Pan-Cancer Tissue

Date of Birth:	00/00/0000	Case/Specimen ID:	AA00-00000 A0	Turnaround:	3 business days
Pan-Cancer Tissue#:	OR000000000, PCDx-19-00000	Collection Site:	R breast	Tumor cells:	50%
Physician:	Dr. Smith	Collection Date:	00/00/0000	Specimen size:	8 mm^2
Facility:	Some Cancer Treatment Center	Received for testing:	00/00/0000	Requirement met:	Optimal

14 NCCN/FDA indications

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

Key Biomarker Findings

Pan cancer	Type specific
TMB: Low (8muts/mb)	ERBB2 CNV: Not Changed
MSI: Stable	ERBB2: Wildtype
NTRK fusion: Negative	ESR1: Wildtype
BRCA1: Wildtype	**PIK3CA: H1047R**
BRCA2: Wildtype	PD-L1 (SP142) IHC: Negative
PD-L1 (22C3) Tumor IHC: Negative	
PD-L1 (22C3) TILs IHC: Negative	

8 Additional Therapy Options

Bicalutamide	Capecitabine	Everolimus
Flutamide	Leuprolide	Medroxyprogesterone
Pazopanib + Everolimus	Sorafenib + carboplatin, paclitaxel	

Specimen

Tumor cells: 50%
Specimen size: 8 mm^2
Residual tissue: No

Ulcerated skin involved by infiltrative poorly differentiated ductal carcinoma with not only causes the ulceration but invaded into some adjacent skin

Gross Description: Xxxxxxxx xxxx Xxxxx Xxxxxx Xxxxxxxx Xxxxxxx Xxxtxx xx 0 Xxxxx xxxxxxx xx X00-0000 X0 (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx X00-0000 X0 (xxx XXXx-00-00000) xxxxtxxxxx xx xxxxxxxxx tx txx xxxxx xxxxx xxtxxxt xxxxx xx txx xxxxxxxxxxx xxxxxxxx xxtxxxxxx xxxxxt xxtx xxxxxxxx xxxxxxtxxx xxtx xx 00/00/0000. Xxxxx X00-0000 X0 xxxx xx xxxxxxxx.

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

4 IHCs

AR	3+	100%	Positive
PD-L1 (22C3) TILs	N/A	0%	Negative
PD-L1 (22C3) Tumor	CPS: 0		Negative
PD-L1 (SP142) IC	N/A	0%	Negative
TP	2+	70%	Positive

10 pathogenic genomic findings

Gene	Variant	Quantity	Gene	Variant	Quantity
CCND1	Amplification	2.03x	MYC	Amplification	2.55x
CDK4	Amplification	2.46x	NF2	Q125*	15%
MAP3K1	A240Cfs*61	26%	PDGFRA	V253	13%
MAP3K1	H848Qfs*15	28%	PIK3CA	H1047R	23%
MAPK3	Amplification	3.20x	SMAD4	Loss	0.59x

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	XXXXX X0000X	XXXX0 X000	XXT T000X XXXX Xxxx	XXX0 X00
XXXX0 X0000T XXXXX0	XXX0X0 X0000T	XXX0 Xxxx	XX X000X XXX0X0	XXXX0 X0000X
X0000X XXX x.0000-0000X>T	XXX00X x.000+0000X>X	XXXX0X Xxxx	T00 XXT0 X000	XXX T000X
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XXX00 Xxxx	XXXXX X0000X	XX000 X000X		XXXXX X00

22 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Abemaciclib	HR+, HER2 -	Yes	I	33,12
Alpelisib + Fulvestrant	PIK3CA mutation, HR + and HER2 -	Yes	I	1,20
Anastrozole + Fulvestrant	ER +, PR + and HER2 -	Yes	II-1	28,29

