Solid Tumor Profile

Test Description:

This is a next generation sequencing (NGS) test to identify molecular abnormalities in DNA of 434 genes implicated in solid tumors. Whenever possible, clinical relevance and implications of detected abnormalities are described below.

Detected Genomic Alterations

<table>
<thead>
<tr>
<th>Level 1 (FDA-Approved)</th>
<th>Level 2 (Standard of Care)</th>
<th>Level 3 (Clinical Evidence)</th>
<th>Level 4 (Biological Relevance)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR : L858</td>
<td>TMB (high)</td>
<td>BRAF: V600E</td>
<td>PTEN: Deletion</td>
<td>TP53: I255S</td>
</tr>
</tbody>
</table>

Tumor Heterogeneity

BRAF and KIT mutations are detected in small subclones

Diagnostic Implications

EGFR Mutation | Lung cancer with EGFR mutation

FDA-Approved Therapeutics

<table>
<thead>
<tr>
<th>EGFR : L858</th>
<th>Afatinib, Osimertinib, Gefitinib, Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMB*</td>
<td>Ipilimumab, Durvalumab, Avelumab, Atezolizumab, Nivolumab, Pembrolizumab</td>
</tr>
</tbody>
</table>

* The drugs are approved, but the marker is not approved as a companion test
Results Summary

- There are mutations in the EGFR (EXON 21), BRAF, TP53, and KIT.
- Tumor mutation burden: high 14/mb (above median, but below upper third).
- The presence of EGFR mutation suggests response to EGFR inhibitors.
- The high TMB suggests possible response to immunotherapy.
- Heterogeneity is noted based on variant allele frequency and only subclones carry the BRAF and KIT mutations.

Biological Relevance of Detected Alterations

- EGFR is widely recognized for its importance in cancer. Amplification and mutations have been shown to be driving events in many cancer types. Its role in non-small cell lung cancer, glioblastoma and basal-like breast cancers has spurred many research and drug development efforts. Tyrosine kinase inhibitors have shown efficacy in EGFR amplified tumors, most notably gefitinib and erlotinib. Mutations in EGFR have been shown to confer resistance to these drugs, particularly the variant T790M, which has been functionally characterized as a resistance marker for both of these drugs. The later generation TKI's have seen some success in treating these resistant cases, and targeted sequencing of the EGFR locus has become a common practice in treatment of non-small cell lung cancer.

- Overproduction of ligands is another possible mechanism of activation of EGFR. ERBB ligands include EGF, TGF-a, AREG, EPG, BTC, HB-EGF, EPR and NRG1-4 (for detailed information please refer to the respective ligand section). In ligand-activated cancers, Cetuximab appears to be more effective than tyrosine-kinase inhibitors (Arteaga et. al.).

- c-KIT activation has been shown to have oncogenic activity in gastrointestinal stromal tumors (GISTs), melanomas, lung cancer, and other tumor types. The targeted therapeutics nilotinib and sunitinib have shown efficacy in treating KIT overactive patients, and are in late-stage trials in melanoma and GIST. KIT overactivity can be the result of many genomic events from...
genomic amplification to overexpression to missense mutations. Missense mutations have been shown to be key players in mediating clinical response and acquired resistance in patients being treated with these targeted therapeutics.

- BRAF mutations are found to be recurrent in many cancer types. Of these, the mutation of valine 600 to glutamic acid (V600E) is the most prevalent. V600E has been determined to be an activating mutation, and cells that harbor it, along with other V600 mutations are sensitive to the BRAF inhibitor dabrafenib. It is also common to use MEK inhibition as a substitute for BRAF inhibitors, and the MEK inhibitor trametinib has seen some success in BRAF mutant melanomas. BRAF mutations have also been correlated with poor prognosis in many cancer types, although there is at least one study that questions this conclusion in papillary thyroid cancer.

- TP53 mutations are universal across cancer types. The loss of a tumor suppressor is most often through large deleterious events, such as frameshift mutations, or premature stop codons. In TP53 however, many of the observed mutations in cancer are found to be single nucleotide missense variants. These variants are broadly distributed throughout the gene, but with the majority localizing in the DNA binding domain. There is no single hotspot in the DNA binding domain, but a majority of mutations occur in amino acid positions 175, 245, 248, 273, and 282 (NM_000546) (Olivier et al., 2010). To fulfill its proper biological function four TP53 polypeptides must form a tetramer which functions as a transcription factor, therefore even if one out of four polypeptides has inactivating mutation it may lead to dominant negative phenotype of variable degree. While a large proportion of cancer genomics research is focused on somatic variants, TP53 is also of note in the germline. Germine TP53 mutations are the hallmark of Li-Fraumeni syndrome, and many (both germline and somatic) variants have been found to have a prognostic impact on patient outcomes. The significance of many polymorphisms for susceptibility and prognosis of disease is still very much up for debate.

