## Pan-Cancer Tissue

| | | | | | |
|---|---|---|---|---|---|
| Date of Birth: | 00/00/0000 | Case/Specimen ID: | AA00-00000 A0 | Turnaround: | 5 business days |
| Pan-Cancer Tissue#: | OR000000000, PCDx-19-00000 | Collection Site: | R paratracheal LN | Tumor cells: | 40% |
| Physician: | Dr. Smith | Collection Date: | 00/00/0000 | Specimen size: | 255 $mm^2$ |
| Facility: | Some Cancer Treatment Center | Received for testing: | 00/00/0000 | Requirement met: | Optimal |

## 7 NCCN/FDA indications

| Therapeutic Option | Indicating biomarkers | Therapeutic Option | Indicating biomarkers |
|---|---|---|---|
| Afatinib | EGFR Exon 19 Del | Dacomitinib | EGFR Exon 19 Del |
| Erlotinib | EGFR Exon 19 Del | Erlotinib + Bevacizumab | EGFR Exon 19 Del |
| Gefitinib | EGFR Exon 19 Del | Osimertinib | EGFR Exon 19 Del |
| Ramucirumab + Erlotinib | EGFR Exon 19 Del | | |

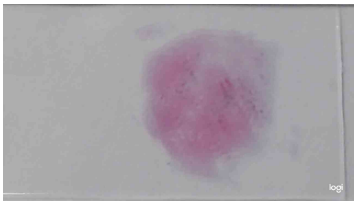
## High Interest

| Pan cancer | Type specific |
|---|---|
| TMB: Low (4muts/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) Tumor IHC: Low** | BRAF: Wildtype |
| PD-L1 (22C3) TILs IHC: Negative | **EGFR: L747_T751del** |
| | ERBB2: Wildtype |
| | KRAS: Wildtype |
| | MET: Wildtype |
| | ALK IHC: Negative |
| | PD-L1 (SP142) IHC: QNS |

## 5 evidence-based therapy associations

| | | |
|---|---|---|
| Cetuximab | Durvalumab | Everolimus |
| Panitumumab | Vandetanib + Docetaxel | |

## Specimen



Tumor cells: 40%
Specimen size: 255 $mm^2$
Residual tissue: No

Epithelial cells with features of adenocarcinoma noted

Gross Description: Xxxxxxxx xxxx XXX Xxxxt Xxxxxxx Xxxxxxx Xxxtxx xx Xxxxx xxxxxxx xx XX00-0000X (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx XX00-0000X (xxx XXXx-00-00000) xxxxtxxxxx xx xxxxxxxxx tx txx xxxxx xxxxx xxtxxxt xxxxx xx txx xxxxxxxxxxx xxxxxxxx xxtxxxxxx xxxxxt xxtx xxxxxxxx xxxxxxtxxx xxtx xx 0/00/0000. Xxxxx XX00-0000X xxxx xx xxxxxxxx.

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

## 4 IHCs

| | | | |
|---|---|---|---|
| ALK | N/A | 0% | Negative |
| PD-L1 (22C3) TILs | N/A | 0% | Negative |
| PD-L1 (22C3) Tumor | TPS: | 5 | Low |
| PD-L1 (SP142) IC | N/A | N/A | Insufficient / Cell Block |
| PD-L1 (SP142) TC | N/A | N/A | Insufficient / Cell Block |
| PTEN | 2+ | 70% | Positive |
| TS | 2+ | 40% | Positive |

## 5 salient genomic findings

| Gene | Variant | Quantity | Gene | Variant | Quantity |
|---|---|---|---|---|---|
| AKT1 | Amplification | 2.09x | NTRK1 | Amplification | 2.37x |
| EGFR | L747_T751del | 31% | TP53 | c.782+1G>C p.? | 63% |
| MYC | Amplification | 3.85x | | | |