22 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Bicalutamide	AR +		II-3	17
Capecitabine	TP +		II-3	22
Everolimus	ER +		II-1	4,2
	PIK3CA mutation		DTT	23
	PR +		II-1	2
Exemestane	ER +	Yes	I	3,14
	PR +	Yes	I	3,14
Exemestane + Everolimus	ER +, PR + and HER2 -	Yes	II-1	19,35
Flutamide	AR +		DTT	13
Fulvestrant	ER +	Yes	II-1	11,37
	PR +	Yes	II-1	11,37
Fulvestrant+Everolimus	ER +, PR + and HER2 -	Yes	II-2	21
Letrozole	ER +	Yes	I	30,24
	PR +	Yes	I	30,24
	PIK3CA mutation, ER + and HER2 -		I	25
	PIK3CA mutation, PR + and HER2 -		I	25
Letrozole+ Fulvestrant	ER +, PR + and HER2 -	Yes	I	9
Leuprolide	AR +		DTT	15
Medroxyprogesterone	AR +		II-3	7,5
	ER +		DTT	39
	PR +		DTT	39
Megestrol	ER +	Yes	I	8,16
	PR +	Yes	I	8,16
Palbociclib	ER+, HER2 -	Yes	I	36
	PR + and HER2 -	Yes	I	36
Pazopanib + Everolimus	PIK3CA mutation, ER +, PR + and HER2 -		III	31
Ribociclib	ER+, HER2 -	Yes	I	18
	PR + and HER2 -	Yes	I	18
Sorafenib + carboplatin, paclitaxel	CCND1 Amplification		DTT	38
Tamoxifen+Everolimus	ER +, PR + and HER2 -	Yes	II-1	2
Toremifene	ER +	Yes	I	40,27
	PR +	Yes	I	40,27

4 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Anastrozole	CCND1 Amplification and ER +	26
	CCND1 Amplification and PR +	26
Cetuximab	PIK3CA mutation	10,34
Fluorouracil	SMAD4 Loss	6
Panitumumab	PIK3CA mutation	10,32

clinical notes

AR expression in breast cancer: Androgen receptor (AR) expression is determined using an anti-human AR monoclonal antibody AR441; if a minimum of 10% of tumor cell nuclei are immunoreactive, the tumor is considered positive for AR. The androgen receptor protein functions as a steroid-hormone activated transcription factor. Upon binding the hormone ligand, the receptor dissociates from accessory proteins, translocates into the nucleus, dimerizes, and then stimulates transcription of androgen responsive genes (RefSeq, Jan 2017). In hormone receptor positive breast cancer, the androgen receptor (AR) is an emerging prognostic marker and therapeutic target expressed in 60–80% of breast cancers (Kensler et al 2019 PMID: 30795773). In a meta-analysis of 13 studies (n = 5648 patients), tumor AR expression was associated with improved disease-free survival in multivariate analysis, irrespective of hormone receptor status (Bozovic-Spasojevic et al. 2017 PMID: 28151718). Although the current AR IHC at a 10% cutoff for total AR nuclear staining may identify those who would benefit from anti-

clinical notes

androgen therapy, it should be noted that this threshold has been associated with only a modest positive predictive value (PPV) of 30% (Kumar et al. 2017 DOI: 10.1200/PO.17.00075), which may restrict its clinical application.

AURKB in solid tumors: The aurora kinase B (AURKB) gene encodes a member of the aurora kinase subfamily of serine/threonine kinases. These kinases participate in the regulation of alignment and segregation of chromosomes during mitosis and meiosis through association with microtubules [provided by RefSeq, Sep 2015]. The AURKB gene may play an oncogenic role in a broad range of human malignancies by overexpression or gene amplification (Tang et al. 2017 PMID: 28147341, Yan et al. 2016 PMID: 27406026). Recent studies have identified additional functions of Aurora kinases during cancer development, which could suggest that Aurora kinase inhibitors may represent promising targets for future anticancer therapeutics (Yan et al. 2016 PMID: 27406026). Additional lines of evidence support a connection between Aurora kinases and DNA repair and apoptotic pathways (Liu et al. 2013 PMID: 23180582). These findings indicate that both AURKA and AURKB work together to guard against DNA damage, providing a rationale to study potential synergisms between small-molecule inhibitors against Aurora kinases and DNA-damaging agents (Ma and Poon 2020 PMID: 32738522).

