oncotype MAP™ Pan-Cancer Tissue

Patient Name
Precision Male

Final Report Date
01/01/2099

Non-Small Cell Lung Cancer (NSCLC)

Pan-Cancer Tissue

Date of Birth:	00/00/0000	Case/Specimen ID:	AA00-00000 A0	Turnaround:	4 business days
Pan-Cancer Tissue#:	OR000000000, PCDx-19-00000	Collection Site:	Right lung	Tumor cells:	20%
Physician:	Dr. Smith	Collection Date:	00/00/0000	Specimen size:	16 mm^2
Facility:	Some Cancer Treatment Center	Received for testing:	00/00/0000	Requirement met:	Optimal

5 NCCN/FDA 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 (9muts/mb)	RET fusion: Negative
MSI: Stable	ROS1 fusion: Negative
NTRK fusion: Negative	MET CNV: QNS
BRCA1: Wildtype	ALK: **EML4-ALK**
BRCA2: Wildtype	BRAF: Wildtype
PD-L1 (22C3) Tumor IHC: High	EGFR: Wildtype
PD-L1 (22C3) TILs IHC: Negative	ERBB2: Wildtype
	KRAS: Low Coverage
	MET: Wildtype
	ALK IHC: Positive
	PD-L1 (SP142) IHC: Positive

6 evidence-based therapy associations

Cetuximab	Crizotinib + Pazopanib	Docetaxel
Entrectinib	Everolimus	Panitumumab

Specimen

Tumor cells: 20%
Specimen size: 16 mm^2
Residual tissue: Yes

Morphological findings compatible with little differentiated squamous carcinoma cell

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

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

9 IHCs

ALK	3+	100%	Positive
HER2	1+	5-9%	Negative
MET	2+	30%	Positive
PD-L1 (22C3) TILs	N/A	0%	Negative
PD-L1 (22C3) Tumor	TPS: 50		High
PD-L1 (SP142) IC	N/A	0%	Negative
PD-L1 (SP142) TC	1+	70%	Positive
PTEN	2+	20%	Positive
TP	3+	100%	Positive
TS	2+	100%	Positive
TUBB3	1+	20%	Not Significant

3 salient genomic findings

Gene	Variant	Quantity	Gene	Variant	Quantity
EML4-ALK	Positive	3%	TP53	Q331*	7%
MAF	K347N	45%			

Genes with indeterminate findings: SMAD9, EPHA7, EPHA5, FUBP1, EZH2, MRE11A, ATM, FAM175A, RB1, CDKN2A, JAK2, NBN, FANCM, CHEK2, MSH2, FBXW7, BRCA2, RECQL, PIK3CA, HGF, RAD51C, KRAS, PTEN, STAT5A, AKT3, RAD50, SDHC

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

11 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Alectinib	ALK + ALK Fusion	Yes Yes	II-3 II-2	23 15,18
Brigatinib	ALK Fusion ALK +	Yes	II-2 II-2	7,12 7
Ceritinib	ALK + ALK Fusion	Yes Yes	I II-2	21 13,2
Cetuximab	KRAS/NRAS/BRAF WT		DTT	16,3
Crizotinib	ALK + ALK Fusion	Yes Yes	I II-1	11,24 1,19
Crizotinib + Pazopanib	ALK Fusion		DTT	22
Docetaxel	EGFR WT		I	6
Entrectinib	ALK Fusion		III	5
Everolimus	KRAS WT		DTT	14,4

11 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Lorlatinib	ALK Fusion	Yes	II-2	17
	ALK +		II-2	17
Panitumumab	KRAS WT		DTT	10

2 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Avelumab	ALK + and PDL1:Tumor +	8
	ALK Fusion and PDL1:Tumor +	8
Fluorouracil	TS +	9,20