## 26 other genomic findings

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

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

## 12 therapies with potential increased benefit

| Therapeutic Option | Biomarkers | NCCN/FDA | Level of evidence | References |
|---|---|---|---|---|
| Afatinib | EGFR Exon 19 Del | Yes | I | 16,23 |
| Cetuximab | KRAS/NRAS/BRAF WT | | DTT | 22,3 |
| Dacomitinib | EGFR Exon 19 Del | Yes | I | 28,17 |
| Durvalumab | EGFR mutation and PDL1:Tumor +<br>PD-L1 (22C3) Tumor + | | II-3<br>II-3 | 6<br>6 |
| Erlotinib | EGFR Exon 19 Del | Yes | I | 19,30 |
| Erlotinib + Bevacizumab | EGFR Exon 19 Del | Yes | I | 21,20 |
| Everolimus | KRAS WT | | DTT | 15,5 |
| Gefitinib | EGFR Exon 19 Del<br>MYC Amplification and EGFR mutation | Yes | II-2<br>II-3 | 13,29<br>2 |
| Osimertinib | EGFR Exon 19 Del | Yes | I | 25 |
| Panitumumab | KRAS WT | | DTT | 10 |
| Ramucirumab + Erlotinib | EGFR Exon 19 Del | Yes | I | 14,18 |
| Vandetanib + Docetaxel | EGFR Exon 19 Del | | I | 8 |

## 7 therapies with potential reduced benefit

| Therapeutic Option | Contraindicating biomarkers | References |
|---|---|---|
| Atezolizumab | EGFR mutation and PD-L1 (22C3) Tumor + | 11 |
| Avelumab | EGFR mutation and PDL1:Tumor + | 7 |
| Capecitabine | TS + | 26,12 |
| Carboplatin | AKT1 Amplification | 4 |
| Cisplatin | AKT1 Amplification | 4 |
| Fluorouracil | TS + | 9,24 |
| Pemetrexed | TS + | 27,1 |

## clinical notes

AKT1 CNV gain/amplification: Infrequent AKT1 gene amplification has been reported in various human cancers, including gastric carcinoma, glioblastoma, and gliosarcoma (Staal et al. 1987 PMID 3037531, Knobbe et al. 2003 PMID 14655756, Actor et al. 2002 PMID 12112531). AKT1 gene amplification has also been implicated as a biomarker of treatment response in ovarian cancer, specifically the association of AKT1 as plausible driver gene associated with reduced OS and platinum resistance. These data suggest that AKT1 amplification could have potential as a marker predictive of treatment outcome in some patients receiving platinum-based chemotherapy (Despierre et al. 2014 PMID 25281495).

ALK IHC negative: 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. Several lines of evidence support the notion that immunohistochemistry with the D5F3 clone can be used as a standalone test to select advanced NSCLC patients for treatment with ALK TKIs. At present, D5F3 is the companion diagnostic for crizotinib, ceritinib, and alectinib. 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). D5F3 positivity is defined as any strong positive staining in any number of cells. Recent studies on D5F3 IHC using a binary scoring algorithm have reported 100% sensitivity and high specificities. According to van der Wekken et al. 2017 (PMID 28183714), dichotomous ALK-IHC (either positive or negative) was found to be superior to ALK-FISH on small biopsies and FNA to predict tumor response and survival to anti-ALK therapy for advanced NSCLC patients. Of note, while all ALK IHC+ patients responded to crizotinib, no tumor response was observed ALK IHC- patients that may have presented with concurrent FISH positivity.