CCND1 CNV gain/amplification in breast cancer: The protein encoded by this gene belongs to the highly conserved cyclin family that function as regulators of cyclin-dependent kinases (CDKs). This cyclin forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose activity is required for cell cycle G1/S transition. This protein has been shown to interact with tumor suppressor protein Rb and the expression of this gene is regulated positively by Rb. Mutations, amplification and overexpression of this gene, which alters cell cycle progression, are observed frequently in a variety of human cancers. [provided by RefSeq, Dec 2019]. CCND1 amplifications are observed in ~5-15% of all breast carcinoma patients (AACR Project GENIE Consortium PMID: 28572459; TCGA PanCancer Atlas PMID: 29625055; COSMIC: the Catalogue of Somatic Mutations in Cancer PMID: 30371878) and are associated with an increased risk of disease recurrence and poor prognosis (Lundgren et al. 2012 PMID: 22475046; Roy et al 2010 PMID: 19904758). In the TransATAC study, which evaluated 1,155 post-menopausal, hormone receptor positive breast cancer patients, CCND1 amplification predicted poor clinical outcome among patients treated with either anastrozole or tamoxifen (Lundgren et al. 2012 PMID: 22475046).

CDK4 CNV gain/amplification: cyclin-dependent kinase 4 amplification occurs in numerous adult malignancies, including breast carcinoma, lymphoma, melanoma, and sarcoma, most notably in >95% of well-differentiated and dedifferentiated liposarcomas. In addition, CDK4 is also amplified or overexpressed in pediatric tumor types, such as neuroblastoma. Recent development of a new generation of highly selective small molecule inhibitors targeting CDK4/6 has renewed attention to CDK4/6 inhibition. Three orally bioavailable, selective CDK4/6 inhibitors are approved, including abemaciclib, palbociclib, and ribociclib. Emerging evidence from select case reports suggest that CDK4 copy number gain/amplification may be associated with benefit from palbociclib, for example Dickson et al. 2013 PMID: 24795392.

HR positive, HER2 negative Breast Cancer: Hormone receptor positive breast cancer is defined as a tumor that demonstrates expression of either the estrogen or progesterone receptor or both, accounting for the majority of breast cancer cases diagnosed (Carey et al. 2006 PMID: 16757721). The treatments of choice in patients with hormone receptor-positive metastatic breast cancer (HR+ mBC) are endocrine therapies, including, but not limited to selective estrogen receptor modulators (SERM), aromatase inhibitors (AI), and selective estrogen receptor degraders (SERD) (Rozeboom et al. 2019 PMID 31911865). While most HR+ breast cancer may initially respond to endocrine treatment, 15–20% of tumors are intrinsically resistant to treatment, and another 30–40% acquire resistance to treatment over a period of many years (Anurag et al. 2018 PMID: 30555626). The resistance that develops in this population of patients may be due to interactions between the hormone receptors, growth factors, and downstream cell-signaling pathways (Lei et al. 2019 PMID: 31839155). Adjuvant chemotherapy may provide additional benefit to HR+ tumors, with decisions regarding the addition of chemotherapy to adjuvant endocrine therapy based on individualized patient and disease factors (Zeidman et al. 2020 PMID: 32740807; Foukakis et al. 2020, https://www.uptodate.com/contents/deciding-when-to-use-adjuvant-chemotherapy-for-hormone-receptor-positive-her2-negative-breast-cancer/).

