Oncomap™ Report

EXACT SCIENCES

Patient Name:	Precision Female	Case/Specimen ID:	AA00-00000 A0	Final Report Date:	1/1/2099
Date of Birth:	00/00/0000	Primary Cancer Diagnosis:	Non-Small Cell Lung Cancer	Turnaround:	3 days
Exact Order#:	OR000000000	Collection Date:	00/00/0000	Tumor cells:	20%
Physician:	Dr. Smith	Received for testing:	00/00/0000	Specimen size:	17 mm²
Facility:	Some Cancer Treatment Center			Requirement met:	Optimal

3 therapies with NCCN® Guideline[1] or FDA approval

Therapeutic Option	Indicating biomarkers
Atezolizumab	PD-L1 (SP142) IC +
Pembrolizumab	TMB High
Sotorasib	KRAS G12C

NCCN Guideline-recommended therapies in **bold**

Key Biomarker Findings

Pan cancer	Type specific
TMB: High (14muts/mb)	ALK fusion: Negative
MSI: Stable	RET fusion: Negative
NTRK fusion: Negative	ROS1 fusion: Negative
BRCA1: Wildtype	MET CNV: Not Changed
BRCA2: Wildtype	ALK: Wildtype
PD-L1 (22C3) TILs IHC: Low	BRAF: Wildtype
PD-L1 (22C3) Tumor IHC: Negative	EGFR: Wildtype
	ERBB2: Wildtype
	KRAS: G12C
	MET: Wildtype
	ALK IHC: Negative
	PD-L1 (SP142) IHC: Positive

4 Additional Therapy Options

Docetaxel	Durvalumab	Nivolumab
Nivolumab + Ipilimumab		

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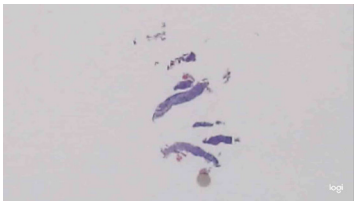
Specimen



Collection Site : Right humerus
Tumor cells: 20%
Specimen size: 17 mm²
Residual tissue: No

Metastatic poorly differentiated non-small cell carcinoma

Gross Description: Xxxxxxxx xxxx Xt. Xxxx'x Xxxxxtxx xx 0 Xxxxx xxxxxxx xx XX-00-00000 X0 (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx XX-00-00000 X0 (xxx XXXx-00-00000) xxxxtxxxxx xx xxxxxxxxx tx txx xxxxx xxxxx xxtxxxt xxxxx xx txx xxxxxxxxxxxx xxxxxxxx xxtxxxxxx xxxxxt xxtx xxxxxxxx xxxxxxtxxx xxtx xx 00/00/0000. Xxxxx XX-00-00000 X0 xxxx xx xxxxxxxx.

Pathologist has performed a comprehensive review of all records and material submitted. (2099-01-01)

5 IHCs

ALK	1+	5-9%	Negative
PD-L1 (22C3) TILs	1+	10%	Low
PD-L1 (22C3) Tumor	TPS: 0		Negative
PD-L1 (SP142) IC	1+	10%	Positive
PD-L1 (SP142) TC	N/A	0%	Negative
PTEN	2+	90%	Positive
TS	2+	10%	Not Significant

6 pathogenic genomic findings

Gene	Variant	Quantity	Gene	Variant	Quantity
ACVRL1	C36S	13%	RB1	I105Cfs*4	8%
CDK12	S889C	9%	SF3B1	R625C	6%
KRAS	G12C	10%	TP53	R249M	12%

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

7 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN[1]/FDA	Level of evidence	References
Atezolizumab	PD-L1 (SP142) IC +	Yes	I	4,11
Docetaxel	EGFR WT		I	5
Durvalumab	PD-L1 (22C3) TILs +		DTT	12,9
Nivolumab	TMB High		I	6
Nivolumab + Ipilimumab	TMB High		I	6,14
Pembrolizumab	TMB High	Yes	II-2	8
Sotorasib	KRAS G12C	Yes	II-3	2

NCCN Guideline-recommended therapies in **bold**

5 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Afatinib	KRAS mutation	10
Cetuximab	KRAS mutation	15,3
Erlotinib	KRAS mutation	7,13
Gefitinib	KRAS mutation	10
Panitumumab	KRAS mutation	15,3

