Paradigm

Patient Name
John Doe

Final Report Date
4/15/2019

Non-Small Cell Lung Cancer (NSCLC)

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:	120 mm^2
Facility:	Some Cancer Treatment Center	Received for testing:	00/00/0000	Requirement met:	Optimal

1 actionable genomic finding

TP53 G245A

Additional Findings: ALK Wildtype, **BRAF Wildtype**, **EGFR Wildtype**, ERBB2 Wildtype, **KRAS Wildtype**, MET Not Amplified, MYC Not Amplified

6 IHCs

ALK	**Positive**	PDL1:TILs	Low
PDL1:Tumor	High	PTEN	Positive
ROS1	Negative	TRKpan	Negative
hENT1	**Positive**		

Immunotherapy TMB: Low (1 muts/mb) MSI: Stable PD-L1: High (TPS: 90)

8 therapies with potential increased benefit

Alectinib*	**ALK**
Ceritinib*	**ALK**
Crizotinib*	**ALK**
Docetaxel*	**EGFR (ERBB1)**
Gemcitabine*	**hENT1**
Cetuximab	BRAF, KRAS
Everolimus	KRAS
Panitumumab	BRAF, KRAS

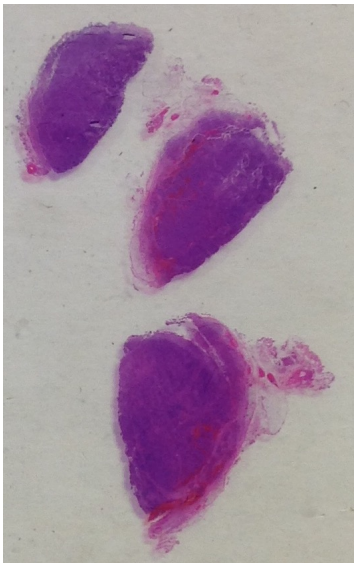
6 therapies with potential reduced benefit

Afatinib	EGFR (ERBB1)
Dabrafenib	BRAF
Erlotinib	EGFR (ERBB1)
Gefitinib	EGFR (ERBB1)
Trametinib	BRAF
Vemurafenib	BRAF

* Indicates associations supported by the highest level of evidence

For additional information or to set up an interactive online account please contact your sales representative or call 1-888-232-4719.

Specimen



Tumor cells: 90 %
Specimen size: 120 mm²
Residual tissue: Yes

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Xxxxx Xxxxxxxtxxx: Xxxxxxxx xxxx Xxtxxxxxx - Xxxxtxx Xxxxxxxx Xxxxxtxx xx 0 Xxxxx xxxxxxx xx XX00-0000 0 (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx XX00-0000 0 (xxx XXXx-00-00000) xxxxtxxxxx xx xxxxxxxxx tx txx xxxxx xxxxx xxtxxxt xxxxx xx txx xxxxxxxxxxxx xxxxxxxx xxtxxxxxx xxxxxt xxtx xxxxxxxx xxxxxxtxxx xxtx xx 0/0/0000. Xxxxx XX00-0000 0 xxxx xx xxxxxxxx.

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6 IHCs

ALK	3+	90%	Positive
PDL1:TILs	1+	1-4%	Low
PDL1:Tumor	TPS:	90	High
PTEN	3+	100%	Positive
ROS1	N/A	0%	Negative
TRKpan	N/A	0%	Negative
hENT1	2+	90%	Positive

