

clinical trials

HER2 - and ER +	NCT04494425	Trastuzumab deruxtecan;Capecitabine;Paclitaxel;Nab-Paclitaxel;

Study of Trastuzumab Deruxtecan (T-DXd) vs Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer

MSI Stable	NCT03711058	Copanlisib | Nivolumab

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

PD-L1 (SP142) IC -	NCT04468061	Sacituzumab Govitecan;Pembrolizumab;

Sacituzumab Govitecan +/- Pembrolizumab in Metastatic TNBC

PIK3CA mutation	NCT02576444	AZD2281 | AZD5363 | AZD1775 | AZD2014

OLAParib COmbinations

PIK3CA mutation	NCT02761694	ARQ 751

ARQ 751 as a Single Agent or in Combination With Other Anti-Cancer Agents, in Solid Tumors With PIK3CA / AKT / PTEN Mutations

PIK3CA mutation	NCT03842228	Copanlisib | Durvalumab | Olaparib

Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations

PIK3CA mutation	NCT04317105	Copanlisib Hydrochloride;

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

PR + and HER2 -	NCT03959891	Ipatasertib;Fulvestrant;Aromatase Inhibitor;Palbociclib;

AKT Inhibitor, Ipatasertib, With Endocrine and CDK 4/6 Inhibitor for Patients With Metastatic Breast Cancer (TAKTIC)

PR + and HER2 -	NCT04305496	Fulvestrant;Capivasertib;Placebo;

Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2- Breast Cancer

PR + and HER2 -	NCT04305236	Abemaciclib;Fulvestrant;

Neo-Adjuvant Abemaciclib With Fulvestrant in Patients With ER/PR +HER Negative Breast Cancer

PR + and HER2 -	NCT04294225	Anastrozole;Letrozole;

Anastrozole and Letrozole After Surgery for the Treatment of Stage I-III Breast Cancer

RAS WT, BRAF WT	NCT02693535	Cetuximab

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TP53 WT	NCT01877382	DS-3032

A Phase 1 Multiple Ascending Dose Study of Milademetan in Subjects With Advanced Solid Tumors or Lymphomas

TP53 WT	NCT03449381	BI 907828

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TP53 WT	NCT03560882	Atorvastatin

A Pilot Trial of Atorvastatin in Tumor Protein 53 (p53) -Mutant and p53 Wild-Type Malignancies

TP53 WT	NCT03725436	MDM2/MDMX Inhibitor ALRN-6924 | Paclitaxel

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

genes negative for small variants

ABCB1	ABCC1	ABCC2	ABL1	ACVR1	ACVR1B	ACVR2A	ACVR2B	ACVRL1	ADAMTS1
ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9	ADAMTSL1	AKT1	AKT2	AKT3	ALK	AMER1
APC	APLNR	AR	ARAF	AREG	ARID1A	ARID1B	ARID2	ATM	ATR
ATRX	AURKA	AURKB	AXIN1	AXL	B2M	BAP1	BARD1	BCOR	BMP6
BMPR1A	BMPR1B	BNIP3	BRAF	BRCA1	BRCA2	BRIP1	BTK	BUB1B	CALR
CBL	CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK12
CDK4	CDK6	CDKN2A	CHEK1	CHEK2	CHFR	CHKA	CIC	CREBBP	CSF1R
CTLA4	CTNNB1	CYP19A1	CYP1A1	CYP2D6	CYP3A4	CYSLTR2	dCK	DDR2	DICER1
DNMT3A	EGFR	EMSY	EP300	EPCAM	EPHA5	EPHA7	ERBB2	ERBB3	ERBB4
ERCC1	ERCC2	ERCC3	ERRFI1	ESR1	ESR2	EWSR1	EZH2	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCM	FAT1	FBXW7	FCGR2A	FGD4
FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FLT3	FLT4	FOXL2	FUBP1
GAS6	GATA3	GLI1	GNA11	GNAQ	GNAS	GSTP1	HAMP	HDAC2	HGF
HNF1A	HRAS	HSD3B1	IDH1	IDH2	IGF1R	IKZF1	IL6R	JAK1	JAK2
JAK3	KDM5C	KDM6A	KDR	KEAP1	KIT	KRAS	MAF	MAP2K1	MAP2K2

genes negative for small variants

MAP3K1	MAPK1	MAPK3	MAPKAPK5	MDM2	MDM4	MED12	MEN1	MET	MGMT
MLH1	MPL	MRE11A	MSH2	MSH6	MTHFR	MTOR	MUTYH	MYC	MYCN
MYOD1	NBN	NF1	NF2	NFE2L2	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS
NTRK1	NTRK2	NTRK3	PALB2	PBRM1	PDCD1LG2	PDGFRA	PDGFRB	PIK3CB	PIK3CD
PIK3CG	PIK3R1	PIM1	PLCB4	PLCG1	PMS2	POLD1	POLE	PPP2R1A	PTCH1
PTEN	PTPN11	RAD50	RAD51C	RAD51D	RAF1	RB1	RBM10	RECQL	RET
RHEB	RICTOR	RIT1	RNF43	ROS1	RPTOR	RRM1	SDHB	SDHC	SETD2
SF3B1	SMAD1	SMAD2	SMAD4	SMAD5	SMAD9	SMARCA4	SMARCB1	SMO	SOCS1
SPOP	STAG2	STAT3	STAT5A	STAT5B	STK11	SUFU	TERT-p	TGFB1	TGFB2
TGFB3	TGFBR1	TGFBR2	TNFAIP3	TNK1	TOP2A	TP53	TSC1	TSC2	TSHR
TYMS	VEGFA	VHL	WT1	XRCC1	YES1				