Continued

5 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References

clinical notes

ACVRL1 in solid tumors: This gene encodes a type I cell-surface receptor for the TGF-beta superfamily of ligands. It shares a high degree of similarity in serine-threonine kinase subdomains with other type I receptors (glycine- and serine-rich region (GS domain) preceding the kinase domain, and a short C-terminal tail). The encoded protein, sometimes termed ALK1, shares similar domain structures with other closely related ALK or activin receptor-like kinase proteins that form a subfamily of receptor serine/threonine kinases. Mutations in this gene are associated with hemorrhagic telangiectasia type 2, also known as Rendu-Osler-Weber syndrome 2. [provided by RefSeq, Jul 2008]. Early reports suggest that ACVRL1 could become an emerging target for antiangiogenic cancer therapy (Cunha and Pietras 2011 PMID: 21467543). Inhibiting ACVRL1 may therefore prove useful to increase tumor blood flow enhancing delivery of chemotherapeutic drugs (Roman et al. 2017 PMID: 28871312).

ALK IHC negative: Oncomap utilizes the VENTANA ALK (D5F3) antibody for the qualitative detection of the ALK protein in FFPE tissue. ALK positivity is defined as any strong positive staining in any number of cells (see product labeling information). Emerging evidence suggests that ALK immunopositivity may serve as a predictive marker for ALK inhibitor response to crizotinib (see prescribing information), ceritinib (see prescribing information), and alectinib (see prescribing information) and lorlatinib (see prescribing information) in non-small-cell lung cancer (NSCLC). At present, NSCLC is the only cancer indication where ALK protein expression has been recommended as a stand-alone (and ALK-FISH equivalent) testing modality (Kalemkerian et al. 2018 PMID:29401004). Studies on D5F3 IHC using a binary scoring algorithm have reported 100% sensitivity and high specificity, attesting to dichotomous ALK-IHC (positive/negative) superiority over ALK FISH on small biopsies and FNA to predict tumor response to anti-ALK therapy for advanced NSCLC (van der Wekken et al. 2017 PMID:28183714). Of note, while all patients who were ALK IHC+ responded to crizotinib, no tumor response was observed in patients who were ALK IHC-negative/FISH+ (van der Wekken et al. 2017 PMID:28183714). Analysis of IHC/NGS-discrepant cases found that ALK positivity by either IHC or NGS can be considered for treatment allocation (Nong et al. 2019 PMID:32030215).

CDK12 in solid tumors: Cyclin-dependent kinase 12 (CDK12) regulates the expression of genes involved in DNA repair and is required for maintaining genomic stability (Blazek et al. 2011 PMID: 22012619). Genetic alterations in CDK12 occur in 3-4% of all cancers, with the greatest prevalence in invasive ductal carcinoma, colon, lung and prostate adenocarcinoma, and invasive breast carcinoma (Cerami and Sawyers 2017 PMID: 28572459). Preclinical data have implicated CDK12 in the response to estrogen inhibitors (Iorns et al. 2009 PMID: 19651820) and anti-HER2+ therapy resistance in human breast cancer (Choi et al. 2019 PMID: 31468695). Genomic profiling data from >142,000 tumors designed to determine the prevalence of CDK12 loss-of-function genomic alterations across tumor types demonstrated that CDK12 alterations associated with the tandem-duplicator phenotype could gain prominence as a pan-cancer biomarker for immunotherapy benefit (Sokol et al. 2019 PMID: 31292271). The observation that CDK12 deficiency may predict immunotherapy sensitivity is further substantiated by a recent prostate cancer study, where patients with CDK-12 altered tumors were shown to respond favorably to PD-1 inhibitors (Antonarakis et al. 2020 PMID: 32462107). In 2020, the FDA approved Olaparib (LYNPARZA, AstraZeneca Pharmaceuticals, LP) for HRR gene-mutated mCRPC. It should be noted that this approval was based on a comparison of olaparib vs abiraterone and enzalutamide (Hussain et al. 2020 PMID: 32955174) and that different CDK12 mutations may result in different biologic effects (Cerami et al. 2012 PMID 22588877, Gao et al. 2013 PMID 23550210), which suggests that not CDK12 alterations are PARP inhibitor sensitive.