1 actionable genomic finding

Gene	Variant	Quantity
TP53	G245A	33%

Genes with indeterminate findings: AREG, GSTT1, PMS2

115 genomic findings of unknown significance

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

XXXX0 X000	XXXX0 X0000X	XXXXX X0000X	XXX0 x.000-0X>T	XTXX0 x.0000+0000X>X
XXXX0 X0000	XXXX0 x.*000X>X	XXXXX x.0000-00T>X	XXX0 x.0000-0X>T	XXXXXX X000X
XXXX0 x.0000-00T>X	XXXX0 x.00+00_00+00xxx	XXXXX x.*00X>X	XXX X000	XXXXXX x.000-0X>X
XXXX0 X0000X	XXX0 X000	XXXXX x.0000+000T>X	XXX X00	XXXXXX X000X
XXXXTX00 x.0000+0X>X	XXX0 T000	XXXXX x.000+00X>T	XXT X000	XXX0XX x.0000+00_0000+00xxx
XXXXTX00 X0000X	XXXX X000X	XXXXX X000	XXX0X0 X000X	XXX0XX X000
XXXXTX00 X000X	XXX00X0 x.*0000X>T	XXXXX X00X	XXX00 x.000-00X>X	XXXX0 x.000+0T>X
XXXXTX0 X000	XXX0X0 X00T	XXXXX0 X000	XXX00 x.0000-00T>X	XXXX0 x.000-00X>X
XXXXTX0 T000	XXX0X0 X000X	XXXXX x.0000-00_0000-00xxx	XXX00 X000	XXXX0 x.0000-0X>T
XXX X0000	XXX0X0 X000X	XXXXX X000X	XXT X000T	XXXX0 x.0000-00X>X
XXX X0000	XXXXTX0 T00	XXXXX X00X	XXT x.0000+00X>X	XXXX0 X0000T
XXX x.0000-00_0000-00xxx	XXXT0X X000	XXT0 X000X	XXXT x.00+00X>T	XXXX0 x.000+00X>T
XXXX0X x.*00X>T	XXXX x.0000-000X>T	XXXX0 x.000-0000X>T	XXX0 x.000-00X>T	XXXX x.0000+00X>T
XXXX0X X000	XXXX x.0000+00X>T	XXX0 X000	XXX00X X000	XTXX0 X0000
XXXX0X X000X	XXXX X000	XXXX0 x.000-00X>X	XTXX x.0000-00X>X	XXX00 X000X
XXXX0X X0000X	XX000 x.0000-00X>X	XXT0 x.000-0X>X	XTXX x.0000+00X>X	XXT0 X000
XTX X0000X	XX000 x.0000+00X>X	XXT0 X0000X	XXX x.0000+0X>T	XXX00 x.0000-00X>T
XTX X0000T	XXXX0 X000	XXX0 x.*00T>X	XXX X000X	XXTXX x.0000+00X>X
XTX x.0000+0000X>X	XXXX0 x.0000+00X>X	XXX0X X00	XXTXX0 X0000X	XXXX x.00+00_00+00xxx
XTX X0000X	XXXX0 x.-0-000T>X	XXX0X X000X	XXTXX0 X000	XXXX0 X000
XTX X0000X	XXXX0 x.0000-0X>X	XXX0X X000X	XXTXX0 X0000X	TXX0 X0000X
XTX X000	XXXX0 x.0000+0X>X	XXX0X x.0000-000xxx	XTXX0 T000X	TXXX x.000-0000X>X
XXXX0 X000X	XXXX0 x.00+00X>T	XXX0 x.000-0T>X	XTXX0 X000	XXXX0 T000X

8 therapies with potential increased benefit

Therapeutic Option	On NCCN	Indicating biomarkers	Level of evidence	References
Alectinib		ALK Positive	II-3	20
Ceritinib		ALK Positive	I	18
Cetuximab		BRAF Wild Type KRAS Wild Type	DTT DTT	15,3 16,4
Crizotinib		ALK Positive	I	23,22
Docetaxel		EGFR (ERBB1) Wild Type	I	8
Everolimus		KRAS Wild Type	DTT	12,5
Gemcitabine		hENT1 Positive	II-3	13
Panitumumab		BRAF Wild Type KRAS Wild Type	DTT DTT	1 16,4