EGFR exon 19 deletion in NSCLC: The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor, thus inducing receptor dimerization and tyrosine autophosphorylation leading to cell proliferation. Mutations in this gene are associated with lung cancer [provided by RefSeq, Jul 2020]. Activating EGFR mutations confer transforming ability to the receptor and lead to its constitutive activation (Greulich et al 2005 PMID 16187797). Exon 19 deletions are observed with a frequency of 41.5% across US meta-data (Li et al. 2019 PMID 30785951) and the pooled prevalence of EGFR exon 19 del appears to be higher in females, non-smokers, and patients with adenocarcinoma (Zhang et al. 2016 PMID 27738317). Front-line EGFR TKI therapy has become the standard of care for lung cancer patients with sensitizing EGFR mutations and numerous phase III studies have demonstrated the superiority of TKIs to chemotherapy in progression-free survival and response rates (Bria et al. 2011 PMID 21325444; Hsu et al. 2018 PMID 29462253; Li et al. 2019 PMID 30785951). Consistently, patients with exon 19 deletion or L858R, have high objective response rates (ORR) and meaningful progression-free survival (PFS) when compared to uncommon EGFR alterations (Patil et al. 2020 PMID 31859066). While exon 19 deletions can also be divided into common and less common alterations, current data support that all exon 19 deletions – irrespective of starting codon of deletion - are equally sensitive to first-line EGFR-TKIs (Rossi et al. 2018 PMID 30473385). Based on FDA approvals, EGFR Exon 19 deletions are strong efficacy predictors for EGFR TKIs, including the "first-generation" drugs erlotinib (TARCEVA- erlotinib [package insert]. Genentech, Inc. Revised: 10/2016) and gefitinib (IRESSA- gefitinib [package insert]. AstraZeneca Pharmaceuticals LP. Revised: 8/2018) and the "second-generation" drug, afatinib (GILOTRIF- afatinib [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc. Revised: 10/2019). In addition, Dacomitinib (VIZIMPRO- dacomitinib [package insert]. U.S. Pharmaceuticals. Revised: 10/2018) and osimertinib (TAGRISSO- osimertinib [package insert]. AstraZeneca Pharmaceuticals LP. Revised: 6/2020) have been approved for the treatment of previously untreated patients with metastatic NSCLC with EGFR exon 19 deletions. The combination of erlotinib and ramucirumab (CYRAMZA- ramucirumab [package insert]. Eli Lilly and Company. Revised: 6/2020) also shows better progression-free survival (PFS) in patients with newly diagnosed EGFR-mutant metastatic NSCLC compared with erlotinib plus placebo, based on findings from the RELAY trial. Multiple clinical trials are currently recruiting patients with exon 19 deletions and are viewable in the clinical trials appendix of this report.

Concurrent PD-L1 positivity and EGFR mutation -- To date, first-line single agent immune checkpoint blockade has demonstrated limited activity in EGFR mutated NSCLC and the combination of immunotherapy and targeted agents has raised safety concerns in both EGFR and ALK positive NSCLC patients. The clinical activity of durvalumab in patients with EGFR+ NSCLC with ≥25% of tumor cells expressing PD-L1 was encouraging, and further investigation of durvalumab in patients with EGFR+/ALK+ NSCLC is warranted (Garassino et al. 2018).

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).

## clinical notes

MYC CNV gain/amplification: MYC regulates a complex biological program by transcriptionally activating and repressing its numerous target genes. As such, MYC is a master regulator of many processes, including cell cycle entry, ribosome biogenesis, and metabolism. In cancer, the activity of the MYC transcriptional network is frequently deregulated, contributing to the initiation and maintenance of disease. Gene amplification of MYC is the most commonly observed marker of MYC deregulation incancer. Gene duplication, taking place through genome doubling or tandem duplications, is the underlying mechanism for copy-number alterations (CNAs) in various oncogenes Pan-cancer analyses of at least 12 cancer types estimated the frequency of MYC amplification at approximately 14% comprised. MYC copy number alteration is particularly frequent in ovarian, breast, and squamous cell lung cancers (Kalkat et al 2017 PMID: 28587062). in ALK-Rearranged Non-Small Cell Lung Cancer, MYC amplification has been identified as a potential mechanism of primary resistance to Crizotinib (Rihawi, et al. 2019). Additionally, MYC amplification may significantly improve response and survival of non-small cell lung cancer patients treated with gefitinib (Cappuzzo et al. 2009).