MAP3K1: Originally described as oncosuppressor genes, preclinical data suggest that MAP3K1 has both tumorigenic and tumor suppressive functions depending on cell type and experimental condition. Transcriptomic analyses have revealed that MAP3K1 mutations associate with a profound deregulation of the MAPK pathway. Mitogen-activated protein kinase kinase kinase 1, E3 ubiquitin protein ligase (MAP3K1) is a gene that encodes a protein that functions as a serine/threonine kinase in multiple cell signaling cascades. Mitogen-activated protein kinase (MAPK) pathways regulate many cellular functions including cell proliferation, differentiation, migration and apoptosis. MAP3K1 may function as a driver in some cancer types (e.g., melanoma) and is inactivated in other types (e.g., luminal A breast cancer). Recent genome-wide association studies from large consortial studies have led to the discovery of novel breast cancer susceptibility loci in genic (including MAP3K1) and non-genic regions. Recent large-scale genomic studies have revealed that MAP3K1 copy number loss and somatic missense or nonsense mutations are observed in a significant number of different cancers. In breast cancer, MAP3K1 mutations occur almost uniquely in Luminal cancers. MAP3K1 mutations are also observed in HER2+ and triple-negative BC. The presence of MAP3K1 mutations may be tightly associated with an immune-unfavorable phenotype (Hendrickx et al. 2017: PMID: 28344865). MAP3K1 alterations in breast cancer are mutually exclusive with those of MAP2K4 and partially overlap with those of PIK3CA Future studies dissecting the role of involution as a determinant of breast cancer subtype and outcome with regard to MAP3K1 functioning are needed (Pham et al. 2013 PMID: 24386504).

MAPK3 CNV gain/amplification: The protein encoded by this gene is a member of the MAP kinase family. MAP kinases, also known as extracellular signal-regulated kinases (ERKs), act in a signaling cascade that regulates various cellular processes such as proliferation, differentiation, and cell cycle progression in response to a variety of extracellular signals. MAPK3 Amplification is present in 0.26% of AACR GENIE cases, with breast carcinoma, colorectal adenocarcinoma, non-small cell lung carcinoma, bladder carcinoma, and uterine corpus neoplasm having the greatest prevalence.

Microsatellite Instability Analysis [MSI] Result Stable (MSS): Cancers are classified as either displaying high-frequency microsatellite instability (MSI-H), lowfrequency 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

clinical notes

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).

MYC CNV gain/amplification in Breast Cancer: MYC is regulated at multiple levels, and the protein is a downstream effector of several signaling pathways. Although the relationship between amplification and overexpression is not clearly delineated, in breast cancer MYC amplification appears to be correlated with aggressive tumor phenotypes and poor clinical outcomes. MYC is a marker of proliferation and there is greater interest in evaluating MYC amplification as a biomarker to predict response in clinical trials, some of which may be listed in the appendix of this report.

NF2: The NF2 gene encodes merlin, also known as schwannomin. Merlin helps regulate several key signaling pathways that are important for controlling cell shape, cell growth, and cell adhesion. This protein functions as a tumor suppressor, preventing cells from growing and dividing too fast or in an uncontrolled way. Germline NF2 gene mutations cause neurofibromatosis type 2 (NF2). Somatic mutations in the NF2 gene are involved in the development of several types of tumors, both benign and cancerous. Loss or inactivation of the NF2 gene is often associated with the development of single (isolated) nervous system tumors, including meningiomas, ependymomas, and schwannomas. While these tumors are part of NF2 and schwannomatosis (described above), isolated tumors can develop in individuals who do not have these disorders. NF2 somatic mutations have also been found in multiple cancer types, including but not limited to mesothelioma, anaplastic thyroid cancer, breast cancers, endometrial and liver cancers, in patients not having constitutional NF2 mutations (Dunbar-Schroeder et al. 2014 PMID: 24393766).