clinical notes

ALK+ and TP53 co-mutation: Pathogenic mutations in TP53 represent by far the most prevalent co-alteration in lung adenocarcinoma (review in Skoulidis and Heymach 2019 PMID 31406302) and most often associated with EGFR and KRAS mutant tumors, while TP53 co-mutation in ALK+ tumors appears to be comparatively rare (Aisner et al. 2018 PMID: 29217530). Mechanistically, an alteration in the TP53 gene should lead to genome instability, thereby accelerating the development of multiple mechanisms of resistance to targeted therapy (Aisner et al. 2018 PMID: 29217530). Alidousty et al. 2018 PMID: 29885057 could show that ALK+ NSCLC represents a heterogeneous subgroup of tumors, and that TP53 mutations in that particular cancer type define a subset of tumors that harbor chromosomal instability, leading to the co-occurrence of pathogenic aberrations. More importantly, Kron et al. 2017 PMID: 30165392 found that about one-fourth of ALK-positive patients do not substantially benefit from recent progress of targeted therapy, specifically that in ALK+ NSCLC co-occurring TP53 mutations predict an unfavorable outcome of systemic therapy with crizotinib, ceritinib, alectinib or brigatinib. This difference was confirmed in all treatment- related subgroups including chemotherapy only (Kron et al. 2017 PMID: 30165392).

ALK IHC+ in NSCLC: Oncotype MAP utilizes the VENTANA ALK (D5F3) CDx Assay for the qualitative detection of the ALK protein in FFPE tissue; per the D5F3 diagnostic, ALK positivity is defined as any strong positive staining in any number of cells (https://diagnostics.roche.com/hk/en/products/tests/ventana-alk-_d5f3-cdx-assay0.html). D5F3 is the companion diagnostic for crizotinib (XALKORI package insert, New York, NY: Pfizer; Revised June 2019), ceritinib (ZYKADIA package insert, Whippany, NJ: Novartis Pharmaceuticals Corporation, revised March 2019) and alectinib (ALECENSA package insert, San Francisco, CA: Genentech; revised June 2018) in NSCLC. The VENTANA ALK (D5F3) Assay recognizes the carboxyl terminus of human ALK protein, and many studies have reported excellent performance characteristics for this clone (review in Uruga and Mino-Kenudson 2018 PMID 30271189). 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 (for example, Ma et al. 2016 PMID 27418132; van der Wekken et al. 2017 PMID 28183714; Cabillic et al. 2018 PMID:30245863). 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 (van der Wekken et al. 2017 PMID 28183714). 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 further 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). Nong et al. 2019 (PMID: 32030215) analyzed IHC/NGS discrepant cases and found that ALK positivity by either IHC or NGS can be considered for treatment allocation. One patient who was ALK positive by IHC but negative for NGS responded to targeted therapy, in addition to individuals with ALK fusions identified by NGS but negative by IHC, who also responded (Nong et al. 2019 PMID: 32030215).

ALK+ and concurrent PD-L1 expression: 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.

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).

MAF: The MAF gene encodes the v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog protein. This protein is a leucine zipper-containing transcription factor of the AP1 superfamily. Depending on the binding site and binding partner, the encoded protein can be a transcriptional activator or repressor. This protein plays a role in the regulation of several cellular processes, including embryonic lens fiber cell development, increased T-cell susceptibility to apoptosis, and chondrocyte terminal differentiation.

clinical notes

MET (c-MET) expression in solid tumors: MET expression is determined using a SP44 antibody. A tumor is considered positive for MET, if a minimum of 10% of tumor cells, membrane and/or cytoplasmic, are immunoreactive. MET encodes a member of the receptor tyrosine kinase family of proteins and the product of the proto-oncogene MET. The encoded preproprotein is proteolytically processed to generate alpha and beta subunits that are linked via disulfide bonds to form the mature receptor. Further processing of the beta subunit results in the formation of the M10 peptide, which has been shown to reduce lung fibrosis. Binding of its ligand, hepatocyte growth factor, induces dimerization and activation of the receptor, which plays a role in cellular survival, embryogenesis, and cellular migration and invasion. Mutations in this gene are associated with papillary renal cell carcinoma, hepatocellular carcinoma, and various head and neck cancers. Amplification and overexpression of this gene are also associated with multiple human cancers [provided by RefSeq, May 2016]. MET is a receptor tyrosine kinase whose phosphorylation activates important proliferation pathways and various studies have demonstrated a correlation between c-MET activation and cancer pathophysiology (Faoro et al. 2009 PMID: 19861919). Multiple studies support c-MET or the HGF/c-MET signaling pathway as relevant targets for personalized cancer treatment based on high frequencies of c-MET overexpression, activation, amplification in across tumor types, including but not limited to NSCLC, gastric, ovarian, pancreatic, thyroid, breast, head and neck, colon and kidney carcinomas (Sierra et al 2011 PMID: 22128285). Deregulation and the consequent aberrant signaling of c-MET may occur by different mechanisms including gene amplification, overexpression, activating mutations, increased autocrine or paracrine ligand-mediated stimulation, and interaction with other active cell-surface receptors (Sierra et al 2011 PMID: 22128285). Treatment experience from lung cancer suggests that c-MET IHC is an inferior marker to determine MET dependency compared to MET amplification or METex14 mutations for such agents as crizotinib (Guo et al 2019 PMID: 31228623). However, MET inhibition by cabozantinib has shown promising results in select tumors types such as GIST (Cohen et al. 2015 (PMID: 25836719; Schöffski et al. 2020 PMID: 32541320) and advanced renal cell carcinoma (Choueiri et al. 2016 PMID 27279544).

