Paradigm

Patient Name
Jane Doe

Final Report Date
1/15/2020

Breast Cancer - Invasive

Paradigm Cancer Diagnostic (PCDx)

Date of Birth:	00/00/0000	Case/Specimen ID:	AA00-00000 A0	Turnaround:	3 business days
PCDx Case#:	PCDx-19-00000	Collection Site:	Lymph node	Tumor cells:	90%
Physician:	Dr. Smith	Collection Date:	00/00/0000	Specimen size:	180 mm^2
Facility:	Some Cancer Treatment Center	Received for testing:	00/00/0000	Requirement met:	Optimal

11 NCCN indications

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

High Interest

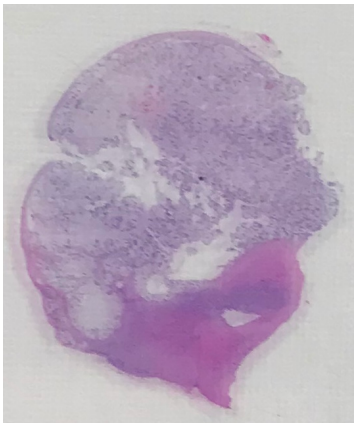
Pan cancer	Type specific
TMB: Low (2muts/mb)	ERBB2 CNV: Not Changed
MSI: Stable	ESR1 mutation: Wildtype
BRCA1: Wildtype	**PIK3CA mutation: H1047R**
BRCA2: Wildtype	
TRKpan: Negative	
PD-L1 (22C3) Tumor: Negative	
PD-L1 (22C3) TILs: Negative	

11 evidence-based therapy associations

Abiraterone	Bicalutamide	Capecitabine
Enzalutamide	Everolimus	Flutamide
Irinotecan	Letrozole	Medroxyprogesterone
Sorafenib	Topotecan	

For additional information or to set up an interactive online account please contact your sales representative or call 1-844-232-4719.

Specimen



Metastatic carcinoma

Tumor cells: 90%
Specimen size: 180 mm^2
Residual tissue: No

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

Pathologist has performed a comprehensive review of all records and material submitted. (2020-01-10)

6 IHCs

AR	3+	100%	Positive
CAIX	2+	30%	Positive
PD-L1 (22C3) TILs	N/A	0%	Negative
PD-L1 (22C3) Tumor	N/A	0%	Negative
TOPO1	3+	100%	Positive
TP	2+	100%	Positive
TRKpan	N/A	0%	Negative

5 salient genomic findings

Gene	Variant	Quantity	Gene	Variant	Quantity
ARID1A	Q1212*	5%	PIK3CA	H1047R	46%
ARID1A	c.4102-483_4102-473del p.?	38%	VEGFA	Amplification	2.55x
MDM4	Amplification	2.24x			

3 external results

Biomarker	Type	Value
ER	IHC	Pos
PR	IHC	Pos
HER2	IHC	Neg

The breast cancer predictive marker (ER, PR, HER2) interpretations in this PCDx report are provided courtesy of an extramural anatomic pathology report and/or provided by the clinical team completing the Paradigm 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 Paradigm.

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
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X0000X XXX x.0000-0000X>T	XXX00X x.000+0000X>X	XXXX0X Xxxx	T00 XXT0 X000	XXX T000X
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22 therapies with potential increased benefit

Therapeutic Option	Biomarkers	On NCCN	Level of evidence	References
Abemaciclib	HR + and HER2 -	Yes	I	35,9

Continued

22 therapies with potential increased benefit

Therapeutic Option	Biomarkers	On NCCN	Level of evidence	References
Abiraterone	AR +		DTT	11
Alpelisib + Fulvestrant	PIK3CA mutation, HR+, HER2 -	Yes	I	42,24
Anastrozole	ER +	Yes	I	10,23
	PR +	Yes	II-1	31,5
Bicalutamide	AR +		II-3	18
Capecitabine	TP +		II-3	25
Enzalutamide	AR +		DTT	12
Eribulin	HER2 -	Yes	II-3	15,38
Everolimus	PIK3CA mutation, HR+		DTT	27
Exemestane	ER +	Yes	I	1,14
Flutamide	AR +		DTT	13
Fulvestrant	ER +	Yes	II-1	8,39
Irinotecan	TOPO1 +		DTT	30,32
Letrozole	PIK3CA mutation, HR + and HER2 -		I	44
Medroxyprogesterone	AR +		II-3	3,43
Megestrol	PR +	Yes	I	4,17
Palbociclib	HR + and HER2 -	Yes	I	37
Ribociclib	HR + and HER2 -	Yes	I	21
Sorafenib	VEGFA Amplification		DTT	22
Tamoxifen	ER +	Yes	II-1	6,40
	PR +	Yes	II-1	6,40
Topotecan	TOPO1 +		DTT	28
Toremifene	ER +	Yes	I	41,29
	PR +	Yes	I	41,29