PD-L1 (22C3) TILs: PD-L1 is an immune inhibitory receptor ligand that is expressed by immune cells, particularly T-cells and B-cells, as well as various types of tumor cells. Interaction of this ligand with its receptor inhibits T-cell activation and cytokine production. In tumor microenvironments, this interaction provides an immune escape for tumor cells through cytotoxic T-cell inactivation [provided by RefSeq, Sep 2015]. In breast cancer, the rate of PD-L1 positivity in TILs was 33% in a pooled meta-analysis. In the same analysis, PD-L1 expression in immune cells was associated with improved DFS and OS in TNBC (Matikas et al 2019 PMID: 31227501). Expression of PD-L1 (22C3) TILs is determined by evaluating the percentage of PD-L1 expressing tumor-infiltrating immune cells of any intensity. Currently, 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 PMID: 30345906). While the PD-L1 (SP142) antibody was used in the referenced study, PD-L1 (22C3) can be used when the specimen is insufficient for evaluation with PD-L1 (SP142). The predictive value of the PD-L1 clone 22C3 for nivolumab, atezolizumab, avelumab or durvalumab is currently unclear.

PD-L1 (22C3) Tumor negative expression in solid tumors without prescribed companion or complementary diagnostic: For the purpose of PD-L1 reporting, and in lieu of tissue-specific guidelines, oncotypeMAP identifies 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). A minimum of 100 viable tumor cells must be present in the PD-L1 stained slide for the specimen to be considered adequate for PD-L1 evaluation. The predictive value of the PD-L1 clone 22C3 for nivolumab, atezolizumab, avelumab or durvalumab is currently unclear. 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 who are PD-L1 negative and this benefit is observable across multiple tumor types and histologies (Patel & Kurzrock 2015 PMID 25695955; Shen and Zhao 2018, PMID 30201790). 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 and that the favorable overall survival achieved in this patient population 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) in breast cancer: PD-L1 is an immune inhibitory receptor ligand that is expressed by immune cells, particularly T-cells and B-cells, as well as various types of tumor cells. Interaction of this ligand with its receptor inhibits T-cell activation and cytokine production. In tumor microenvironments, this interaction provides an immune escape for tumor cells through cytotoxic T-cell inactivation [provided by RefSeq, Sep 2015]. In breast cancer, the rate of PD-L1 positivity in TILs was 33% in a pooled meta-analysis. In the same analysis, PD-L1 expression in immune cells was associated with improved DFS and OS in TNBC (Matikas et al 2019 PMID: 31227501).

PD-L1 (SP142) assay is a qualitative immunohistochemical assay intended for use in the assessment of the PD-L1 protein in triple-negative breast carcinoma (TNBC) tissue (PMA Number P160002 Supplement 009). Evaluation is based on the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity. 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) with PD-L1 stained tumor-infiltrating immune cells [TILs] of any intensity covering ≥ 1% of the tumor area (Schmid et al. 2018 PMID: 30345906). In patients whose tumors express PD-L1, median progression-free survival (PFS) was 7.4 months for patients receiving atezolizumab with paclitaxel protein-bound and 4.8 months for those receiving placebo with paclitaxel protein-bound (Schmid et al. 2018 PMID: 30345906).

PDGFRA: Platelet-derived growth factor (PDGF) receptors are receptor tyrosine kinases that are required for embryonal development. Two genes, PDGFRA and PDGFRB, encode the receptor a and b isoforms, which are highly homologous and share a common architecture. Activating point mutations in PDGFRA have been described in a small subset of patients with gastrointestinal stromal tumors (GIST) but somatic point mutations in PDGFRA have also been reported in a variety of cancers, including glioblastoma, melanoma, acute myeloid leukemia (AML), peripheral nerve sheath tumors and neuroendocrine carcinoma. Most mutations are located in the juxtamembrane domain or in the activation loop and are likely to disrupt the inhibited conformation of the kinase domain while stabilizing the active one. The most noted alteration is PDGFRA-D842V, which is resistant to imatinib, whereas juxtamembrane mutants are highly sensitive to this drug (Velghe et al. 2013 PUBMED 23752188).

clinical notes

PIK3CA c.3140A>G p.H1047R: A mutation detected in the Kinase Domain (exon 20) of PIK3CA was c.3140A>G p.H1047R. PIK3CA mutations identify patients who are less likely to benefit from anti-HER2 inhibition, especially trastuzumab, lapatinib alone or in combination. Results from the EMILIA Trial suggest that single-agent T-DM1 may be active in HER2-positive MBC with PIK3CA mutations, which is less sensitive to other standard HER2-directed therapies. 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.