genes negative for fusions and structural variants

ALK	BRAF	EGFR	FGFR1	FGFR2	FGFR3	MET	RET	ROS1	NTRK1
NTRK2	ETV6-NTRK3								

genes negative for copy number variants (amplifications)

ABCB1	ABCC1	ABCC2	ABL1	ACVR1	ACVR1B	ACVR2A	ACVR2B	ACVRL1	ADAMTS1
ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9	ADAMTSL1	AKT1	AKT2	AKT3	ALK	AMER1
APC	APLNR	AR	ARAF	AREG	ARID1A	ARID1B	ARID2	ATM	ATR
ATRX	AURKA	AURKB	AXIN1	AXL	B2M	BAP1	BARD1	BCOR	BMP6
BMPR1A	BMPR1B	BNIP3	BRAF	BRCA1	BRCA2	BRIP1	BTK	BUB1B	CALR
CBL	CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK12
CDK4	CDK6	CDKN2A	CHEK1	CHEK2	CHFR	CHKA	CIC	CREBBP	CSF1R
CTLA4	CTNNB1	CYP19A1	CYP1A1	CYP2D6	CYP3A4	CYSLTR2	dCK	DDR2	DICER1
DNMT3A	EGFR	EMSY	EP300	EPCAM	EPHA5	EPHA7	ERBB2	ERBB3	ERBB4
ERCC1	ERCC2	ERCC3	ERRFI1	ESR1	ESR2	EWSR1	EZH2	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCM	FAT1	FBXW7	FCGR2A	FGD4
FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FLT3	FLT4	FOXL2	FUBP1
GAS6	GATA3	GLI1	GNA11	GNAQ	GNAS	GSTP1	HAMP	HDAC2	HGF
HNF1A	HRAS	HSD3B1	IDH1	IDH2	IGF1R	IKZF1	IL6R	JAK1	JAK2
JAK3	KDM5C	KDM6A	KDR	KEAP1	KIT	KRAS	MAF	MAP2K1	MAP2K2
MAP3K1	MAPK1	MAPK3	MAPKAPK5	MDM2	MDM4	MED12	MEN1	MET	MGMT
MLH1	MPL	MRE11A	MSH2	MSH6	MTHFR	MTOR	MUTYH	MYC	MYCN
MYOD1	NBN	NF1	NF2	NFE2L2	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS
NTRK1	NTRK2	NTRK3	PALB2	PBRM1	PDCD1LG2	PDGFRA	PDGFRB	PIK3CA	PIK3CB
PIK3CD	PIK3CG	PIK3R1	PIM1	PLCB4	PLCG1	PMS2	POLD1	POLE	PPP2R1A
PTCH1	PTEN	PTPN11	RAD50	RAD51C	RAD51D	RAF1	RB1	RBM10	RECQL
RET	RHEB	RICTOR	RIT1	RNF43	ROS1	RPTOR	RRM1	SDHB	SDHC
SETD2	SF3B1	SMAD1	SMAD2	SMAD4	SMAD5	SMAD9	SMARCA4	SMARCB1	SMO
SOCS1	SPOP	STAG2	STAT3	STAT5A	STAT5B	STK11	SUFU	TERT-p	TGFB1
TGFB2	TGFB3	TGFBR1	TGFBR2	TNFAIP3	TNK1	TOP2A	TP53	TSC1	TSC2
TSHR	TYMS	VEGFA	VHL	WT1	XRCC1	YES1			

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IHC thresholds

Biomarker	Negative	Not Significant	Positive
AR	≤1+ or ≤10%	Not applicable	≥1+ and ≥10%
PD-L1 (22C3) TILs	NA and 0%	Not applicable	≥1+ and ≥50%
PD-L1 (22C3) Tumor	NA and 0%	Not applicable	≥1+ and ≥50%
PD-L1 (SP142) IC	≤1+ and <1%	Not applicable	≥1+ and ≥1%
TP (TYMP)	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%

Performance

Biomarker	Sensitivity	Specificity
SNVs, Indels ≥ 7.5%:	>99%	>99%
SNVs, Indels ≥ 5%:	>97%	>99%
CNV:	>90%	>99%
Fusions:	>91%	>99%
IHC:	>94%	>94%

Limitations: Mutation calls may not be available from some regions due to pseudogenes or sequence context. Select IHCs may not be run if already performed within the last six months unless indicated in the notes section.