6 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Bevacizumab	CAIX +	20,33
Cetuximab	PIK3CA mutation	7,36
Doxorubicin	CAIX +	2
Epirubicin	CAIX +	16
Fluorouracil	CAIX +	19,26
Panitumumab	PIK3CA mutation	7,34

clinical notes

The breast cancer predictive marker (ER, PR, HER2) interpretations in this PCDx report are provided courtesy of an extramural anatomic pathology report and/or provided by the clinical team completing the Paradigm 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 Paradigm.

AR positivity 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

clinical notes

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 the Paradigm Registry.

ARID1A; As one of the primary members of SWI/SNF chromatin remodeling complexes, ARID1A contains frequent loss-of-function mutations in many types of cancers. ARID1A mutations are among the most frequently mutated epigenetic regulator genes across human malignancies, with mutations particularly common in clear cell ovarian, endometrial, colorectal, stomach, and bladder cancers. In breast cancer, ARID1A has been characterized as a key tumor-suppressor gene. Emerging preclinical data suggest that loss-of-function mutations in the tumor suppressor gene ARID1A disrupt DNA mismatch repair (MMR) and thereby potentially improving outcomes in treatment scenarios involving PD-1-targeting immune checkpoint inhibitors.

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.

MDM4 CNV gain, MDM4, a homolog of MDM2, is considered a key negative regulator of p53. Gene amplification of MDM4 has been identified in a variety of tumors and is considered to be potentially targetable. Emerging evidence suggests a role of MDM4 amplification in hyperprogression (HPD) after immunotherapy. Although the exact mechanism linking MDM2/4 amplification and HPD is unclear, MDM2/4 amplification may be a promising biomarker of HPD risk assessment and prognosis (Kato et al. 2018 PMID 28351930).

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 viable tumor cells showing partial or complete membrane staining at 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 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, patients with low(er) PD-L1 expression have also had meaningful responses and clinical benefit across multiple tumor types and histologies (Patel & Kurzrock 2015).

PIK3CA c.3140A>G p.H1047R; A mutation in the Kinase Domain (exon 20) of PIK3CA was detected (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.

HR+, HER2- Breast Cancers 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).

TMB - Tumor Mutation Burden TMB is defined as the total number of DNA mutations per megabase in a tumor sequence. TMB appears to have an evolving role as a predictive marker for immunotherapy treatment in various cancers, including melanoma, lung, and bladder cancer [1]. The threshold for TMB has not been clearly defined, and there remains no consensus for the optimal quantitative or qualitative threshold by cancer type [2]. For the purpose of TMB stratification, PCDx adopted the high (≥ 10 mutations per megabase) and low (< 10 mutations per megabase) TMB cutoffs based on the retrospective analysis of TMB in the

clinical notes

CheckMate 227 trial (Hellmann et al. 2018, PMID: 29658845). TMB may correlate with PFS but it is not prognostic for OS in lung cancer. TMB has not yet been investigated with respect to OS in prospective trials [3](see also Ramalingam webcast at AACR 2018). Some tumors possess high TMB as a consequence of a defective mismatch repair of DNA [4] and tumors with high TMB are often mismatch repair deficient [5]. Additionally, there appears to be a correlation between smoking status and TMB. POLE mutations are also associated with TMB. Paradigm will continue to evaluate/monitor the evidence including a standardized/ consensus driven TMB [6] as a predictive and prognostic marker for immunotherapy treatment. To develop additional information about the utility of TMB, please consider enrolling in the Paradigm Registry.

[1] TMB is believed to be a surrogate marker for immunogenicity and the likelihood of clinical response or benefit from immunotherapy.
[2] While no clear threshold or consensus has been identified (high vs low). Positive results for immunotherapy benefit have been reported by various studies at 10-20 mutations per megabase.
[3] All patients with high TMB should be considered candidates for a trial of immunotherapy. Low/intermediate TMB does not rule out a response to immunotherapy, nor should it preclude the patient pursuing a clinical trial of immunotherapy.
[4] While defective MMR is clearly associated with TMB, not all MMRD tumors have elevated TMB, probably reflecting that loss of MMR proficiency is a recent or branching event in the tumor rather than a truncal or founding event.
[5] High TMB is also reported in some cancers with intact MMR, notably those with POLE mutations. These patients also appear to have robust responses to checkpoint immunotherapy.
[6] TMB in context: the presence of other immune checkpoints, including TIM3, LAG3, PD-L2, IDO, and the composition of the tumor microenvironment (MDSC, FOX3P+ TIL), B2M loss, and aberrations within particular intracellular pathways (i.e. PTEN loss, IFN gamma defects) are also known to play key roles in the resistance/response to immunotherapy.