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 on tumor-infiltrating lymphocytes (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 in NSCLC: 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 (PD-L1 IHC 22C3 pharmDx [package insert]. Carpinteria, CA: Dako, Agilent Pathology Solutions; 2019). Pembrolizumab (KEYTRUDA) is indicated (1) in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations; (2) in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC; (3) as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic; (4) as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy (Keytruda [package insert]. Kenilworth, NJ: Merck & Co., Inc.; revised 06/2020). Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA (Keytruda [package insert]. Kenilworth, NJ: Merck & Co., Inc.; revised 06/2020). The predictive value of the PD-L1 clone 22C3 for nivolumab, atezolizumab, avelumab or durvalumab is currently unclear.

PD-L1 (SP142) TC in NSCLC: PD-L1 (SP142) assay is a complementary diagnostic to identify PD-L1 expression levels in patients considering treatment with the FDA-approved immunotherapy Tecentriq (atezolizumab) for previously treated metastatic non-small cell lung cancer (NSCLC). PD-L1 (SP142) TC is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in 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 IHC SP142 [package insert]. Tuscon, AZ: Ventana Medical Systems, Inc; 2019). 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). Indications: (1) TECENTRIQ, as a single agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1–stained ≥50% of tumor cells [TC ≥50%] or PD-L1–stained tumor-infiltrating immune cells [IC] covering ≥10% of the tumor area [IC ≥10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; (2) TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous, non-small cell lung cancer (nsqNSCLC) with no EGFR or ALK genomic tumor aberrations (3) TECENTRIQ, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations; (4) TECENTRIQ, as a single agent, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ. (Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc; revised 07/2020). 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 in NSCLC: PD-L1 (SP142) assay is a complementary diagnostic to identify PD-L1 expression levels in patients considering treatment with the FDA-approved immunotherapy Tecentriq (atezolizumab) for previously treated metastatic non-small cell lung cancer (NSCLC). Evaluation is based on the

clinical notes

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 IHC SP142 [package insert]. Tuscon, AZ: Ventana Medical Systems, Inc; 2019). 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). Indications: (1) TECENTRIQ, as a single agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1–stained ≥50% of tumor cells [TC ≥50%] or PD-L1–stained tumor-infiltrating immune cells [IC] covering ≥10% of the tumor area [IC ≥10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; (2) TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous, non-small cell lung cancer (nsqNSCLC) with no EGFR or ALK genomic tumor aberrations (3) TECENTRIQ, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations; (4) TECENTRIQ, as a single agent, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ. (Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc; revised 07/2020). 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.