NTRK1/TrkA CNV gain/amplification: The Trk family of receptors consists of three members named NTRK1, NTRK2, and NTRK3 (or TrkA, B, and C, respectively), displaying binding specificity for different neurothrophins. NTRK abnormalities (other than fusions, which are exceedingly rare), affect 14% of patients with cancer. Among all alterations in NTRK genes, transcript fusions are currently the best characterized and the most pharmacologically tractable. Additional genomic and transcriptomic NTRK alterations—mutation, amplification, and mRNA overexpression are generally found in 14% of samples (Okamura et al. 2018 PMID 30637364). Nonfusion NTRK alterations—for example, mutation or amplification—have been associated with a lack of response with some NTRK inhibitors. NTRK1 (TrkA) is a TK receptor for the nerve growth factor (NGF), which primarily regulates growth, differentiation, and programmed cell death of neurons in both the peripheral and central nervous system. NTRK1 activation in human malignancies occurs by several mechanisms, mainly structural rearrangements and altered expression. Although oncogenic activation of NTRK plays a major role in malignant behavior, its clinical and therapeutic application is currently limited to gene rearrangements in the NTRK genes. Select clinical trials for NTRK1 over-expressing malignancies may be viewed in the appendix of this report.

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. 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) QNS, Insufficient / Cell Block: The OncotypeMAP™ test has validated the SP142 assay in accordance with current companion and complementary diagnostics guidelines. To date, the evidence of PD-L1 SP142 testing on cell block specimens is scant; therefore, the feasibility of cell block evaluation remains controversial. While some studies have shown that cytology cell block specimens containing sufficient tumor cells could be a surrogate for PD-L1 staining in patients with NSCLC (Dong et al. 2020 PMID 31942178), most studies conclude that PD-L1 expression in cell blocks is difficult to interpret, and the percentage of patients with PD-L1 expression detected in cell blocks appears to be lower than in FFPE tissue specimens (Krawczyk et al. 2017 PMID 28969070). This suggests that reliable assessment of PD-L1 expression on immune cells in cell blocks cannot be achieved.

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.

TP53 in NSCLC: This gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome [provided by RefSeq, Dec 2016]. TP53 mutations are found in more than half of lung tumors, with highest frequency in SCC and lower prevalence in adenocarcinomas (review in Mogi and Kuwano 2011 PMID 21331359). It has been noticed that TP53 mutations are closely related to smoking status, whereby

## clinical notes

~30% of TP53 mutations are G:C to T:A transversions observed in smokers, but not in never-smokers and mutational hotspots within the TP53 gene, for example, codon 157, have been identified for tobacco-related lung cancer, whereas these same mutations are rarely found in other cancers (review in Mogi and Kuwano 2011 PMID 21331359). The majority of TP53 mutations are either missense or nonsense and altered TP53 can result in one of three possible outcomes: mutations that interfere with its tumor-suppressor properties (loss of function), mutations that confer the protein with a dominant-negative phenotype, and conformational mutations that contribute to the emergence of new functions (gain of function). The latter contribute to genomic instability, inhibition of apoptosis, cell migration, and drug resistance (Brosh and Rotter 2009 PMID 19693097). TP53 mutations are present in all segments of the gene, including >20% of mutations that occur outside the DNA-binding domain. Only 12 mutations are highly recurrent, representing each at least 1% of the entire mutation data set and hotspots have been observed in codons 213, 220, 245 and 282, in addition to a frequently mutated area in the oligomerization domain (residues 326–355) (Hainaut and Pfeifer 2016 PMID: 27503997). Somatic mutations in TP53 represent by far the most prevalent co-alteration in EGFR- mutant lung adenocarcinoma (Hainaut and Pfeifer 2016 PMID: 27503997) and appear to impact the natural history of EGFR-mutant NSCLC, whereby co-mutation EGFR/TP53 is associated with shorter progression-free survival following upfront treatment with 1st or 2nd generation EGFR TKIs (Masago et al. 2015 PMID 26572169; Canale et al. 2016 PMID 27780855; Lim et al. 2016 PMID 27121209; Labbé et al. 2017 PMID 28838393; Shen et al. 2017 29143497). Additionally there is emerging evidence that TP53 mutations, especially those in exon 8, could adversely impact clinical outcomes with the third generation inhibitors (Liu et al. 2019 PMID 31452792).