These tests were developed and the performance characteristics determined by Exact Sciences. NGS is performed by Exact Sciences on genomic DNA extracted from a formalin fixed paraffin-embedded tumor. **Immunohistochemistry: Detection:** IHC testing is done on formalin fixed, paraffin-embedded tissue (FFPE) utilizing the detection method of avidin-biotin free polymer is employed according to an optimized protocol. **Scoring:** HER2 testing meets the 2013 ASCO-CAP HER2 testing guidelines in breast cancer and results are reported using the ASCO/CAP scoring criteria as defined in the references below. For ER and PR, historical cutoffs for all non-breast tissues are followed. The following are antibody clones for each test: HER2 - CB11, ER - SP1, PR - PgR636. Note that these assays have not been validated on decalcified specimens. Controls: External controls are reviewed on all stains for appropriate positive and negative immunoreactivity and found to be satisfactory. If HER2 by FISH is run, it is currently performed and interpreted by PhenoPath at 551 N. 34th St., Seattle, WA 98103. If RNA Fusion testing is run, it is currently performed by PathGroup - Molecular Pathology Accessioning at 658 Grassmere Park, Suite 101, Nashville, TN 37211.

Pan-Cancer Tissue tests were developed and their performance characteristics determined by Exact Sciences. These tests have not been cleared or approved by the U.S. Food and Drug Administration. These tests are used for clinical purposes to guide patient care under the responsibility of the physician.

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Clinical trials

The clinical trials information provided with the potential biomarker were compiled from www.clinicaltrials.gov a service provided by the U.S. NIH. The presentation is for informational purposes only and may not include all relevant trials. Health care providers should employ their clinical judgment in interpreting this information for individual patients. Specific enrollment criteria for each clinical trial should be carefully reviewed as additional inclusion criteria may apply and the biomarker may be associated with contraindications or exclusion criteria. The attending physician may need to contact the clinical trial administrator to ensure the patient is a possible candidate for admission to a particular clinical trial.

NCCN compendium

This report includes information about therapeutic agents that appear to be associated with clinical benefit based on NCCN Compendium guidelines, relevance of tumor lineage, level of publishing evidence and strength of biomarker expression, as available, as reviewed and assessed by Exact Sciences. The agents are not ranked in order of potential or predicted efficacy. The finding of a biomarker expression does not necessarily indicate effectiveness or lack thereof. The agents identified may or may not be suitable for use with a particular patient and the report does not guarantee or suggest that any particular agent will be effective with the treatment of any particular condition.

Reimbursement and acknowledgment

Exact Sciences makes no representations or guarantee that an insurer, third party payor, or healthcare provider, whether private or governmental, will provide payment or reimbursement for the cost of tests performed. By accessing this report you agree that the analysis and associated report is owned by Exact Sciences and that you only have a limited right to use the information to potentially assist with the clinical treatment of the associated patient.

Pan-Cancer Tissue panel core components

Unless fewer tests are ordered on the requisition, every Pan-Cancer Tissue test run interrogates a wide panel of targets including the following clinically actionable genes for specific therapeutic interventions. Pan-Cancer Tissue tests are not intended to displace other specific standard of care tests for other gene targets. The BRCA1 and BRCA2 component is not intended to diagnose or identify a hereditary condition, and mutations detected may be somatic or germline in origin and are to be used primarily for individualized therapeutic purposes while appropriate genetic counseling and testing may be advisable.

Levels of evidence

U.S. Preventive Services Task Force Level of Evidence Rankings are summarized from: American journal of preventive medicine (2001), 20(3 Suppl), 21-35. Level of evidence doesn't necessarily indicate greater potential utility.

Level 1: Evidence from at least one properly designed randomized controlled trial.
Level II-1: Evidence from well-designed controlled trials without randomization.
Level II-2: Evidence from well-designed cohort or case- control analytic studies, preferably from more than one center or research group.
Level II-3: Evidence from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.
Different Tumor Type (DTT): Alteration in biomarker present, however published evidence of biomarker utility was in a tumor type different from patient's tumor type.

No warranty or guarantee

This report does not make any promise or guarantee that a particular drug or treatment regimen will be effective or helpful in the treatment of disease in any patient. This report also makes no promise or guarantee that a drug with a potential clinical benefit will in fact provide a clinical benefit or that a drug with potential lack of clinical benefit will in fact provide no clinical benefit. Exact Sciences expressly disclaims and makes no representation or warranties whatsoever relating, directly or indirectly, to this review of evidence or identified scientific literature, the conclusions drawn from it or any of the information set forth in this report that is derived from such review, including information and conclusions relating to therapeutic agents that are included or omitted from this report.

This assay has not been validated on decalcified tissues. Results should be interpreted with caution given the possibility of false negative results on decalcified specimens.

Treatment decisions

Treatment Decisions Reside with Treating Physician and Patient. The selection of any treatment or potential treatment suggested by a biomarker resides within the discretion and judgment of the treating physician and patient. Decisions on patient care should be based on the independent medical judgment of the treating physician based upon all available clinical information, according to the applicable standard of care and should not be based solely on the tests and information contained in this report.