6 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Afatinib	EGFR (ERBB1) Wild Type	14,17
Dabrafenib	BRAF Wild Type	9,11
Erlotinib	EGFR (ERBB1) Wild Type	21,7
Gefitinib	EGFR (ERBB1) Wild Type	21,7
Trametinib	BRAF Wild Type	6,10
Vemurafenib	BRAF Wild Type	2,19

clinical notes

According to the Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors (Kalemkerian et al. 2018), IHC is an equivalent alternative to FISH for ALK testing, as emerging evidence suggests that ALK immunopositivity may also serve as a predictive marker for ALK inhibitor response. In a recent study where ALK IHC and FISH tests were compared, dichotomous ALK-IHC (either positive or negative) was found to be superior to ALK-FISH on small biopsies and FNA to predict tumor response and survival to anti-ALK therapy for advanced NSCLC patients. Of note, while all ALK-IHC-positive patients responded to crizotinib, no tumor response was observed in ALK-FISH-positive but ALK-IHC-negative patients (van der Wekken et al. 2017).

TP53; the predicted effect of this mutation is pathogenic/likely pathogenic. Research has shown that mutations in the TP53 gene are frequent in almost all types of cancers, and are present in approximately 50% of all NSCLC. Numerous of these mutations may be due to smoking history and most clinical studies suggest that

clinical notes

NSCLC with TP53 alterations carries a worse prognosis and may be relatively more resistant to chemotherapy and radiation. Multiple clinical trials are currently enrolling patients with TP53 alterations for investigational agents.

TRKpan: IHC negative – VITRAKVI (Larotrectinib) is 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.

PD-L1 (22C3) expression is determined by using a Tumor Proportion Score (TPS), which is 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. Pembrolizumab (KEYTRUDA) is indicated for the treatment of: (1) Patients with metastatic NSCLC whose tumors have high PD-L1 expression [TPS ≥50%] with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC. (2) Patients with metastatic NSCLC whose tumors express PD-L1 [TPS ≥1%], with disease progression on or after platinum-containing chemotherapy. The predictive value of the PD-L1 clone 22C3 for nivolumab, atezolizumab, avelumab or durvalumab is currently unclear.

PD-L1 (22C3) expression on TILs is determined by evaluating 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). Please note that for PD-L1 (22C3) TILs, the referenced studies utilize a prototype immunohistochemical assay with a proprietary antibody and cutoff.

Cetuximab is on Compendium for NSCLC. However, the NCCN specifies that cetuximab may be considered in combination with afatinib as subsequent therapy for metastatic disease in patients with a known sensitizing EGFR mutation who are T790M negative, have progressed on EGFR tyrosine kinase inhibitor therapy, and have multiple symptomatic systemic lesions.

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 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.

Microsatellite Instability Analysis (MSI): 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).

clinical trials

in tumor type

ALK	NCT02321501	Ceritinib (LDK378) | Ceritinib (LDK378) | Everolimus

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

ALK	NCT00585195	PF-02341066 | Rifampin | Ketoconazole

A Study Of Oral PF-02341066, A c-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer

ALK	NCT01625234	X-396

Phase 1 Safety Study of X-396, an Oral ALK Inhibitor, in Patients With Advanced Solid Tumors

ALK	NCT02521051	Alectinib | Bevacizumab

Phase I/II Trial of Alectinib and Bevacizumab in Patients With Advanced, Anaplastic Lymphoma Kinase (ALK)-Positive, Non-Small Cell Lung Cancer

ALK	NCT02513667	Ceritinib

Ceritinib in Combination With Stereotactic Ablative Radiation Metastatic Lung Adenocarcinoma

ALK	NCT03052608	Lorlatinib | Crizotinib

A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC

ALK	NCT02927340	Lorlatinib

A Study of Lorlatinib in Advanced ALK and ROS1 Rearranged Lung Cancer With CNS Metastasis in the Absence of Measurable Extracranial Lesions

ALK	NCT03088930	Crizotinib

Evaluating Crizotinib in the Neoadjuvant Setting in Patients With Non-small Cell Lung Cancer