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 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.

## clinical trials

**in tumor type**

| | | |
|---|---|---|
| EGFR mutation | NCT01306045 | AZD \| MK-2206 \| Lapatinib \| Erlotinib \| sunitinib |
| Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies | | |
| EGFR mutation | NCT02314364 | SBRT with protons or photons |
| A Trial of Integrating SBRT With Targeted Therapy in Stage IV Oncogene-driven NSCLC | | |
| EGFR mutation | NCT02496663 | EGFR Inhibitor AZD9291 \| Necitumumab |
| Osimertinib and Necitumumab in Treating Patients With EGFR-Mutant Stage IV or Recurrent Non-small Cell Lung Cancer Who Have Progressed on a Previous EGFR Tyrosine Kinase Inhibitor | | |
| EGFR mutation | NCT02520778 | EGFR Inhibitor AZD9291 \| Navitoclax |
| Osimertinib and Navitoclax in Treating Patients With EGFR-Positive Previously Treated Advanced or Metastatic Non-small Cell Lung Cancer | | |
| EGFR mutation | NCT02716116 | AP32788 |
| A Trial of TAK-788 (AP32788) in Non-small Cell Lung Cancer (NSCLC) | | |
| EGFR mutation | NCT02729298 | TP-0903 |
| First-in-human Study of Oral TP-0903 (a Novel Inhibitor of AXL Kinase) in Patients With Advanced Solid Tumors | | |
| EGFR mutation | NCT02759835 | Osimertinib |
| Local Ablative Therapy for Treatment of Oligoprogressive, EGFR-Mutated, Non-Small Cell Lung Cancer After Treatment With Osimertinib | | |
| EGFR mutation | NCT02955290 | Nivolumab \| Vaccine Therapy |
| CIMAvax Vaccine, Nivolumab, and Pembrolizumab in Treating Patients With Advanced Non-small Cell Lung Cancer or Squamous Head and Neck Cancer | | |
| EGFR mutation | NCT02971501 | Bevacizumab \| Osimertinib |
| Osimertinib With or Without Bevacizumab in Treating Patients With EGFR Positive Non-small Cell Lung Cancer and Brain Metastases | | |
| EGFR mutation | NCT03256136 | Carboplatin \| Nivolumab \| Pemetrexed \| Ipilimumab |
| Nivolumab in Combination With Chemotherapy, or Nivolumab in Combination With Ipilimumab, in Advanced EGFR-Mutant or ALK-Rearranged NSCLC | | |
| EGFR mutation | NCT03292133 | EGF816 \| Gefitinib |
| A Study of EGF816 and Gefitinib in TKI-naïve EGFR-mutant Non-Small Cell Lung Cancer | | |
| EGFR mutation | NCT03333343 | EGF816 \| trametinib \| ribociclib \| LXH254 \| INC280 \| gefitinib |
| Study of EGF816 in Combination With Selected Targeted Agents in EGFR-mutant NSCLC | | |
| EGFR mutation | NCT03410043 | Osimertinib |
| Osimertinib, Surgery, and Radiation Therapy in Treating Patients With Stage IIIB or IV Non-small Cell Lung Cancer With EGFR Mutations | | |