KRAS in NSCLC: The KRAS gene provides instructions for making a protein that is part of a signaling pathway known as the RAS/MAPK pathway, which is responsible for relaying signals from outside the cell to the cell's nucleus. Mutations in KRAS result in the constituitive activation of KRAS and activation of downstream pathways [provided by RefSeq, Jul 2008]. Meta-analyses demonstrate that mutation profiles in NSCLC are heavily influenced by tumor histology, patient ethnicity and smoking history. KRAS mutations occur in 20-40% of lung adenocarcinomas, a prevalence that is higher in Western vs Asian populations (26% vs. 11%) and smokers vs non- smokers (30% vs. 10%) (Dearden et al. 2013 PMID 23723294). In the case of NSCLC, the most frequent KRAS mutations occur in codons 12 and 13, with the most common subtypes including G12C, G12 V, and G12D (Adderley et al. 2019 PMID 30852159). It has been suggested that the type of point mutation may differentially affect downstream signaling, which could translate into different clinical features and ultimately lead to different drug sensitivity (Biernacka et al. 2016 PMID 27068338). In addition, co-mutations of tumor suppressor genes in KRAS-mutant adenocarcinoma patients (including but not limited to STK11/LKB1, TP53, ATM, and KEAP1) appear to exert control over distinct tumorigenic pathways (Skoulidis et al 2015 PMID 26069186),which can impact therapy response, survival, and duration of response to initial platinum-based chemotherapy, and survival from the start of immune therapy (Arbour et al. 2018 PMID 29089357). Because the efficacy of chemotherapy in patients with KRAS-mutant NSCLC is heterogenous, numerous novel therapeutic strategies have been developed. These approaches include targeting KRAS membrane associations, targeting downstream signaling pathways, the use of KRAS synthetic lethality, direct targeting of KRAS, and immunotherapy (Ferrer et al. 2018 PMID 30268480). Immunotherapy may be one of the most promising new therapies in KRAS-mutant NSCLC. Although the clinical benefit of immunotherapy appears to be similar in NSCLC with and without KRAS mutation, an association between PD-L1 expression and immunotherapy efficacy was found in KRAS-mutant NSCLC (Jeanson et al. 2019 PMID 30738221).

KRAS c.34G>T p.G12C: The KRAS proto-oncogene GTPase (KRAS), regulates mitogen activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways, and mutations in KRAS are one of the most common genomic alterations identified in solid tumors (Salgia et al. 2021 PMID: 33521700). KRAS, the GTPase RAS gene family member, catalyzes the hydrolysis of GTP to GDP to activate the MAPK/PI3K oncogenic signaling pathway of receptor tyrosine kinases (RTK) (Ahearn et al. 2011 PMID: 22189424). Activating KRAS mutations mostly occur in major hotspots and promote cellular proliferation (Scheffzek et al. 1997 PMID: 9219684; Stephen et al. 2014 PMID: 24651010; Gao et al. 2017 PMID: 28115009; the Catalogue of Somatic Mutations in Cancer (COSMIC) 2018 PMID: 30371878). Despite efforts, KRAS remains a challenging therapeutic target (Mattox et al. 2020 PMID: 31878223). KRAS G12C is most commonly found in patients with non-small cell lung cancer (NSCLC) (~13%), and at a lower frequency in those with colorectal cancer (~3%), uterine cancer (~2%), mesothelioma (~1%),

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pancreatic cancer (<1%), cervical cancer (<1%), bladder cancer (<1%) and gastric cancer (<1%) (The Cancer Genome Atlas [TCGA]; Cerami et al. 2012 PMID: 22588877). Both AMG 510 from Amgen and MRTX849 from Mirati Therapeutics covalently bind to KRAS G12C at the cysteine at residue 12, keeping KRASG12C in its inactive GDP-bound state and inhibiting KRAS-dependent signaling for patients with NSCLC and other solid tumors (Nagasaka et al. 2020 PMID: 32014824; NCT03785249). More than 50% of NSCLC patients with KRAS G12C failed to respond to G12C selective inhibitors (Jänne et al. 2020 doi:10.1016/S0959-8049(20)31076-5; Hong et al. 2020 PMID: 32955176). Preclinical studies have suggested that individual tumors may have intrinsic resistance (weak dependance on KRAS signaling for proliferation, or concurrent genetic mutations that impede the activity of G12C inhibitors [secondary mutations such as A59G, Q61L, A146V]) (Lito et al 2016, PMID: 26841430), or acquired resistance (restoration of overall RAS activity) to KRAS G12C inhibitors (Xue et al. 2020 PMID: 31915379; Ryan et al. 2020, PMID: 31776128). Combinations of G12C inhibitors with other anticancer drugs, which are also being evaluated in clinical trials, have shown promising preclinical results and may provide effective therapies to overcome resistance to G12C inhibitors (Jiao et al. 2020 PMID: 32939510). In addition, two novel KRAS G12C inhibitors JNJ-74699157 and LY3499446 have recently entered phase 1 studies (Nagasaka et al. 2020 PMID: 32014824). On May 28, 2021, the Food and Drug Administration granted accelerated approval to sotorasib (Lumakras™, Amgen, Inc.), a RAS GTPase family inhibitor, for adult patients with KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received at least one prior systemic therapy (Hong et al. 2020 PMID: 32955176; NCT03600883).

