oncotype MAP™ Pan-Cancer Tissue

Patient Name
Precision Male

Final Report Date
1/1/2099

Non-Small Cell Lung Cancer (NSCLC)

Pan-Cancer Tissue

Date of Birth:	00/00/0000	Case/Specimen ID:	AA00-00000 A0	Turnaround:	3 business days
Pan-Cancer Tissue#:	PCDx-19-00000	Collection Site:	Lower cervical LN	Tumor cells:	80%
Physician:	Dr. Smith	Collection Date:	00/00/0000	Specimen size:	20 mm^2
Facility:	Some Cancer Treatment Center	Received for testing:	00/00/0000	Requirement met:	Optimal

5 NCCN indications

Therapeutic Option	Indicating biomarkers	Therapeutic Option	Indicating biomarkers
Alectinib	ALK + ALK Fusion	Brigatinib	ALK Fusion
Ceritinib	ALK + ALK Fusion	Crizotinib	ALK + ALK Fusion
Lorlatinib	ALK Fusion		

High Interest

Pan cancer	Type specific
TMB: Low	**ALK fusion: EML4-ALK**
MSI: Stable	RET fusion: Negative
NTRK fusion: Negative	ROS1 fusion: Negative
BRCA1: Wildtype	MET CNV: Not Changed
BRCA2: Wildtype	ALK: Wildtype
PD-L1 (22C3) Tumor IHC: Low	BRAF: Wildtype
PD-L1 (22C3) TILs IHC: Low	EGFR: Wildtype
	ERBB2: Wildtype
	KRAS: Wildtype
	MET: Wildtype
	ALK IHC: Positive
	PD-L1 (SP142) IHC: Negative

7 evidence-based therapy associations

Cetuximab	Crizotinib + Pazopanib	Docetaxel
Entrectinib	Everolimus	Panitumumab
Pemetrexed		

Specimen

Tumor cells: 80%
Specimen size: 20 mm^2
Residual tissue: Yes

Metastatic pulmonary adenocarcinoma

Gross Description: Xxxxxxxx xxxx Xxtxxxxxx - Xxxxxxx Xxxxxxx Xxxtxx xx 0 Xxxxx xxxxxxx xx 00X00000X X;0 (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx 00X00000X X;0 (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 00X00000X X;0 xxxx xx xxxxxxxx.

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

5 IHCs

ALK	2+	90%	Positive
PD-L1 (22C3) TILs	1+	1-4%	Low
PD-L1 (22C3) Tumor	TPS: 15		Low
PD-L1 (SP142) IC	N/A	0%	Negative
PD-L1 (SP142) TC	1+	1-4%	Negative
PTEN	3+	100%	Positive
TS	1+	100%	Not Significant

1 salient genomic finding

Gene	Variant	Quantity
EML4-ALK	Positive	10%

26 other genomic findings

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

XXXXTX00 x.0000-0X>X
XXXX0 X0000T XXXXX0
X0000X XXX x.0000-0000X>T
XXX0XX X000X
XXXXTX00 X0000
XXX00 Xxxx
XXXXX X0000X
XXX0X0 X0000T
XXX00X x.000+0000X>X
XXX X0000
XXXXXX X0000
XXXXX X0000X
XXXX0 X000
XXX0 Xxxx
XXXX0X Xxxx
XTXX0 x.0000-00000X>X
XTXX X000X
XX000 X000X
XXT T000X XXXX Xxxx
XX X000X XXX0X0
T00 XXT0 X000
XTXX x.0000+00X>X
XXX0 Xxxx
XXX0 X00
XXXX0 X0000X
XXX T000X
XXX0 X000
XXXX0 X00
XXXXXX X00

12 therapies with potential increased benefit

Therapeutic Option	Biomarkers	On NCCN	Level of evidence	References
Alectinib	ALK + ALK Fusion	Yes Yes	II-3 II-2	28 19,23
Brigatinib	ALK Fusion ALK +	Yes	II-2 II-2	10,14 10
Ceritinib	ALK + ALK Fusion	Yes Yes	I II-2	26 15,4
Cetuximab	KRAS WT, NRAS WT and BRAF WT		DTT	21,5
Crizotinib	ALK + ALK Fusion	Yes Yes	I II-1	13,29 2,25
Crizotinib + Pazopanib	ALK Fusion		DTT	27
Docetaxel	EGFR WT		I	9
Entrectinib	ALK + and ALK Fusion ALK Fusion ALK Fusion		DTT III	1 8 7
Everolimus	KRAS WT		DTT	18,6
Lorlatinib	ALK Fusion ALK +	Yes	II-2 II-2	22 22
Panitumumab	KRAS WT		DTT	12