ALK	NCT02706626	Brigatinib

Trial of Brigatinib After Treatment With Second-Generation ALK Inhibitors

KRAS	NCT02047344	Antroquinonol

Efficacy, Safety and Pharmacokinetics Study of Antroquinonol to Treat NSCLC

PDL1:Tumor	NCT02716038	MPDL3280A | Carboplatin | Nab-Paclitaxel

Neoadjuvant MPDL3280A, Nab-paclitaxel and Carboplatin (MAC) in NSCLC

PDL1:Tumor	NCT02655822	CPI-444 | CPI-444 + Atezolizumab

Phase 1/1b Study to Evaluate the Safety and Tolerability of CPI-444 Alone and in Combination With Atezolizumab in Advanced Cancers

PDL1:Tumor	NCT02785952	Ipilimumab | Nivolumab

Lung-MAP: Nivolumab With or Without Ipilimumab as Second-Line Therapy in Treating Patients With Recurrent Stage IV Squamous Cell Lung Cancer and No Matching Biomarkers

PDL1:Tumor	NCT02595944	Nivolumab

Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer

PDL1:Tumor	NCT02273375	MEDI4736 | Placebo

Double Blind Placebo Controlled Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC

PDL1:Tumor	NCT02888743	Durvalumab | Radiation | Tremelimumab

Durvalumab and Tremelimumab With or Without High or Low-Dose Radiation Therapy in Treating Patients With Metastatic Colorectal or Non-small Cell Lung Cancer

PDL1:Tumor	NCT03164616	Durvalumab | Tremelimumab | Chemotherapy

Study of Durvalumab + Tremelimumab With Chemotherapy or Durvalumab With Chemotherapy or Chemotherapy Alone for Patients With Lung Cancer (POSEIDON).

PDL1:Tumor	NCT03330405	Avelumab | Talazoparib | Avelumab | Talazoparib

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

PDL1:Tumor	NCT03409458	PT-112 | Avelumab

A Dose Escalation and Confirmation Study of PT-112 in Advanced Solid Tumors in Combination With Avelumab

PDL1:Tumor	NCT03455556	Anetumab Ravtansine | Atezolizumab

Anetumab Ravtansine and Atezolizumab in Treating Participants With Advanced Non-small Cell Lung Cancer

PDL1:Tumor	NCT03520686	ALT-803 + Pembrolizumab | Pembrolizumab

QUILT-2.023: A Study of ALT-803, a Fusion Protein Activator of Natural Killer and T-Cells, in Combination With Pembrolizumab vs Pembrolizumab Alone as First-Line Treatment for Patients With Metastatic NSCLC.

PDL1:Tumor	NCT03523702	Pembrolizumab + RT | Chemotherapy + RT

The Selective Personalized Radio-Immunotherapy for Locally Advanced NSCLC Trial.

clinical trials

PDL1:Tumor	NCT03563716	Atezolizumab | MTIG7192A | Placebo

A Study of MTIG7192A in Combination With Atezolizumab in Chemotherapy-Naïve Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer

PDL1:Tumor	NCT03583086	VEGFR/PDGFR Dual Kinase Inhibitor X-82 | Nivolumab

H I/II Eval Safety & Prelim Activity Nivolumab Comb W/Vorolanib Pts W/Refractory Thoracic Tumors

PDL1:Tumor	NCT03631706	M7824 | Pembrolizumab

M7824 Versus Pembrolizumab as a First-line (1L) Treatment in Participants With Programmed Death-ligand 1 (PD-L1) Expressing Advanced Non-small Cell Lung Cancer (NSCLC)

PDL1:Tumor	NCT03679767	INCMGA00012

A Study of INCMGA00012 in Participants With Selected Solid Tumors (POD1UM-203)

PDL1:Tumor	NCT03735628	Copanlisib | Nivolumab

An Study to Evaluate the Safety and Efficacy of Copanlisib in Combination With Nivolumab in Patients With Advanced Solid Tumors

PDL1:Tumor	NCT03800134	Durvalumab | Carboplatin/Paclitaxel | Cisplatin/Gemcitabine | Pemetrexed/Cisplatin | Pemetrexed/Carboplatin

A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer

PDL1:Tumor	NCT03829332	Biological: Pembrolizumab | Lenvatinib

Efficacy and Safety Study of Pembrolizumab (MK-3475) With or Without Lenvatinib (MK-7902/E7080) in Adults With Programmed Cell Death-Ligand 1 (PD-L1)-Positive Treatment-naïve Non-small Cell Lung Cancer (NSCLC)(MK-7902-007/E7080-G000-314/LEAP-007)