TRKpan: IHC negative – VITRAKVI (larotrectinib) and ROZLYTREK (entrectinib) are indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation. Activating NTRK fusions are highly targetable and define certain tumors. However, with the exception of select tumor types, rearrangement of NTRK oncogenes is of such low prevalence (Amatu et al. 2016 PMID 27843590), that TRKpan IHC has emerged as a time- and tissue-efficient screen for NTRK fusions, particularly in driver-negative advanced malignancies. Immunohistochemical analysis for TRKpan confers several benefits such as quick turnaround time, limited material required, only transcribed and translated fusions are detected rather than all DNA-level rearrangements, high sensitivity and specificity, and lower cost. TRKpan IHC targets a conserved epitope in the kinase domain of all three TRK proteins and is a useful tool to detect expression of TRKA, B and C in solid tumors, because fusion of NTRK1-3 with various upstream partners leads to aberrant protein expression and unchecked proliferation. A TRKpan negative result by IHC indicates that the TRK signaling pathway is likely not constitutively activated and, therefore, no follow-up testing is necessary.

VEGFA CNV gain; Vascular endothelial growth factor-A (VEGFA) is a growth factor that promotes new blood vessel and endothelial cell growth. Increases in VEGFA copy number induce endothelial cell proliferation, promote cell migration, inhibit apoptosis and induce permeabilization of blood vessels. This gene is upregulated in many known tumors and its expression is correlated with tumor stage and progression. While VEGFA amplification may be a poor prognostic indicator for tumor-free survival, tumors with this amplification demonstrate sensitivity to treatment with the multi-kinase inhibitor sorafenib.

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 Talazoparib in BRCA1 +BRCA2 Wild-Type &Triple-Neg /HER2-Negative Breast Cancer /SolidTumors		
ER +	NCT01042379	AMG 386 | Ganitumab | MK-2206 | T-DM1 | Ganetespib | ABT-888 | Neratinib | PLX3397 | Pembrolizumab
I-SPY 2 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		

clinical trials

ER +	NCT03294694	Ribociclib | PDR001 | Fulvestrant

Ribociclib + PDR001 in Breast Cancer and Ovarian Cancer

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 -	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, 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 -	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

clinical trials

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

Study of a New Drug Combination, Copanlisib and Fulvestrant, in Postmenopausal Women With 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: ASPIRE Bosutinib

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 - Dose-Finding Study

ER +, HER2 - and PIK3CA MUT	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 2 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

clinical trials

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 Paclitaxel 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 MUT	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 MUT, 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 2 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)		
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: ASPIRE Bosutinib		
PR + and HER2 -	NCT03901339	SacituzumabGovitecanlEribulinlCapecitabinelGemcitabinelVinorelbine
Study of IMMU-132 in HR+/HER2- MBC (TROPICS-02)		

clinical trials

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	AbemaciclibICopanlisibIFulvestrant

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

multi-indication trials

ARID1A MUT	NCT02576444	AZD2281 I AZD5363 I AZD1775 I AZD2014

OLAParib COmbinations

ARID1A MUT	NCT03207347	Niraparib

A Trial of Niraparib in BAP1 and Other DNA Damage Response (DDR) Deficient Neoplasms (UF-STO-ETI-001)

ARID1A MUT	NCT03297424	PLX2853

A Study of PLX2853 in Advanced Malignancies.

ARID1A MUT	NCT03718091	M6620

M6620 (VX-970) in Selected Solid Tumors

ARID1A MUT	NCT03842228	Copanlisib I Durvalumab I Olaparib

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

MDM4 Gain	NCT01877382	DS-3032

A Phase 1 Multiple Ascending Dose Study of DS-3032b, an Oral Murine Double Minute 2 (MDM2) Inhibitor, in Subjects With Advanced Solid Tumors or Lymphomas

MSI Stable	NCT03711058	Copanlisib I 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

NRAS WT, KRAS WT and 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

PIK3CA MUT	NCT02576444	AZD2281 I AZD5363 I AZD1775 I AZD2014

OLAParib COmbinations

PIK3CA MUT	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 MUT	NCT03842228	Copanlisib I Durvalumab I Olaparib

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TP53 WT	NCT01877382	DS-3032

A Phase 1 Multiple Ascending Dose Study of DS-3032b, an Oral Murine Double Minute 2 (MDM2) Inhibitor, 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 I Paclitaxel