Continued

12 therapies with potential increased benefit

Therapeutic Option	Biomarkers	On NCCN	Level of evidence	References
Pemetrexed	ALK Fusion		II-1	20,3

4 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Atezolizumab	ALK + and PD-L1 (22C3) TILs+	17
	ALK + and PD-L1 (22C3) Tumor +	17
	ALK Fusion and PD-L1 (22C3) TILs	17
	ALK Fusion and PD-L1 (22C3) Tumor +	17
Avelumab	ALK + and PDL1:Tumor +	11
	ALK Fusion and PDL1:Tumor +	11
Erlotinib	ALK Fusion	16,24
Gefitinib	ALK Fusion	16,24

clinical notes

EML4-ALK: Fusion between EML4 (echinoderm microtubule associated protein-like 4), a microtubule-associated protein, and ALK (anaplastic lymphoma kinase), a tyrosine kinase receptor belonging to the insulin receptor superfamily, was the first oncogenic fusion to be detected in lung cancer (Soda et al. 2007 PMID: 17625570). The EML4-ALK fusion protein is expressed in 2–9% of lung adenocarcinomas, and has also been identified in breast and colorectal cancers (Lin et al. 2009 PMID: 19737969). Fusion of EML4 to the kinase domain of ALK results in abnormal signalling and consequently increased cell growth, proliferation, and cell survival. Patients expressing this fusion are therefore treated with an ALK inhibitor, although PFS may be improved by alectinib and brigatinib relative to other ALK inhibitors (Eliott et al. 2020 PMID: 32074131).

ALK protein expression in NSCLC: 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 serve as a predictive marker for ALK inhibitor response. The VENTANA ALK (D5F3) CDx Assay defines positivity as any strong positive staining in any number of cells; D5F3 is the companion diagnostic for crizotinib, ceritinib, alectinib. 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 PMID 28183714). Similarly, Cabillic et al. 2018 (PMID:30245863) show that patients who were ALK FISH negative but IHC positive show complete or partial responses to ALK-targeted therapy. This is also supported by data indicating that the ORR for ALK FISH–positive/ALK IHC–negative patients was similar to that of patients treated with chemotherapy (Thorne-Nuzzo et al. 2017 PMID 28147239).

ALK+ and concurrent PD-L1 expression: Per the current NCCN Guidelines for NSCLC (6.2020), although PD-L1 expression can be elevated in patients with oncogenic driver alterations, targeted therapy for the oncogenic driver should take precedence over treatment with an immune checkpoint inhibitor. Oncogenic driver alterations are defined as EGFR, ALK, ROS1, METex14, and RET alterations.

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 of PD-L1 (22C3) TILs is determined by evaluating the percentage of PD-L1 expressing tumor-infiltrating immune cells of 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.

PD-L1 (22C3) Tumor: 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.

clinical notes

PD-L1 (SP142) TC: A qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in non-small cell lung cancer (NSCLC). Evaluation is based on the percentage of PD-L1 expressing tumor cells (% TC) of any intensity. Primary or metastatic NSCLC tissues may be submitted. PD-L1 expression in ≥50% tumor cells as determined by this assay in NSCLC tissue may be associated with enhanced overall survival from TECENTRIQ (atezolizumab). This test is a complementary diagnostic for use of Tecentriq in certain NSCLC cases. PD-L1 SP142 is deemed positive when either TC or IC expression is positive.

PD-L1 (SP142) IC: A qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in non-small cell lung cancer (NSCLC). Evaluation is based on the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity. Primary or metastatic NSCLC tissues may be submitted. PD-L1 expression in ≥ 10% tumor infiltrating immune cells as determined by this assay in NSCLC tissue may be associated with enhanced overall survival from TECENTRIQ (atezolizumab). This test is a complementary diagnostic for use of Tecentriq in certain NSCLC cases. PD-L1 SP142 is deemed positive when either TC or IC expression is positive.