PIK3CA: HR+, HER2 breast bancers with PIK3CA mutations may derive greater benefit from letrozole than tamoxifen; The Breast International Group (BIG) 1-98 trial randomized 8010 postmenopausal patients with hormone receptorpositive, operable, invasive BC to monotherapy with letrozole, tamoxifen, or a sequential strategy for 5 years and found that patients with tumors harboring kinase or helical domain PIK3CA mutations derived significantly greater benefit from letrozole over tamoxifen than patients whose tumors did not (Luen et al. 2018).

SMAD4 CNV loss: SMAD4 is involved in the regulation of cell proliferation, differentiation, migration, and apoptosis. Emerging data suggest a putative relationship between SMAD4 and immune evasion and underscore the clinical importance of SMAD4 as a potential prognostic biomarker. In clinical samples, SMAD4 loss has been associated with worse outcomes and correlates with resistance to chemotherapy.

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 +, 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		
CCND1 Amplification	NCT03454529	Simvastatin
The Effect of Simvastatin on Breast Cancer Cell Growth in Women With Stage I-II Breast Cancer		
CCND1 Amplification and PR +	NCT03344536	Fulvestrant | Debio 1347
A Study of Debio 1347 Plus Fulvestrant in Patients With Metastatic Breast Cancer		
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		

clinical trials

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

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 Endocrine Therapy, 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 -	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 -	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 -	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

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

clinical trials

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 -	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 -	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

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

T-VEC With Chemotherapy or Endocrine Therapy in Treating Participants With Metastatic, Unresectable, or Locoregionally 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]

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

Continued

clinical trials

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 + 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)		
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 ProlonglTamoxifen and Prolong
A Window of Opportunity Study of Pre-operative Endocrine Therapy With and Without Prolong in Postmenopausal Women With Early Stage Breast Hormone Receptor Positive (HR+) Human Epidermal Receptor 2 Negative (HER2-) Breast Cancer.		
PR + and HER2 -	NCT03939897	AbemaciclibICopanlisiblFulvestrant
Testing the Addition of Copanlisib to Usual Treatment (Fulvestrant and Abemaciclib) in Metastatic Breast Cancer		

multi-indication trials

CCND1 Amplification	NCT02896335	Palbociclib
Palbociclib In Progressive Brain Metastases		
CCND1 Amplification	NCT03310879	Abemaciclib
Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6		
CDK4 Amplification	NCT02693535	Palbociclib
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		
CDK4 Amplification	NCT02896335	Palbociclib
Palbociclib In Progressive Brain Metastases		

clinical trials

CDK4 Amplification	NCT03310879	Abemaciclib

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

CDK4 Amplification	NCT03237390	Gemcitabine l Ribociclib

Ribociclib and Gemcitabine Hydrochloride in Treating Patients With Advanced or Metastatic Solid Tumors

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 -	NCT04305834	Abemaciclib;

Abemaciclib Monotherapy in Treating Older Patients With Hormone Receptor Positive Metastatic 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 + and HER2 -	NCT03032406	Hydroxychloroquine;Everolimus;

CLEVER Pilot Trial: A Phase II Pilot Trial of HydroxyChLoroquine, EVErolimus or the Combination for Prevention of Recurrent Breast Cancer

ER + and HER2 -	NCT03616587	AZD9833;AZD9833 with palbociclib/everolimus

Study of AZD9833 Alone or in Combination in Women With Advanced Breast Cancer

ER + and HER2 -	NCT04568616	Letrozole 2.5mg;

Neoadjuvant ArOMatase Inhibitor Therapy for ER+ Breast Cancer (NAOMI)

ER +, PR + and HER2 +	NCT04553770	Anastrozole;