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

genes negative for small variants

ABCB1	ABCC1	ABCC2	ABL1	ADAMTS1	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9	ADAMTSL1
AKT1	AKT2	AKT3	ALK	AMER1	APC	APLNR	AR	ARAF	AREG
ARID1B	ARID2	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXL	B2M
BAP1	BARD1	BCOR	BNIP3	BRAF	BRCA1	BRCA2	BRIP1	BTK	BUB1B
CBL	CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK4
CDK6	CDK12	CDKN2A	CHEK1	CHEK2	CHFR	CHKA	CIC	CREBBP	CSF1R
CTLA4	CTNNB1	CYP1A1	CYP2D6	CYP3A4	CYP19A1	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

Continued

genes negative for small variants

GATA3	GLI1	GNA11	GNAQ	GNAS	GSTP1	HDAC2	HGF	HNF1A	HRAS
HSD3B1	IDH1	IDH2	IGF1R	IKZF1	JAK1	JAK2	JAK3	KDM5C	KDM6A
KDR	KEAP1	KIT	KRAS	MAF	MAP2K1	MAP2K2	MAP3K1	MAPKAPK5	MAPK1
MAPK3	MDM2	MDM4	MED12	MEN1	MET	MGMT	MLH1	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	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	SMAD2	SMAD4	SMARCA4	SMARCB1
SMO	SOCS1	SPOP	STAG2	STAT3	STK11	SUFU	TERT-p	TGFBR2	TNFAIP3
TOP2A	TP53	TYMS	TSC1	TSC2	TSHR	VEGFA	VHL	WT1	YES1
XRCC1									

genes negative for copy number variants (amplifications)

ABCB1	ABCC1	ABCC2	ABL1	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	BNIP3	BRAF	BRCA1	BRCA2	BRIP1	BTK
BUB1B	CBL	CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1
CDK4	CDK6	CDK12	CDKN2A	CHEK1	CHEK2	CHFR	CHKA	CIC	CREBBP
CSF1R	CTLA4	CTNNB1	CYP1A1	CYP2D6	CYP3A4	CYP19A1	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	GATA3	GLI1	GNA11	GNAQ	GNAS	GSTP1	HDAC2	HGF	HNF1A
HRAS	HSD3B1	IDH1	IDH2	IGF1R	IKZF1	JAK1	JAK2	JAK3	KDM5C
KDM6A	KDR	KEAP1	KIT	KRAS	MAF	MAP2K1	MAP2K2	MAP3K1	MAPKAPK5
MAPK1	MAPK3	MDM2	MED12	MEN1	MET	MGMT	MLH1	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	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	SMAD2	SMAD4	SMARCA4
SMARCB1	SMO	SOCS1	SPOP	STAG2	STAT3	STK11	SUFU	TERT-p	TGFBR2
TNFAIP3	TOP2A	TP53	TYMS	TSC1	TSC2	TSHR	VHL	WT1	YES1
XRCC1									

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IHC thresholds

Biomarker	Negative	Not Significant	Positive
AR	≤1+ or ≤10%	Not applicable	≥1+ and ≥10%
CA IX	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
PD-L1 (22C3) TILs	NA and 0%	Not applicable	≥1+ and ≥50%
PD-L1 (22C3) Tumor	NA and 0%	Not applicable	≥1+ and ≥50%
TOP1	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%

IHC thresholds

Biomarker	Negative	Not Significant	Positive
TP (TYMP)	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
TRKpan	≤1+ or <10%	Not applicable	≥1+ and ≥10%

Performance

Biomarker	Sensitivity	Specificity
SNV, ins, del up to 40bp:		
≥7.5% allele frequency	>99%	>99%
≥5.0% allele frequency	>97%	>99%
Amplifications >5 fold	>90%	>99%
Immunohistochemistry	>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 Paradigm. NGS is performed by Paradigm 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 - EP3, 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 ROS1 by FISH is run, it is currently performed and interpreted by PhenoPath at 551 N. 34th St., Seattle, WA 98103. Fusion testing may be performed by PathGroup - Molecular Pathology Accessioning at 658 Grassmere Park, Suite 101, Nashville, TN 37211.

PCDx tests were developed and their performance characteristics determined by Paradigm Diagnostics, Inc. 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.

1. Wolff et al. (2013) J Clin Oncol. 31:3997-4013.
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 Paradigm. 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

Paradigm 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 Paradigm and that you only have a limited right to use the information to potentially assist with the clinical treatment of the associated patient.

PCDx panel core components

Unless fewer tests are ordered on the requisition, every PCDx test run interrogates a wide panel of targets including the following clinically actionable genes for specific therapeutic interventions. PCDx is 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. Paradigm 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.