PTEN expression: PTEN expression is determined using a 6H2.1 antibody. A tumor is considered positive for MET, if a minimum of 10% of tumor cells, nuclear and/or cytoplasmic, are immunoreactive. PTEN has been identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. It contains a tensin like domain as well as a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases. Unlike most of the protein tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates. It negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway [provided by RefSeq, Feb 2015]. Loss of function of PTEN can occur through mutations, deletions or transcriptional silencing (Chalboub and Baker 2009 PMID: 18767981). While the effect of PTEN loss on the response to EGFR-targeted monoclonal antibodies (mAbs) has been extensively studied in patients with metastatic colorectal cancer, the most recent Guidelines "Molecular Biomarkers for the Evaluation of Colorectal Cancer" provide no recommendation for PTEN analysis as a treatment stratifier (Sepulveda et al. 2017 PMID: 28185757). Cetuximab and panitumumab are two distinct monoclonal antibodies targeting the epidermal growth factor receptor (EGFR), and both are widely used in combination with chemotherapy or as monotherapy to treat patients with RAS wild-type metastatic colorectal cancer and other solid tumors (García-Foncillas et al. 2019 PMID: 31616627). Meta-analyses (Mao et al. 2010 PMID: 20160728; Shen et al. 2012 PMID: 22690082; Therkildsen et al. 2014 PMID: 24666267) have shown that non-functional PTEN is associated with poorer overall response rate and shorter overall survival in patients with RAS wild-type CRC treated with cetuximab and panitumumab. Importantly, Therkildsen et al. 2014 PMID:24666267 show an independent predictive value for PTEN - i.e., independent from KRAS, NRAS, BRAF, PIK3CA - and demonstrate increased response rates in tumors that are wild-type in multiple biomarker assessment. Loss of PTEN has also been associated with inferior EGFR TKI responsiveness (Boeck et al. 2013 PMID:23169292, Buckingham et al. 2077 PMID: 17473657) and potential benefit from everolimus therapy (Park et al. 2015 PMID: 25886409; Rodrigues et al. 2015 PMID:25902899). Emerging evidence suggests that PTEN loss may be associated with reduced PFS in patients treated with vemurafenib alone but not in patients treated with cobimetinib combined with vemurafenib (Wongchenko et al. 2018 DOI: 10.1200/PO.17.00242).

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

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

TS (TYMS): The folate-dependent enzyme thymidylate synthase (TS) plays a pivotal role in DNA replication/repair and cancer cell proliferation and represents a valid target for the treatment of several tumor types. TS catalyzes the de novo synthesis of deoxythymidylate and is a key rate-limiting enzyme of DNA synthesis. Thymidylate synthase (TS) is an important target for chemotherapy drugs, such as 5-fluorouracil (5-FU), 5-fluorodeoxyuridine (FUDR), oral 5-FU prodrugs (e.g., uracil/tegafur [UFT], S-1, and capecitabine), and other folate-based drugs (e.g., raltitrexed, pemetrexed, and nolatrexed). Overexpression of TS is generally linked to resistance to TS-targeted chemotherapy drugs (March 2005 PMID: 16267625). Although conflicting results have been reported, higher thymidylate synthase (TS) protein and mRNA expression levels in tumors have generally been associated with poor clinical outcome in patients treated with 5-FU-based chemotherapy regimens. However, the cause of the variability in TS expression still remains not fully understood, although several germ-line polymorphisms seem to affect the

clinical notes

expression of TS, some of which have been found to have an effect on prognosis and the probability of response to 5-FU-based chemotherapy.

TUBB3: Class III beta-tubulin (βIII-tubulin, also known as TUBB3) is a microtubule protein, normally expressed in cells of neuronal origin. Its expression has been reported in various other tumor types. In the classical view, TUBB3 expression and drug resistance have been linked, and together they have been associated with a perturbation in microtubule dynamics such as aberrant protein folding of tubulins due to mutation and/or dysfunction of tubulin-specific chaperons. The association between TUBB3 and chemoresistance may derive from its role during development, as TUBB3 is expressed during mesenchymal dedifferentiation. It is also associated with histologically high-grade malignancies, cell dedifferentiation, anaplastic transformation, and acquisition of progenitor- or stem cell–like phenotypic properties, a hallmark of cancer stem cells, which are often chemotherapy-resistant. TUBB3 is therefore of clinical relevance as overexpression has been linked to poor response to microtubule-targeting anti-cancer drugs, specifically taxane- or vinca-alkaloid-containing regimens (Person et al. 2017 PMID: 29022485). High expression of TUBB3 correlates with low response rates to these agents and in addition to being prognostically relevant (reduced survival in patients with overexpression).