- PTEN is a multi-functional tumor suppressor that is very commonly lost in human cancer. Observed in prostate cancer, glioblastoma, endometrial, lung and breast cancer to varying degrees. Up to 70% of prostate cancer patients have been observed to have loss of expression of the gene. It is a part of the PI3K/AKT/mTOR pathway and mTOR inhibitors have been relatively ineffective in treating patients with PTEN loss. New approaches using microRNAs are currently being investigated.

### Drug Information

#### Afatinib:

A radiation sensitizing agent and an ErbB2 tyrosine kinase inhibitor.

**EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer**

GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [see Clinical Pharmacology and Clinical Studies].

**Limitation of Use:** The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations [see Clinical Studies].

**Previously Treated, Metastatic Squamous NSCLC**

GILOTRIF is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy [see Clinical Studies].

#### Osimertinib

An EGFR tyrosine kinase inhibitor.

**EGFR inhibitor AZD9291.** An orally available, irreversible, third-generation, mutant-selective epidermal growth factor receptor (EGFR) inhibitor, with potential antineoplastic activity. Upon oral administration, AZD9291 selectively and covalently binds to and inhibits the activity of the mutant forms of EGFR, including the T790M EGFR mutant form, thereby preventing EGFR-mediated signaling. This may both induce cell death and inhibit tumor growth in EGFR-overexpressing tumor cells. EGFR, a receptor tyrosine kinase overexpressed or mutated in many types of cancers, plays a key role in tumor cell proliferation and tumor vascularization. As AZD9291 inhibits T790M, a secondarily acquired resistance mutation, this agent may have therapeutic benefits in tumors with T790M-mediated resistance. As this agent is selective towards mutant forms of EGFR, its toxicity profile may be reduced as compared to non-selective EGFR inhibitors, which also inhibit wild-type EGFR. (NCI Thesaurus) First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

**Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC.**

TAGRISSO is indicated for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

#### Gifitinib

An anilinoquinazoline with antineoplastic activity. Gefitinib inhibits the catalytic activity of numerous tyrosine kinases including the epidermal growth factor receptor (EGFR), which may result in inhibition of tyrosine kinase-dependent tumor growth. Specifically, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction. Gefitinib may also induce cell cycle arrest and inhibit angiogenesis.
RESSA is indicated for the first-line treatment of patients with or metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution.

Erlotinib

An inhibitor of epidermal growth factor receptor tyrosine kinase.

Non-Small Cell Lung Cancer (NSCLC)

TARCEVA® is indicated for:
- The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.

Limitations of use:
- Safety and efficacy of TARCEVA have not been established in patients with NSCLC whose tumors have other EGFR mutations.
- TARCEVA is not recommended for use in combination with platinum-based chemotherapy.
- Pancreatic Cancer

TARCEVA in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Iplimumab

YERVOY is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for:
- Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older).
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.
- Treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab.
- Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Durvalumab

Targets PD-L1 protein; in phase 1 clinical trials (2014).

A Fc optimized monoclonal antibody directed against programmed death 1 ligand 1 (PD-L1; B7 homolog 1; B7H1), with potential immune checkpoint inhibitory and antineoplastic activities. Upon intravenous administration, durvalumab binds to PD-L1, thereby blocking its binding to and activation of its receptor programmed death 1 (PD-1) expressed on activated T-cells. This may reverse T-cell inactivation and activate the immune system to exert a cytotoxic T-lymphocyte (CTL) response against PD-L1-expressing tumor cells. PD-L1, a member of the B7 protein superfamily, is overexpressed on certain tumor cell types and on various tumor-infiltrating immune cells. PD-L1 binding to PD-1 on T-cells suppresses the immune system and results in increased immune evasion. The Fc region of durvalumab is modified in such a way that it does not induce either antibody-dependent cell toxicity (ADCC) or complement-dependent cytotoxicity (CDC).

- Urothelial Carcinoma

IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[].
- Non-Small Cell Lung Cancer

IMFINZI is indicated for the treatment of patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Avelumab

Targets programmed cell death protein 1 ligand; has antineoplastic activity.