Microsatellite Instability Analysis [MSI] Result Stable (MSS): The stability of MSI sites has been determined by detecting five nucleotide markers and MSI status has been classified as following: two or more of the unstable loci is MSI-H, the instability of one of the loci is MSI-L, MSS is defined as the instability of zero loci (Nowak et al. 2017 PMID: 27863258). MSS cancers generally show less immune cell infiltration compared with MSI-H cancers (Yang et al. 2019 PMID: 31617076). On September 17, 2019, FDA granted accelerated approval to pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is MSS or mismatch repair deficient (dMMR).

PD-L1 (22C3) expression on tumor-infiltrating lymphocytes (TILs): PD-L1 can be expressed by an extended number of cell types, including tumor cells, lymphocytes, macrophages-lineage cells, endothelial cells, and others (Cottrell and Taube 2019 PMID:29360727). It has been suggested that PD-L1 expression on TILs may reflect intratumor effector T cell activation, a major mechanism of adaptive immune control in cancer (Kong et al. 2019 PMID:31205530). While PD-L1 expression in the pre-treatment tumor microenvironment (TME) represents the most well-studied potential biomarker of response to anti-PD-(L)1 therapy, a number of other markers are currently under investigation, including PD-L1 expression on TILs (Cottrell and Taube 2019 PMID:29360727). According to Herbst and colleagues (2014 PMID:25428504), PD-L1 expression on TILs can predict for response to select immune checkpoint inhibitors such as atezolizumab across multiple tumor types. In line with this, Oncomap evaluates activated expression of PD-L1 22C3 on TILs as a potential candidate biomarker for select PD-1/PD-L1 blockade. PD-L1 (22C3) expression on 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).

PD-L1 (22C3) Tumor Negative (TPS: 0) 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 straining at any intensity. The scoring system divides the results into 3 groups: those with ≥50% of tumor cells showing any level of positivity (high), those with <50% of tumor cells but ≥1% of tumor cells showing positivity (low), and those with <1% of tumor cells showing positivity (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 (see product labeling information). Pembrolizumab is indicated (1) in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous non-small-cell lung cancer (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 whose tumors express PD-L1 (TPS ≥1% as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations and who are stage III, where patients are not candidates for surgical resection or definitive chemoradiation, or who are metastatic; (4) as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%), with disease progression on or after platinum-containing chemotherapy (see prescribing information). Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab (see prescribing information). Please note that according to the most recent ASCO and Ontario Health (Cancer Care Ontario) Joint Guideline Update for Therapy for Stage IV Non-Small-Cell Lung Cancer WIthout Driver Alterations, for patients with negative PD-L1 (TPS 0%), in the absence of contraindications to immune checkpoint therapies, treatment options may still include pembrolizumab (Hanna et al. 2020 PMID:31990617). For most patients with non-squamous cell carcinoma (SCC) and negative (TPS 0%) PD-L1, the expert panel recommends pembrolizumab/carboplatin/pemetrexed.

PD-L1 (SP142) TC in NSCLC: PD-L1 (SP142) assay is used to identify PD-L1 expression levels in patients considering treatment with the FDA-approved immunotherapy 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. Evaluation is based on the percentage of PD-L1-expressing tumor cells (% TC) of any intensity. Primary or metastatic NSCLC tissues may be submitted (see product labeling information). PD-L1 SP142 is deemed positive when either TC or IC expression is positive. Indications for use include the following: Atezolizumab, as a single agent, is indicated for the first-line treatment of adult patients with metastatic 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%]), with no EGFR or ALK genomic tumor aberrations (see prescribing information). Atezolizumab, in combination with bevacizumab, paclitaxel, 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 (see prescribing information). Atezolizumab, 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(see prescribing information). Atezolizumab, as a single agent, is indicated for the treatment of adult patients with NSCLC who have disease progression during or following platinum-containing chemotherapy (see prescribing information). Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving atezolizumab (see prescribing information).