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, the Paradigm PCDx™ test 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.

clinical trials

in tumor type

ALK +	NCT01625234	X-396
Phase 1/2 Study of X-396, an Oral ALK Inhibitor, in Patients With ALK-positive Non-Small Cell Lung Cancer		
ALK +	NCT02321501	Ceritinib (LDK378) | Ceritinib (LDK378) | Everolimus
Ceritinib and Everolimus in Treating Patients With Locally Advanced or Metastatic Solid Tumors or Stage IIIB-IV Non-small Cell Lung Cancer		
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 +	NCT02706626	Brigatinib
Trial of Brigatinib After Treatment With Next-Generation ALK Inhibitors		
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 +	NCT03052608	Lorlatinib | Crizotinib
A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC		
ALK +	NCT03088930	Crizotinib
Evaluating Crizotinib in the Neoadjuvant Setting in Patients With Non-small Cell Lung Cancer		
ALK +	NCT03256136	Carboplatin | Nivolumab | Pemetrexed | Ipilimumab
Nivolumab in Combination With Chemotherapy, or Nivolumab in Combination With Ipilimumab, in Advanced EGFR-Mutant or ALK-Rearranged NSCLC		
ALK Fusion	NCT01625234	X-396
Phase 1/2 Study of X-396, an Oral ALK Inhibitor, in Patients With ALK-positive Non-Small Cell Lung Cancer		
ALK Fusion	NCT02314364	SBRT with protons or photons
A Trial of Integrating SBRT With Targeted Therapy in Stage IV Oncogene-driven NSCLC		
ALK Fusion	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 Fusion	NCT02706626	Brigatinib
Trial of Brigatinib After Treatment With Next-Generation ALK Inhibitors		
ALK Fusion	NCT02927340	Lorlatinib
A Study of Lorlatinib in Advanced ALK and ROS1 Rearranged Lung Cancer With CNS Metastasis in the Absence of Measurable Extracranial Lesions		

clinical trials

ALK Fusion	NCT03052608	Lorlatinib | Crizotinib
A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC		
ALK Fusion	NCT03088930	Crizotinib
Evaluating Crizotinib in the Neoadjuvant Setting in Patients With Non-small Cell Lung Cancer		
ALK Fusion	NCT03178552	Alectinib | Atezolizumab | Pemetrexed | Cisplatin | Carboplatin | Gemcitabine
A Study to Evaluate Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)		
ALK Fusion	NCT03256136	Carboplatin | Nivolumab | Pemetrexed | Ipilimumab
Nivolumab in Combination With Chemotherapy, or Nivolumab in Combination With Ipilimumab, in Advanced EGFR-Mutant or ALK-Rearranged NSCLC		
ALK Fusion	NCT03535740	Brigatinib
A Study of Brigatinib in Participants With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non-Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib		
ALK Fusion	NCT03707938	Brigatinib | Local Consolidation Therapy
Local Consolidative Therapy and Brigatinib in Treating Patients With Stage IV or Recurrent Non-small Cell Lung Cancer		
EGFR WT	NCT02414139	INC280 (Capmatinib)
Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer		
EGFR WT	NCT02903914	CB-1158 | Nivolumab
Arginase Inhibitor INCB001158 as a Single Agent and in Combination With Immune Checkpoint Therapy in Patients With Advanced/Metastatic Solid Tumors		
EGFR WT	NCT02991651	IRX4204 | Erlotinib
Study of IRX4204 With Erlotinib in Previously Treated Advanced NSCLC		
EGFR WT and ALK -	NCT03647488	capmatinib | spartalizumab | docetaxel
Study of Capmatinib and Spartalizumab Combination Therapy vs Docetaxel in Non-small Cell Lung Cancer		
PDL1:TILs +	NCT02655822	CPI-444 | CPI-444 + Atezolizumab
Phase 1/1b Study to Evaluate the Safety and Tolerability of Ciforadenant Alone and in Combination With Atezolizumab in Advanced Cancers		
PDL1:Tumor +	NCT02273375	MEDI4736 | Placebo
Double Blind Placebo Controlled Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC		
PDL1:Tumor +	NCT02595944	Nivolumab
Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer (An ALCHEMIST Treatment Trial)		
PDL1:Tumor +	NCT02655822	CPI-444 | CPI-444 + Atezolizumab
Phase 1/1b Study to Evaluate the Safety and Tolerability of Ciforadenant Alone and in Combination With Atezolizumab in Advanced Cancers		
PDL1:Tumor +	NCT02716038	MPDL3280A | Carboplatin | Nab-Paclitaxel
Neoadjuvant MPDL3280A, Nab-paclitaxel and Carboplatin (MAC) in NSCLC		
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 +	NCT03409614	REGN2810 | Chemotherapy
Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-based Doublet Chemotherapy in Patients With Lung Cancer		
PDL1:Tumor +	NCT03455556	Anetumab Ravtansine | Atezolizumab
Anetumab Ravtansine and Atezolizumab in Treating Participants With Advanced Non-small Cell Lung Cancer		
PDL1:Tumor +	NCT03523702	Pembrolizumab + RT | Chemotherapy + RT
The Selective Personalized Radio-Immunotherapy for Locally Advanced NSCLC Trial.		
PDL1:Tumor +	NCT03546361	CCL21-gene modified dendritic cells | Pembrolizumab
Intratumoral Administration of CCL21-gene Modified Dendritic Cell With Intravenous Pembrolizumab for Advanced NSCLC		
PDL1:Tumor +	NCT03583086	VEGFR/PDGFR Dual Kinase Inhibitor X-82 | Nivolumab
Phase 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)		