**Continued**

## clinical trials

| | | |
|---|---|---|
| EGFR mutation | NCT03446417 | ZN-e4 |
| A Study of ZN-e4 in Subjects With Epidermal Growth Factor Receptor Mutated Non-Small Cell Lung Cancer | | |
| EGFR mutation | NCT03455829 | G1T38 \| Osimertinib |
| G1T38, a CDK 4/6 Inhibitor, in Combination With Osimertinib in EGFR-Mutant Non-Small Cell Lung Cancer | | |
| EGFR mutation | NCT03515837 | Pembrolizumab \| Pemetrexed \| Carboplatin \| Cisplatin |
| Study of Pemetrexed + Platinum Chemotherapy With or Without Pembrolizumab (MK-3475) in Adults With Tyrosine Kinase Inhibitor- (TKI)-Resistant Epidermal Growth Factor Receptor-(EGFR)-Mutated Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) (MK-3475-789/KEYNOTE-789) | | |
| EGFR mutation | NCT03521154 | Osimertinib \| Placebo Osimertinib |
| A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA) | | |
| EGFR mutation | NCT03521154 | Osimertinib \| Placebo Osimertinib |
| A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA) | | |
| EGFR mutation | NCT03535363 | Osimertinib |
| Osimertinib With Stereotactic Radiosurgery (SRS) in Brain Metastases From EGFR Positive NSCLC | | |
| EGFR mutation | NCT03586453 | Osimertinib |
| Osimertinib In EGFR Mutant Lung Cancer | | |
| EGFR mutation | NCT03786692 | Atezolizumab \| Carboplatin \| Pemetrexed \| Bevacizumab |
| Phase II Randomized Trial of Carboplatin+Pemetrexed+Bevacizumab+/- Atezolizumab in Stage IV NSCLC | | |
| EGFR mutation | NCT03810807 | Dacomitinib and Osimertinib |
| Study of Dacomitinib and Osimertinib for Patients With Advanced EGFR Mutant Lung Cancer | | |
| EGFR mutation | NCT03891615 | NiraparibIOsimertinib |
| Niraparib in Combination With Osimertinib in EGFR-Mutated Advanced Lung Cancer | | |
| EGFR mutation and TP53 mutation | NCT03567642 | Osimertinib \| Platinum \| Etoposide |
| A Study of the Combination of Osimertinib, Platinum and Etoposide for Patients With Metastatic EGFR Mutant Lung Cancers | | |
| PDL1:Tumor + | NCT02273375 | MEDI4736 \| Placebo |
| Double Blind Placebo Controlled Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC | | |
| PDL1:Tumor + | NCT02595944 | Nivolumab |
| Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer (An ALCHEMIST Treatment Trial) | | |
| PDL1:Tumor + | NCT02655822 | CPI-444 \| CPI-444 + Atezolizumab |
| Phase 1/1b Study to Evaluate the Safety and Tolerability of Ciforadenant Alone and in Combination With Atezolizumab in Advanced Cancers | | |
| PDL1:Tumor + | NCT02716038 | MPDL3280A \| Carboplatin \| Nab-Paclitaxel |
| Neoadjuvant MPDL3280A, Nab-paclitaxel and Carboplatin (MAC) in NSCLC | | |
| PDL1:Tumor + | NCT03330405 | Avelumab \| Talazoparib \| Avelumab \| Talazoparib |
| Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors | | |
| PDL1:Tumor + | NCT03409458 | PT-112 \| Avelumab |
| A Dose Escalation and Confirmation Study of PT-112 in Advanced Solid Tumors in Combination With Avelumab | | |
| PDL1:Tumor + | NCT03409614 | REGN2810 \| Chemotherapy |
| Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-based Doublet Chemotherapy in Patients With Lung Cancer | | |
| PDL1:Tumor + | NCT03455556 | Anetumab Ravtansine \| Atezolizumab |
| Anetumab Ravtansine and Atezolizumab in Treating Participants With Advanced Non-small Cell Lung Cancer | | |
| PDL1:Tumor + | NCT03523702 | Pembrolizumab + RT \| Chemotherapy + RT |
| The Selective Personalized Radio-Immunotherapy for Locally Advanced NSCLC Trial. | | |
| PDL1:Tumor + | NCT03546361 | CCL21-gene modified dendritic cells \| Pembrolizumab |
| Intratumoral Administration of CCL21-gene Modified Dendritic Cell With Intravenous Pembrolizumab for Advanced NSCLC | | |
| PDL1:Tumor + | NCT03583086 | VEGFR/PDGFR Dual Kinase Inhibitor X-82 \| Nivolumab |
| Phase I/II Eval Safety & Prelim Activity Nivolumab Comb W/Vorolanib Pts W/Refractory Thoracic Tumors | | |