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PD-L1 (SP142) IC in NSCLC: PD-L1 (SP142) assay is used to identify PD-L1 expression levels in patients considering treatment with the FDA-approved immunotherapy atezolizumab for previously treated metastatic non-small-cell lung cancer (mNSCLC). Evaluation is based on the proportion of tumor area occupied by PD-L1-expressing TILs (% immune cells [IC]) of any intensity. Primary or mNSCLC tissues may be submitted (see product labeling information. PD-L1 SP142 is deemed positive when either TC or IC expression is positive. PD-L1 expression in ≥10% TILs as determined by this assay in NSCLC tissue may be associated with enhanced OS from atezolizumab (see product labeling information). Indications include the following (see prescribing information): (1) Atezolimuzab, as a single agent, is indicated for the first-line treatment of adult patients with mNSCLC whose tumors have high PD-L1 expression (PD-L1-stained ≥50% of tumor cells [TC ≥50%] or PD-L1-stained TILs covering ≥10% of the tumor area [IC ≥10%]), with no EGFR or ALK genomic tumor aberrations. (2) Atezolizumab, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations. (3) Atezolizumab, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic nsqNSCLC with no EGFR or ALK genomic tumor aberrations. (4) Atezolizumab, as a single agent, is indicated for the treatment of adult patients with mNSCLC 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 atezolizumab (see prescribing information).

PTEN expression: PTEN expression is determined using a 6H2.1 antibody. A tumor is considered positive for PTEN if a minimum of 10% of tumor cells show nuclear or cytoplasmic immunostaining. PTEN has been identified as a tumor suppressor that is mutated in a large number of cancers at high frequency (Yin et al. 2008 PMID:18794879). Loss of function of PTEN can occur through mutations, deletions, or transcriptional silencing (Chalboub and Baker 2009 PMID:18767981). Cetuximab and panitumumab are 2 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 (CRC) 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 ORR and shorter OS in patients with RAS wild-type CRC treated with cetuximab and panitumumab. Importantly, an independent predictive value for PTEN—that is, independent from KRAS, NRAS, BRAF, and PIK3CA—has been shown and demonstrated increased response rates in tumors that are wild-type in multiple biomarker assessment (Therkildsen et al. 2014 PMID:24666267). Loss of PTEN has also been associated with inferior EGFR tyrosine kinase inhibitor 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).

RB1 mutation in NSCLC: The retinoblastoma tumor suppressor gene (RB1) is often cited as a gatekeeper, whose inactivation is a rate-limiting step for tumor initiation (Guzman et al. 2020 PMID: 33003565). RB1 LOF/inactivating mutations have been identified in 4-8% of non-small cell lung carcinoma cases (NSCLC), most commonly as indel alterations (Collisson et al. 2014 PMID: 25079552; Bhateja et al. 2019 PMID: 30773851). Sequencing studies have found that mutations in RB1 are associated with poorer prognosis and overall survival in NSCLC patients as compared to RB1 wildtype tumors (Choi et al. 2015 PMID: 25294902). Emerging evidence suggests that the poorer prognosis and overall survival observed in RB1 mutation tumors may be due to poor response to immunotherapy, with a correlation observed between a cohort of NSCLC patients harboring an RB1 mutation and lack of response when treated with first line pembrolizumab or second line nivolumab (Bhateja et al. 2019 PMID: 30773851).

SF3B1 in solid tumors: SF3B1 is the largest subunit of the spliceosome factor 3b (SF3B) complex, which is a core component of spliceosomes (Zhou et al. 2020 PMID: 32905346). Recurrent somatic mutations in SF3B1 have been detected in human cancers, including hematological malignancies and solid tumors, and found to be related to patient prognosis (Zhou et al. 2020 PMID: 32905346). Studies have identified SF3B1 mutations in uveal melanomas, pancreatic cancers, and breast cancers (Scott et al. 2013 PMID: 24052622). A recent preclinical study showed that SF3B1 mutation confers sensitivity to the SF3b complex inhibitor spliceostatin A in breast cancer (Maguire et al. 2015 PMID: 25424858).

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 (Lee et al. 2020 PMID: 31361563). While this effect is seen in most 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, Oncomap has adopted the high (≥ 10 mut/Mb) and low (< 10 mut/Mb) 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). The TMB threshold follows 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 (Marabelle et al. 2020 PMID: 31682550).

TP53 R249X mutation: These missense mutations occur within a hotspot in the the DNA binding domain (DBD) of the TP53 gene (Levine et al. 1991 PMID: 2046748). Functional studies have found that alternations at amino acid residue R249 (including R249S, R249W, R249K, R249T, R249M, R249G) impact the structure and transactivation activities of the TP53 protein (Kato et al. 2003 PMID: 12826609; Joerger et al. 2006 PMID: 17015838). The R249S change also results in an oncogenic gain-of-function- (GOF) phenotype upon CDK4 phosphorylation at Serine 249 and consequent PIN1 Binding (Liao et al. 2017 PMID: 29225033)

TS (TYMS) expression in solid tumors: Thymidylate synthase (TS/TYMS) is involved in the folate pathways, specifically in the de novo pyrimidine biosynthesis (Marsh 2005 PMID:16267625; Costi et al. 2005 PMID:16178783). Inhibitors of thymidylate biosynthesis have remained among the most effective chemotherapies used in the treatment of cancer (Eliason and Megyeri 2004 PMID:15134221; Wilson et al 2014 PMID:24732946). Although conflicting results have been reported, some