clinical trials

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
CM082 and JS001 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC).		
PDL1:Tumor +	NCT03867175	Radiationl Pembrolizumab
Immunotherapy With or Without SBRT in Patients With Stage IV Non-small Cell Lung Cancer		

multi-indication trials

ALK +	NCT01625234	X-396
Phase 1/2 Study of X-396, an Oral ALK Inhibitor, in Patients With ALK-positive Non-Small Cell Lung Cancer		
ALK +	NCT02584933	Ceritinib
Roll-over Study to Allow Access to Certinib (LDK378) for Patients Who Are on Ceritinib Treatment in a Novartis-sponsored Study		
ALK +	NCT03868423	Brigatinib
Brigatinib in Treating Patients With ALK and ROS1 Gene Alterations and Locally Advanced or Metastatic Solid Cancers		
ALK +	NCT04362072	Lorlatinib;
Study of Lorlatinib In Participants With Anaplastic Lymphoma Kinase (ALK) -Positive NSCLC		
ALK Fusion	NCT02584933	Ceritinib
Roll-over Study to Allow Access to Certinib (LDK378) for Patients Who Are on Ceritinib Treatment in a Novartis-sponsored Study		
ALK Fusion	NCT02693535	Crizotinib
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		
ALK Fusion	NCT03093116	TPX-0005
A Study of Repotrectinib (TPX-0005) in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements		
ALK Fusion	NCT03868423	Brigatinib
Brigatinib in Treating Patients With ALK and ROS1 Gene Alterations and Locally Advanced or Metastatic Solid Cancers		
ALK Fusion	NCT04005144	Binimetinib;Brigatinib;
Brigatinib and Binimetinib in Treating Patients With Stage IIIB-IV ALK or ROS1-Rearranged Non-small Cell Lung Cancer		
ALK Fusion	NCT04292119	Lorlatinib;Crizotinib;Binimetinib;
Lorlatinib Combinations in Lung Cancer		
ALK Fusion	NCT02201992	Crizotinib;
Crizotinib in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer That Has Been Removed by Surgery and ALK Fusion Mutations (An ALCHEMIST Treatment Trial)		
MSI Stable	NCT03711058	Copanlisib | Nivolumab
Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer		
PD-L1 (22C3) TILs + and EGFR WT	NCT04385368	Durvalumab + SoC chemotherapy;
Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)		
PD-L1 (22C3) Tumor +	NCT03956680	BMS-986301;Nivolumab;Ipilimumab;
An Investigational Immunotherapy Study of BMS-986301 Alone or in Combination With Nivolumab, and Ipilimumab in Participants With Advanced Solid Cancers		
PD-L1 (22C3) Tumor +	NCT04007744	Sonidegib;
Sonidegib and Pembrolizumab in Treating Patients With Advanced Solid Tumors		