**Continued**

## clinical trials

| | | |
|---|---|---|
| PDL1:Tumor + | NCT03631706 | M7824 \| Pembrolizumab |

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

| | | |
|---|---|---|
| PDL1:Tumor + | NCT03679767 | INCMGA00012 |

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

| | | |
|---|---|---|
| PDL1:Tumor + | NCT03735628 | Copanlisib \| Nivolumab |

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

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

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

| | | |
|---|---|---|
| PDL1:Tumor + | NCT03829332 | Biological: Pembrolizumab \| Lenvatinib |

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

| | | |
|---|---|---|
| PDL1:Tumor + | NCT03848611 | CM082 + JS001 |

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

| | | |
|---|---|---|
| EGFR mutation | NCT02091141 | Erlotinib |

My Pathway: A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, Erivedge, Alecensa, and Tecentriq Treatment Targeted Against Certain Molecular Alterations in Participants With Advanced Solid Tumors

| | | |
|---|---|---|
| EGFR mutation | NCT02451553 | Afatinib \| Capecitabine |

Afatinib Dimaleate and Capecitabine in Treating Patients With Advanced Refractory Solid Tumors, Pancreatic Cancer or Biliary Cancer

| | | |
|---|---|---|
| EGFR mutation | NCT03065387 | Neratinib \| Everolimus \| Palbociclib \| Trametinib |

Neratinib and Everolimus, Palbociclib, or Trametinib in Treating Participants With Refractory and Advanced or Metastatic Solid Tumors With EGFR Mutation/Amplification, HER2 Mutation/Amplification, or HER3/4 Mutation or KRAS Mutation

| | | |
|---|---|---|
| EGFR mutation | NCT04120454 | Ramucirumab \| Pembrolizumab |

Ramucirumab and Pembrolizumab for the Treatment of EGFR Mutant Recurrent or Metastatic Non-small Cell Lung Cancer

| | | |
|---|---|---|
| EGFR mutation | NCT04410796 | Osimertinib;Carboplatin;Pemetrexed; |

Osimertinib Alone or With Chemotherapy for EGFR-Mutant Lung Cancers

| | | |
|---|---|---|
| EGFR mutation | NCT04085315 | Osimertinib;Alisertib; |

Alisertib in Combination With Osimertinib in Metastatic EGFR-mutant Lung Cancer

| | | |
|---|---|---|
| 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

| | | |
|---|---|---|
| MYC Amplification | NCT02873975 | LY2606368 |

A Study of LY2606368 (Prexasertib) in Patients With Solid Tumors With Replicative Stress or Homologous Repair Deficiency

| | | |
|---|---|---|
| MYC Amplification | NCT03718091 | M6620 |

M6620 (VX-970) in Selected Solid Tumors

| | | |
|---|---|---|
| NTRK1 Amplification | NCT03556228 | VMD-928 |

Oral TrkA Inhibitor VMD-928 for Treatment of Advanced Adult Solid Tumors or Lymphoma

| | | |
|---|---|---|
| PD-L1 (22C3) Tumor + | NCT03956680 | BMS-986301;Nivolumab;Ipilimumab; |