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evidence suggests that higher tumor TS protein and gene expression levels appear to be associated with poor clinical outcome in patients treated with fluoropyrimidine-based regimens (March 2005 PMID:16267625; Wilson et al. 2014 PMID:24732946; Blondy et al. 2020 PMID: 32536012). Elucidating the potential resistance factors for fluoropyrimidines remains an active field of study (Lurje et al. 2009 PMID: 19383851; Blondy et al. 2020 PMID:32536012).

clinical trials

in tumor type

ALK-, EGFR WT	NCT03611738	Ceritinib | Docetaxel
Ceritinib Plus Docetaxel in ALK-Negative, EGFR WT Advanced NSCLC		
EGFR WT	NCT02991651	IRX4204 | Erlotinib
Study of IRX4204 With Erlotinib in Previously Treated Advanced NSCLC		
KRAS mutation	NCT03170206	Binimetinib | Palbociclib
Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor Binimetinib (MEK162) for Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer		
KRAS mutation	NCT03808558	TVB-2640
Phase 2 Study of TVB-2640 in KRAS Non-Small Cell Lung Carcinomas		
KRAS mutation	NCT04892017	DCC-3116;Trametinib;
A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.		
TMB High	NCT03516981	Pembrolizumab | MK-1308 | MK-4280 | Lenvatinib
A Study of Biomarker-Directed, Pembrolizumab (MK-3475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (MK-3475-495/KEYNOTE-495)		
TMB High	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		

multi-indication trials

ALK WT, ROS1 WT, BRAF WT, and EGFR WT	NCT04581824	Dostarlimab;Pembrolizumab;Chemotherapy;
Efficacy Comparison of Dostarlimab Plus Chemotherapy Versus Pembrolizumab Plus Chemotherapy in Participants With Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC)		
CDK12 mutation	NCT03570619	Nivolumab | Ipilimumab
Immunotherapy in Patients With Metastatic Cancers and CDK12 Mutations		
CDK12 mutation	NCT03742895	Olaparib;
Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)		
CDK12 mutation	NCT03842228	Copanlisib | Durvalumab | Olaparib
Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations		
CDK12 mutation	NCT04123366	Olaparib;
Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)		
CDK12 mutation	NCT04266912	Avelumab;Berzosertib;
Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors		
CDK12 mutation	NCT04550494	Talazoparib;
Measuring the Effects of Talazoparib in Patients With Advanced Cancer and DNA Repair Variations		
CDK12 mutation	NCT04826341	Berzosertib;Sacituzumab Govitecan;
A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors		
CDK12 mutation	NCT04983745	Combination drug;
Niraparib and Dostarlimab in HRD Solid Tumors		
KRAS G12C	NCT04585035	D-1553;Other;
Study to Evaluate D-1553 in Subjects With Solid Tumors		
KRAS G12C	NCT04625647	Sotorasib;
Testing the Use of Targeted Treatment (AMG 510) for KRAS G12C Mutated Advanced Non-squamous Non-small Cell Lung Cancer (A Lung-MAP Treatment Trial)		