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		
ALK Fusion	NCT03052608	Lorlatinib | Crizotinib
A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC		
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	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 (Geometry Mono-1)		

clinical trials

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		
EGFR WT and MET +	NCT02323126	EGF816 | INC280 | Nivolumab
Study of Efficacy and Safety of Nivolumab in Combination With EGF816 and of Nivolumab in Combination With INC280 in Patients With Previously Treated Non-small Cell Lung Cancer		
EGFR WT and MET +	NCT02323126	EGF816 | INC280 | Nivolumab
Study of Efficacy and Safety of Nivolumab in Combination With EGF816 and of Nivolumab in Combination With INC280 in Patients With Previously Treated Non-small Cell Lung Cancer		
MET +	NCT03539536	Telisotuzumab
Study of Telisotuzumab Vedotin (ABBV-399) in Subjects With Previously Treated c-Met+ 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 +	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 +	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 N-803 in Combination With Current Standard of Care vs Standard of Care as First-Line Treatment for Patients With Stage 3 or 4 NSCLC.		
PDL1:Tumor +	NCT03523702	Pembrolizumab + RT | Chemotherapy + RT
The Selective Personalized Radio-Immunotherapy for Locally Advanced NSCLC Trial.		
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 +	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 +	NCT02584933	Ceritinib
Roll-over Study to Allow Access to Certinib (LDK378) for Patients Who Are on Ceritinib Treatment in a Novartis-sponsored Study		

Continued

clinical trials

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 +	NCT03456076	Alectnib;Cisplatin;Vinorelbine;Gemcitabine;Pemetrexed;Carboplatin;
A Study Comparing Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With ALK Positive Non-Small Cell Lung Cancer		
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)		
ALK Fusion	NCT03456076	Alectnib;Cisplatin;Vinorelbine;Gemcitabine;Pemetrexed;Carboplatin;
A Study Comparing Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With ALK Positive Non-Small Cell Lung Cancer		
ALK Fusion	NCT04541407	Temozolomide plus Osimertinib;Temozolomide plus Lorlatinib;
Temodar Plus Tyrosine Kinase Inhibitors for Progressive CNS Disease		
BRAF WT	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);
Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors		
HRAS WT	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);
Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors		
KRAS WT	NCT03225664	Trametinib;
Trametinib and Pembrolizumab in Treating Patients With Recurrent Non-small Cell Lung Cancer That Is Metastatic, Unresectable, or Locally Advanced		
MET +	NCT03175224	CBT-101
APL-101 Study of Subjects With NSCLC With c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advanced Solid Tumors		
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	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);
Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors		
PD-L1 (22C3) Tumor +	NCT03956680	BMS-986301;
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		
PD-L1 (22C3) Tumor +	NCT03228667	N-803 + Pembrolizumab;N-803 + Nivolumab;N-803 + Atezolizumab;N-803 + Avelumab;N-803 + Durvalumab;N-803 + Pembrolizumab + PD-L1 t-haNK;N-803 + Nivolumab + PD-L1 t-haNK;N-803 + Atezolizumab + PD-L1 t-haNK;N-803 + Avelumab + PD-L1 t-haNK;N-803 + Durvalumab + PD-L1 t-haNK;
QUILT-3.055: A Study of Combination Immunotherapies in Patients Who Have Previously Received Treatment With Immune Checkpoint Inhibitors		

Continued

clinical trials

PD-L1 (SP142) TC +	NCT03977467	Atezolizumab;

Atezolizumab in Patients With NSCLC or Advanced Solid Tumors Having Had Prior Treatment With a PD-1 Inhibitor

PD-L1 (SP142) TC +	NCT04294810	Atezolizumab;Tiragolumab;Matching Placebo;

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

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 +	NCT02785952	Ipilimumab I 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 +	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

PTPN11 WT	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);

Dose Finding Study of TNO155 in Adult Patients With 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 mutation	NCT03560882	Atorvastatin

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

TP53 mutation	NCT04293094	AMG 650;

Study of AMG 650 in Adult Participants With Advanced 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	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	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

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IHC thresholds

Biomarker	Negative	Not Significant	Positive
ALK	2+ or <5%	Not applicable	≥2+ and ≥5%
HER2 (ERBB2)	≤2+ and ≤10%	Equivocal = 2+ in ≤100% or 3+ in ≤10%	≥3+ and ≥10%
MET	≤1+ or <10%	Not applicable	≥1+ and ≥10%
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%
TP (TYMP)	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
TS (TYMS)	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
TUBB3	≤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.

1. Wolff et al. (2013) J Clin Oncol. 31:3997-4013.
2. Hammond et al. (2010) Arch Pathol Lab Med. 134:48-72.
3. Tse, et al. (2011) J Clin Oncol. 29:4168-4174.

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.