An Investigational Immunotherapy Study of BMS-986301 Alone or in Combination With Nivolumab, and Ipilimumab in Participants With Advanced Solid Cancers

| | | |
|---|---|---|
| PD-L1 (22C3) Tumor + | NCT04007744 | Sonidegib; |

Sonidegib and Pembrolizumab in Treating Patients With Advanced Solid Tumors

| | | |
|---|---|---|
| PD-L1 (22C3) Tumor + | NCT04340882 | Docetaxel; |

Phase 2 TaxRamPem for Patients With Metastatic or Recurrent NSCLC Who Progressed on Platinum-Doublet and PD-1/PD-L1 Blockade

| | | |
|---|---|---|
| PDL1:Tumor + | NCT02608268 | MBG453 \| PDR001 |

Phase I-Ib/II Study of MBG453 as Single Agent and in Combination With PDR001 in Patients With Advanced Malignancies

## clinical trials

| | | |
|---|---|---|
| PDL1:Tumor + | NCT02614456 | Interferon-gamma and Nivolumab |
| Combination of Interferon-gamma and Nivolumab for Advanced Solid Tumors | | |
| PDL1:Tumor + | NCT03474640 | TAB001, Recombinant Humanized anti-PD-1 Monoclonal Antibody |
| Safety, Tolerability and Pharmacokinetics of an Anti-PD-1 Monoclonal Antibody in Subjects With Advanced Malignancies | | |
| PDL1:Tumor + | NCT03729596 | MGC018 I MGA012 |
| MGC018 With or Without MGA012 in Advanced Solid Tumors | | |
| RAS WT, BRAF WT | NCT02693535 | Cetuximab |
| TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer | | |
| TP53 mutation | NCT02576444 | AZD2281 I AZD5363 I AZD1775 I AZD2014 |
| OLAParib COmbinations | | |
| TP53 mutation | NCT02935907 | APG-115 |
| APG-115 in Patients With Advanced Solid Tumors or Lymphomas | | |
| 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 | 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 | TSC1 | TSC2 | TSHR | TYMS |
| VEGFA | VHL | WT1 | XRCC1 | YES1 | | | | | |

## genes negative for fusions and structural variants

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

## genes negative for copy number variants (amplifications)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ABCB1 | ABCC1 | ABCC2 | ABL1 | ACVR1 | ACVR1B | ACVR2A | ACVR2B | ACVRL1 | ADAMTS1 |
| ADAMTS16 | ADAMTS18 | ADAMTS6 | ADAMTS9 | ADAMTSL1 | 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 |





**Continued**

## genes negative for copy number variants (amplifications)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 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 | MYCN | MYOD1 | NBN |
| NF1 | NF2 | NFE2L2 | NOTCH1 | NOTCH2 | NOTCH3 | NPM1 | NRAS | NTRK2 | NTRK3 |
| PALB2 | PBRM1 | PDCD1LG2 | PDGFRA | PDGFRB | PIK3CA | PIK3CB | PIK3CD | PIK3CG | PIK3R1 |
| PIM1 | PLCB4 | PLCG1 | PMS2 | POLD1 | POLE | PPP2R1A | PTCH1 | PTEN | PTPN11 |
| RAD50 | RAD51C | RAD51D | RAF1 | RB1 | RBM10 | RECQL | RET | RHEB | RICTOR |
| RIT1 | RNF43 | ROS1 | RPTOR | RRM1 | SDHB | SDHC | SETD2 | SF3B1 | SMAD1 |
| SMAD2 | SMAD4 | SMAD5 | SMAD9 | SMARCA4 | SMARCB1 | SMO | SOCS1 | SPOP | STAG2 |
| STAT3 | STAT5A | STAT5B | STK11 | SUFU | TERT-p | TGFB1 | TGFB2 | TGFB3 | TGFBR1 |
| TGFBR2 | TNFAIP3 | TNK1 | TOP2A | TP53 | TSC1 | TSC2 | TSHR | TYMS | VEGFA |
| VHL | WT1 | XRCC1 | YES1 | | | | | | |

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## IHC thresholds

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

## Performance

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

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

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

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

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## Clinical trials

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

## NCCN compendium

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

## Reimbursement and acknowledgment

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

## Pan-Cancer Tissue panel core components

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

## Levels of evidence

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

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

## No warranty or guarantee

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

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

## Treatment decisions

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