Continued

clinical trials

KRAS G12C	NCT04699188	JDQ443;TNO155;
Study of JDQ443 in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation		
KRAS G12C	NCT04956640	LY3537982;Abemaciclib;Erlotinib;Sintilimab;Temuterkib;LY3295668;Cetuximab;
Study of LY3537982 in Cancer Patients With a Specific Genetic Mutation (KRAS G12C)		
KRAS G12C	NCT04973163	BI 1823911;BI 1701963;Midazolam;
A Study to Test Different Doses of BI 1823911 Alone and Combined With Other Medicines in People With Different Types of Advanced Cancer With KRAS Mutation		
KRAS G12C	NCT04975256	MRTX849;BI 1701963;
Adagrasib in Combination With BI 1701963 in Patients With Cancer (KRYSTAL 14)		
KRAS G12C	NCT05118854	AMG 510;Cisplatin;Carboplatin;Pemetrexed;
A Phase II Study of Neoadjuvant Sotorasib in Combination With Cisplatin or Carboplatin and Pemetrexed for Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a KRAS p.G12C Mutation		
KRAS G12C	NCT05119933	YL-15293
A Phase 1/2, Study of YL-15293 in Subjects With Advanced Solid Tumors With a KRAS G12C Mutation		
KRAS mutation	NCT02079740	Trametinib;
Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors		
KRAS mutation	NCT03095612	Selinexor;
Phase 1/2 Trial of Selinexor (KPT-330) With Docetaxel for Non-small Cell Lung Cancer (NSCLC)		
KRAS mutation	NCT03146962	Vitamin C;
High Dose Vitamin C Intravenous Infusion in Patients With Resectable or Metastatic Solid Tumor Malignancies		
KRAS mutation	NCT03162627	Selumetinib;Olaparib;
Selumetinib and Olaparib in Solid Tumors		
KRAS mutation	NCT03520842	Methotrexate;Regorafenib;
Regorafenib and Methotrexate in Treating Participants With Recurrent or Metastatic KRAS Mutated Non-Small Cell Lung Cancer		
KRAS mutation	NCT03600701	Atezolizumab;Cobimetinib;
Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer		
KRAS mutation	NCT03600883	AMG 510
A Phase 1/2, Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation (CodeBreaK 100)		
KRAS mutation	NCT03634982	RMC-4630;
Dose Escalation of RMC-4630 Monotherapy in Relapsed/Refractory Solid Tumors		
KRAS mutation	NCT03756818	Paclitaxel | Spleen Tyrosine Kinase Inhibitor TAK-659
TAK-659 and Paclitaxel in Treating Patients With Advanced Solid Tumors		
KRAS mutation	NCT03819387	NBF-006;
A Study of NBF-006 in Non-Small Cell Lung, Pancreatic, or Colorectal Cancer		
KRAS mutation	NCT03905148	Lifirafenib;mirdametinib;
Study of the Safety and Pharmacokinetics of BGB-283 (Lifirfenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors		
KRAS mutation	NCT03919292	Neratinib;Divalproex Sodium;
Neratinib + Valproate in Advanced Solid Tumors, w/Expansion Cohort in Ras-Mutated Ca		
KRAS mutation	NCT03948763	V941 | Pembrolizumab
A Study of mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001)		
KRAS mutation	NCT04092673	eFT226;
Study of eFT226 in Subjects With Selected Advanced Solid Tumor Malignancies		
KRAS mutation	NCT04111458	BI 1701963;Trametinib;
A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)		
KRAS mutation	NCT04185883	Sotorasib
Sotorasib Activity in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101)		

Continued

clinical trials

KRAS mutation	NCT04214418	Cobimetinib;Hydroxychloroquine;Atezolizumab;

Study of Combination Therapy With the MEK Inhibitor, Cobimetinib, Immune Checkpoint Blockade, Atezolizumab, and the AUTOphagy Inhibitor, Hydroxychloroquine in KRAS-mutated Advanced Malignancies

KRAS mutation	NCT04249843	BGB-3245;

Study of Safety, Pharmacokinetics, and Antitumor Activity of BGB-3245 in Participants With Advanced or Refractory Tumors

KRAS mutation	NCT04263090	Rigosertib;Nivolumab;

Rigosertib Plus Nivolumab for KRAS+ NSCLC Patients Who Progressed on First-Line Treatment

KRAS mutation	NCT04418167	JSI-1187;Dabrafenib;

JSI-1187-01 Monotherapy and in Combination With Dabrafenib for Advanced Solid Tumors With MAPK Pathway Mutations

KRAS mutation	NCT04449874	GDC-6036;Atezolizumab;Cetuximab;Bevacizumab;Erlotinib;GDC-1971;

A Study to Evaluate the Safety, Pharmacokinetics, and Activity of GDC-6036 Alone or in Combination in Participants With Advanced or Metastatic Solid Tumors With a KRAS G12C Mutation

KRAS mutation	NCT04528836	BBP-398 (Formerly Known as IACS-15509);

First-in-Human Study of the SHP2 Inhibitor BBP-398 in Patients With Advanced Solid Tumors

KRAS mutation	NCT04586270	TAS0612;

A Study of TAS0612 in Participants With Advanced or Metastatic Solid Tumor Cancer

KRAS mutation	NCT04613596	MRTX849 | Pembrolizumab

Phase 2 Trial of MRTX849 Monotherapy and in Combination With Pembrolizumab for NSCLC With KRAS G12C Mutation KRYSTAL-7

KRAS mutation	NCT04620330	VS-6766;VS-6766 and Defactinib;

A Study of VS-6766 v. VS-6766 + Defactinib in Recurrent G12V or Other KRAS-Mutant Non-Small Cell Lung Cancer

KRAS mutation	NCT04735068	Binimetinib Pill;Hydroxychloroquine Pill;

Binimetinib and Hydroxychloroquine in Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer

KRAS mutation	NCT04800822	PF-07284892;lorlatinib;binimetinib;encorafenib;

PF-07284892 in Participants With Advanced Solid Tumors

KRAS mutation	NCT04870034	Binimetinib;Palbociclib;

Binimetinib and Palbociclib Before Surgery for the Treatment of Operable KRAS-Positive Lung, Colorectal, or Pancreatic Cancer

KRAS mutation	NCT04892017	DCC-3116;Trametinib;

A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.