PDL1:Tumor	NCT03848611	CM082 + JS001

Phase II Study of the Combination of CM082 With JS001 in Patients With Advanced NSCLC.

multi-indication trials

ALK	NCT02584933	Ceritinib

Roll-over Study to Allow Access to Certinib (LDK378) for Patients Who Are on Ceritinib Treatment in a Novartis-sponsored Study

MSI	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

PDL1:Tumor	NCT02614456	Interferon-gamma and Nivolumab

Combination of Interferon-gamma and Nivolumab for Advanced Solid Tumors

PDL1:Tumor	NCT02608268	MBG453 | PDR001

Safety and Efficacy of MBG453 as Single Agent and in Combination With PDR001 in Patients With Advanced Malignancies

PDL1:Tumor	NCT03474640	TAB001, Recombinant Humanized anti-PD-1 Monoclonal Antibody

Safety, Tolerability and Pharmacokinetics of an Anti-PD-1 Monoclonal Antibody in Subjects With Advanced Malignancies

PDL1:Tumor	NCT03729596	MGC018 | MGA012

MGC018 With or Without MGA012 in Advanced Solid Tumors

TP53	NCT02935907	APG-115

APG-115 in Patients With Advanced Solid Tumors or Lymphomas

TP53	NCT03560882	Atorvastatin

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

genes negative for small variants

ABCB1	AURKB	CDA	DDR2	FGF4	IGF1R	MEN1	PBRM1	RET	STK11
ABL1	AXIN1	CDC73	DICER1	FGFR1	IKZF1	MSH2	PDCD1LG2	RHEB	SUFU
ADAMTS1	AXL	CDH1	EPCAM	FGFR3	JAK1	MSH6	PDGFRB	RICTOR	TERT-p
ADAMTS6	B2M	CDK6	EPHA7	FGFR4	JAK2	MTHFR	PIK3CB	ROS1	TGFBR2
ADAMTSL1	BAP1	CDK12	ERBB2	FOXL2	KDM5C	MUTYH	PIK3CG	RRM1	TNFAIP3
AKT1	BCOR	CDKN2A	ERBB3	FUBP1	KDM6A	MYC	PIK3R1	SDHB	TOP2A
AKT2	BNIP3	CHEK1	ERRFI1	GATA3	KEAP1	MYCN	PLCB4	SETD2	TYMS
AKT3	BRAF	CHEK2	ESR1	GNA11	KRAS	MYOD1	PPP2R1A	SF3B1	TSC1
AMER1	BRCA1	CHKA	ESR2	GNAQ	MAF	NF1	PTEN	SMAD4	VEGFA
APC	BRIP1	CIC	EWSR1	GNAS	MAP2K1	NF2	PTPN11	SMARCA4	VHL
APLNR	BTK	CREBBP	EZH2	GSTP1	MAP3K1	NFE2L2	RAD51C	SMARCB1	WT1
AR	BUB1B	CSF1R	FAM175A	HDAC2	MAPKAPK5	NOTCH1	RAD51D	SMO	YES1

Continued

genes negative for small variants

ARAF	CBL	CTLA4	FANCE	HGF	MAPK1	NPM1	RAF1	SOCS1
ARID2	CCND2	CTNNB1	FANCF	HRAS	MAPK3	NRAS	RB1	SPOP
ATRX	CCND3	CYP3A4	FCGR2A	HSD3B1	MDM2	NTRK3	RBM10	STAG2
AURKA	CD274	dCK	FGF3	IDH2	MDM4	PALB2	RECQL	STAT3

genes negative for copy number variants (amplifications)