Continued

clinical trials

PD-L1 (22C3) Tumor +	NCT04340882	Docetaxel;
Phase 2 TaxRamPem for Patients With Metastatic or Recurrent NSCLC Who Progressed on Platinum-Doublet and PD-1/PD-L1 Blockade		
PDL1:Tumor +	NCT02608268	MBG453 I PDR001
Phase I-Ib/II Study of MBG453 as Single Agent and in Combination With PDR001 in Patients With Advanced Malignancies		
PDL1:Tumor +	NCT02614456	Interferon-gamma and Nivolumab
Combination of Interferon-gamma and Nivolumab for Advanced Solid Tumors		
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 I MGA012
MGC018 With or Without MGA012 in Advanced Solid Tumors		
RAS WT, BRAF WT	NCT02693535	Cetuximab
TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer		
TP53 WT	NCT01877382	DS-3032
A Phase 1 Multiple Ascending Dose Study of Milademetan in Subjects With Advanced Solid Tumors or Lymphomas		
TP53 WT	NCT03449381	BI 907828
This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)		
TP53 WT	NCT03560882	Atorvastatin
A Pilot Trial of Atorvastatin in Tumor Protein 53 (p53) -Mutant and p53 Wild-Type Malignancies		
TP53 WT	NCT03725436	MDM2/MDMX Inhibitor ALRN-6924 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	ACVR1	ACVR1B	ACVR2A	ACVR2B	ACVRL1	ADAMTS1
ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9	ADAMTSL1	AKT1	AKT2	AKT3	ALK	AMER1
APC	APLNR	AR	ARAF	AREG	ARID1A	ARID1B	ARID2	ATM	ATR
ATRX	AURKA	AURKB	AXIN1	AXL	B2M	BAP1	BARD1	BCOR	BMP6
BMPR1A	BMPR1B	BNIP3	BRAF	BRCA1	BRCA2	BRIP1	BTK	BUB1B	CALR
CBL	CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK12
CDK4	CDK6	CDKN2A	CHEK1	CHEK2	CHFR	CHKA	CIC	CREBBP	CSF1R
CTLA4	CTNNB1	CYP19A1	CYP1A1	CYP2D6	CYP3A4	CYSLTR2	dCK	DDR2	DICER1
DNMT3A	EGFR	EMSY	EP300	EPCAM	EPHA5	EPHA7	ERBB2	ERBB3	ERBB4
ERCC1	ERCC2	ERCC3	ERRFI1	ESR1	ESR2	EWSR1	EZH2	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCM	FAT1	FBXW7	FCGR2A	FGD4
FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FLT3	FLT4	FOXL2	FUBP1
GAS6	GATA3	GLI1	GNA11	GNAQ	GNAS	GSTP1	HAMP	HDAC2	HGF
HNF1A	HRAS	HSD3B1	IDH1	IDH2	IGF1R	IKZF1	IL6R	JAK1	JAK2
JAK3	KDM5C	KDM6A	KDR	KEAP1	KIT	KRAS	MAF	MAP2K1	MAP2K2
MAP3K1	MAPK1	MAPK3	MAPKAPK5	MDM2	MDM4	MED12	MEN1	MET	MGMT
MLH1	MPL	MRE11A	MSH2	MSH6	MTHFR	MTOR	MUTYH	MYC	MYCN
MYOD1	NBN	NF1	NF2	NFE2L2	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS
NTRK1	NTRK2	NTRK3	PALB2	PBRM1	PDCD1LG2	PDGFRA	PDGFRB	PIK3CA	PIK3CB
PIK3CD	PIK3CG	PIK3R1	PIM1	PLCB4	PLCG1	PMS2	POLD1	POLE	PPP2R1A
PTCH1	PTEN	PTPN11	RAD50	RAD51C	RAD51D	RAF1	RB1	RBM10	RECQL
RET	RHEB	RICTOR	RIT1	RNF43	ROS1	RPTOR	RRM1	SDHB	SDHC
SETD2	SF3B1	SMAD1	SMAD2	SMAD4	SMAD5	SMAD9	SMARCA4	SMARCB1	SMO
SOCS1	SPOP	STAG2	STAT3	STAT5A	STAT5B	STK11	SUFU	TERT-p	TGFB1
TGFB2	TGFB3	TGFBR1	TGFBR2	TNFAIP3	TNK1	TOP2A	TP53	TSC1	TSC2
TSHR	TYMS	VEGFA	VHL	WT1	XRCC1	YES1			

genes negative for fusions and structural variants

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

genes negative for copy number variants (amplifications)

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

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IHC thresholds

Biomarker	Negative	Not Significant	Positive
ALK	2+ or <5%	Not applicable	≥2+ and ≥5%
PD-L1 (22C3) TILs	NA and 0%	Not applicable	≥1+ and ≥50%
PD-L1 (22C3) Tumor	TPS < 1	Not applicable	TPS ≥ 1
PD-L1 (SP142) IC	≤1+ and <1%	Not applicable	≥1+ and ≥1%
PD-L1 (SP142) TC	≤1+ or <50%	Not applicable	≥1+ and ≥50%
PTEN	≤1+ or <10%	Not applicable	≥1+ and ≥10%
TS (TYMS)	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%

Performance

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

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

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

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

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Clinical trials

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

NCCN compendium

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

Reimbursement and acknowledgment

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

Pan-Cancer Tissue panel core components

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

Levels of evidence

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

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

No warranty or guarantee

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

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

Treatment decisions

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