KRAS mutation	NCT04967079	Trametinib;Anlotinib;

MEK Inhibitor Combined With Anlotinib in the Treatment of KRAS-mutated Advanced Non-small Cell Lung Cancer

KRAS mutation	NCT05054725	RMC-4630;Sotorasib;

Combination Study of RMC-4630 and Sotorasib for NSCLC Subjects With KRASG12C Mutation After Failure of Prior Standard Therapies

KRAS mutation	NCT05118854	AMG 510;Cisplatin;Carboplatin;Pemetrexed;

A Phase II Study of Neoadjuvant Sotorasib in Combination With Cisplatin or Carboplatin and Pemetrexed for Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a KRAS p.G12C Mutation

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 +	NCT02947386	Nimotuzumab | Nivolumab

Nimotuzumab and Nivolumab in Treating Patients With Advanced Non-small Cell Lung 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) TILs +, EGFR WT and ALK WT	NCT04262856	Zimberelimab;Domvanalimab;Etrumadenant;

Study to Evaluate Monotherapy and Combination Immunotherapies in Participants With PD-L1 Positive Non-small Cell Lung Cancer

PD-L1 (22C3) Tumor -	NCT02947386	Nimotuzumab | Nivolumab

Nimotuzumab and Nivolumab in Treating Patients With Advanced Non-small Cell Lung Cancer

Continued

clinical trials

PD-L1 (22C3) Tumor -	NCT04348292	Durvalumab;Sirolimus;

Sirolimus and Durvalumab for the Treatment of Stage I-IIIA Non-small Cell Lung Cancer

PD-L1 (SP142) IC +	NCT02947386	Nimotuzumab | Nivolumab

Nimotuzumab and Nivolumab in Treating Patients With Advanced Non-small Cell Lung Cancer

PD-L1 (SP142) IC +	NCT03977467	Atezolizumab;

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

PD-L1 (SP142) IC +	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

PD-L1 (SP142) IC +, EGFR WT and ALK WT	NCT04262856	Zimberelimab;Domvanalimab;Etrumadenant;

Study to Evaluate Monotherapy and Combination Immunotherapies in Participants With PD-L1 Positive Non-small Cell Lung Cancer

PD-L1 (SP142) TC -	NCT02947386	Nimotuzumab | Nivolumab

Nimotuzumab and Nivolumab in Treating Patients With Advanced Non-small Cell Lung Cancer

TMB High	NCT02693535	Pembrolizumab or Nivolumab + Ipilimumab

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

TMB High	NCT03911557	Durvalumab | Tremelimumab

Durvalumab and Tremelimumab Combination in Somatically Hypermutated Recurrent Solid Tumors

TMB High	NCT04632992	Atezolizumab+Chemotherapy

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TP53 mutation	NCT03560882	Atorvastatin

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

TP53 mutation	NCT04022876	ALRN-6924;Carboplatin;Pemetrexed;Placebo;ALRN-6924;Topotecan;

A Study of ALRN-6924 for the Prevention of Chemotherapy-induced Side Effects (Chemoprotection)

TP53 mutation	NCT04293094	AMG 650;

Study of AMG 650 in Adult Participants With Advanced Solid Tumors

TP53 mutation	NCT04586335	CYH33;

Study of CYH33 in Combination With Olaparib an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.

genes negative for small variants

ABCB1	ABCC1	ABCC2	ABL1	ACVR1	ACVR1B	ACVR2A	ACVR2B	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	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	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	RBM10	RECQL	RET	RHEB	RICTOR	RIT1
RNF43	ROS1	RPTOR	RRM1	SDHB	SDHC	SETD2	SMAD1	SMAD2	SMAD4

Continued

genes negative for small variants

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

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

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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1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Therapeutic options are listed based on associations with biomarkers in the soma and/or germline and are not applicable in all disease settings. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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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+ or <10%	Not applicable	≥1+ and ≥10%
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%

Continued

Performance

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

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.

Test results

This report includes information about therapeutic agents that appear to be associated with clinical benefit based on NCCN 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.

The assay has been validated as a Laboratory Developed Test per institutional and applicable CLIA regulation. The test is not FDA cleared or approved. This assay has not been validated on decalcified tissues. Results should be interpreted with caution given the possibility 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.