Trastuzumab Deruxtecan Alone or in Combination With Anastrozole for the Treatment of Early Stage HER2 Low, Hormone Receptor Positive Breast Cancer

ER +, PR + and HER2 -	NCT04052555	Berzosertib;

Testing the Addition of an Anti-cancer Drug, Berzosertib, 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)

ER +, PR + and HER2 -	NCT04563507	Letrozole 2.5Mg Tab;Palbociclib 125mg;

Combined Immunotherapies in Metastatic ER+ Breast Cancer

ER +, PR + and HER2 -	NCT04557449	PF-07220060;

Study to Test the Safety and Tolerability of PF-07220060 in Participants With Advance Solid Tumors

clinical trials

ER +, PR + and HER2 -	NCT04553133	PF-07104091 monotherapy;PF-07104091 + palbociclib;PF-07104091 + palbociclib + letrozole;
PF-07104091 as a Single Agent and in Combination Therapy		
ER +, PR + and HER2 -	NCT04305496	Fulvestrant;Capivasertib;Placebo;
Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2- Breast Cancer		
HER2 -	NCT03952325	Tesetaxel;Tesetaxel;Tesetaxel;Nivolumab;Pembrolizumab;Atezolizumab;Tesetaxel;
Tesetaxel Plus 3 Different PD-(L)1 Inhibitors in Patients With Triple-Negative MBC 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		
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		
MAP3K1 mutation	NCT02857270	LY3214996 | Midazolam | Abemaciclib | Nab-paclitaxel | Gemcitabine
A Study of LY3214996 Administered Alone or in Combination With Other Agents in Participants With Advanced/Metastatic Cancer		
MAPK3 Amplification	NCT03520075	ASTX029
Study of ASTX029 in Subjects With Advanced Solid Tumors		
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		
MYC Amplification	NCT02873975	LY2606368
A Study of LY2606368 (Prexasertib) in Patients With Solid Tumors With Replicative Stress or Homologous Repair Deficiency		
MYC Amplification	NCT03718091	M6620
M6620 (VX-970) in Selected Solid Tumors		
PD-L1 (SP142) IC -	NCT04468061	Sacituzumab Govitecan;Pembrolizumab;
Sacituzumab Govitecan +/- Pembrolizumab in Metastatic TNBC		
PDGFRA mutation	NCT02272998	Ponatinib
Ponatinib for Patients Whose Advanced Solid Tumor Cancer Has Activating Mutations Involving the Following Genes: FGFR1, FGFR2, FGFR3, FGFR4, RET, KIT.		
PDGFRA mutation	NCT02693535	Sunitinib
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		
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		
PIK3CA mutation	NCT04632992	Entrectinib;GDC-0077;Alectinib;Ipatasertib;Atezolizumab;Trastuzumab Emtansine;Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf;Tucatinib;Investigator's Choice of Chemotherapy;
A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response		
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 -	NCT04305834	Abemaciclib;
Abemaciclib Monotherapy in Treating Older Patients With Hormone Receptor Positive Metastatic Breast Cancer		
PR + and HER2 -	NCT04305496	Fulvestrant;Capivasertib;Placebo;
Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2- Breast Cancer		

clinical trials

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	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
MAPK1	MAPK3	MAPKAPK5	MDM2	MDM4	MED12	MEN1	MET	MGMT	MLH1
MPL	MRE11A	MSH2	MSH6	MTHFR	MTOR	MUTYH	MYC	MYCN	MYOD1
NBN	NF1	NFE2L2	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NTRK1	NTRK2
NTRK3	PALB2	PBRM1	PDCD1LG2	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	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK12	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

genes negative for copy number variants (amplifications)

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
MAPKAPK5	MDM2	MDM4	MED12	MEN1	MET	MGMT	MLH1	MPL	MRE11A
MSH2	MSH6	MTHFR	MTOR	MUTYH	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
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	CPS < 10	Not applicable	CPS ≥ 10
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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2. Hammond et al. (2010) Arch Pathol Lab Med. 134:48-72.
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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.