ABCB1	ATR	CDC73	EGFR	FANCM	HNF1A	MDM4	NTRK1	RAD51D	STAG2
ABCC1	ATRX	CDH1	EMSY	FAT1	HRAS	MED12	NTRK2	RAF1	STAT3
ABCC2	AURKA	CDK4	EP300	FBXW7	HSD3B1	MEN1	NTRK3	RB1	STK11
ABL1	AURKB	CDK6	EPCAM	FCGR2A	IDH1	MET	PALB2	RBM10	SUFU
ADAMTS1	AXIN1	CDK12	EPHA5	FGD4	IDH2	MGMT	PBRM1	RECQL	TERT-p
ADAMTS16	AXL	CDKN2A	EPHA7	FGF3	IGF1R	MLH1	PDCD1LG2	RET	TGFBR2
ADAMTS18	B2M	CHEK1	ERBB2	FGF4	IKZF1	MRE11A	PDGFRA	RHEB	TNFAIP3
ADAMTS6	BAP1	CHEK2	ERBB3	FGFR1	JAK1	MSH2	PDGFRB	RICTOR	TOP2A
ADAMTS9	BARD1	CHFR	ERBB4	FGFR2	JAK2	MSH6	PIK3CA	RIT1	TP53
ADAMTSL1	BCOR	CHKA	ERCC1	FGFR3	JAK3	MTHFR	PIK3CB	RNF43	TYMS
AKT1	BNIP3	CIC	ERCC2	FGFR4	KDM5C	MTOR	PIK3CD	ROS1	TSC1
AKT2	BRAF	CREBBP	ERCC3	FLT3	KDM6A	MUTYH	PIK3CG	RPTOR	TSC2
AKT3	BRCA1	CSF1R	ERRFI1	FLT4	KDR	MYC	PIK3R1	RRM1	TSHR
ALK	BRCA2	CTLA4	ESR1	FOXL2	KEAP1	MYCN	PLCB4	SDHB	VEGFA
AMER1	BRIP1	CTNNB1	ESR2	FUBP1	KIT	MYOD1	PLCG1	SDHC	VHL
APC	BTK	CYP1A1	EWSR1	GATA3	KRAS	NBN	PMS2	SETD2	WT1
APLNR	BUB1B	CYP2D6	EZH2	GLI1	MAF	NF1	POLD1	SF3B1	YES1
AR	CBL	CYP3A4	FAM175A	GNA11	MAP2K1	NF2	POLE	SMAD2	XRCC1
ARAF	CCND1	CYP19A1	FANCA	GNAQ	MAP2K2	NFE2L2	PPP2R1A	SMAD4	
AREG	CCND2	CYSLTR2	FANCC	GNAS	MAP3K1	NOTCH1	PTCH1	SMARCA4	
ARID1A	CCND3	dCK	FANCD2	GSTP1	MAPKAPK5	NOTCH2	PTEN	SMARCB1	
ARID1B	CCNE1	DDR2	FANCE	GSTT1	MAPK1	NOTCH3	PTPN11	SMO	
ARID2	CD274	DICER1	FANCF	HDAC2	MAPK3	NPM1	RAD50	SOCS1	
ATM	CDA	DNMT3A	FANCG	HGF	MDM2	NRAS	RAD51C	SPOP	

references

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IHC thresholds

Biomarker	Negative	Not Significant	Positive
ALK	2+ or <5%	Not applicable	≥2+ and ≥5%
PDL1:TILs	NA and 0%	Not applicable	≥1+ and ≥50%
PDL1:Tumor	TPS < 1	Not applicable	TPS ≥ 1
PTEN	≤1+ or <10%	Not applicable	≥1+ and ≥10%

Continued

IHC thresholds

Biomarker	Negative	Not Significant	Positive
ROS1	2+ or <5%	Not applicable	≥2+ and ≥5%
TRKpan	≤1+ or <10%	Not applicable	≥1+ and ≥10%
hENT1	≤2+ or <50%	Not applicable	≥2+ and ≥50%

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.The tests have neither been cleared nor approved by the U.S. Food and Drug Administration (FDA). However, the FDA has determined that such clearance or approval is not necessary. Paradigm is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing. The Laboratory Director is Bradly Clark, MD.

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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 biomarkerÂ 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.

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.