A human immunoglobulin G1 (IgG1) monoclonal antibody directed against the human immunosuppressive ligand programmed death-ligand 1 (PD-L1) protein, with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, avelumab binds to PD-L1 and prevents the interaction of PD-L1 with its receptor programmed death protein 1 (PD-1). This inhibits the activation of PD-1 and its downstream signaling pathways. This may restore immune function through the activation of cytotoxic T-lymphocytes (CTLs) targeted to PD-L1-overexpressing tumor cells. In addition, avelumab induces an antibody-dependent cellular cytotoxic (ADCC) response against PD-L1-expressing tumor cells. PD-1, a cell surface receptor belonging to the immunoglobulin superfamily expressed on T-cells, negatively regulates T-cell activation and effector function when activated by its ligand, and plays an important role in tumor evasion from host immunity. PD-L1, a transmembrane protein, is overexpressed on a variety of tumor cell types and is associated with poor prognosis.

-Metastatic Merkel Cell Carcinoma
BAVENCIO (avelumab) is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [see Clinical Studies (14.1)].

-Locally Advanced or Metastatic Urothelial Carcinoma

BAVENCIO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Atezolizumab

A monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and is used to treat urothelial carcinoma, the most common type of bladder cancer.

TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- are not eligible for cisplatin-containing chemotherapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or
- have disease progression during or following any platinum-containing chemotherapy, regardless of PD-L1 status, or
- have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Nivolumab


OPDIVO @ as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

OPDIVO as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma.

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

-Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

-Metastatic Non-Small Cell Lung Cancer

OPDIVO is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

-Advanced Renal Cell Carcinoma

OPDIVO as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).

1.5 Classical Hodgkin Lymphoma

OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (CHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- or more lines of systemic therapy that includes autologous HSCT.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

-Squamous Cell Carcinoma of the Head and Neck

OPDIVO is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

-Urothelial Carcinoma

OPDIVO (nivolumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

-Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of adults and pediatric patients 12 years and older with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Hepatocellular Carcinoma

OPDIVO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**Pembrolizumab**

A humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumor cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on APCs. Activated PD-1 negatively regulates T-cell activation and plays a key role in tumor evasion from host immunity.

**Melanoma**

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

- Non-Small Cell Lung Cancer

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

- KEYTRUDA, as a single agent, is indicated 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, in combination with pembrolizumab and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

- Head and Neck Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

- Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

- Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitation of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

- Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10], or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

- Microsatellite Instability-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

- Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test and who have disease progression following treatment with a fluoropyrimidine, oxaliplatin, and/or irinotecan. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Small Cell Lung Cancer

KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Combined Positive Score (CPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

- Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test and who have disease progression following treatment with a fluoropyrimidine, oxaliplatin, and/or irinotecan. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Hematologic Malignancies

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

-**Cervical Cancer**

**KEYTRUDA** is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

### Potential Clinical Trials

<table>
<thead>
<tr>
<th>Trial #</th>
<th>Status</th>
<th>Title</th>
<th>Disease</th>
<th>Drug</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02716311</td>
<td>Recruiting</td>
<td>Combination of Cetuximab With Afatinib for Patient With EGFR Mutated Lung Cancer</td>
<td>Non Small Cell Lung Cancer</td>
<td>Drug: Afatinib, Cetuximab</td>
<td>Centre Hospitalier du Pays d'Aix, Aix-en-Provence, France, Clinique de L'Europe, Amiens, France, Angers - CHU, (and 30 more...)</td>
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<tr>
<td>NCT03567642</td>
<td>Recruiting</td>
<td>A Study of the Combination of Osimertinib, Platinum and Etoposide for Patients With Metastatic EGFR Mutant Lung Cancers</td>
<td>Lung Cancer</td>
<td>Drug: Osimertinib, Platinum, Etoposide</td>
<td>Memorial Sloan Kettering Cancer Center, Basking Ridge, New Jersey, United States, Memorial Sloan Kettering Monmouth, Memorial Sloan Kettering Commack, Middletown, New Jersey, United States,</td>
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<tr>
<td>NCT03122717</td>
<td>Recruiting</td>
<td>Osimertinib and Gefitinib in EGFR Inhibitor naïve Advanced EGFR Mutant Lung Cancer</td>
<td>Non-Small Cell Lung Cancer</td>
<td>Drug: Gefitinib, Osimetinib</td>
<td>Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States, Dana Farber Cancer Institute, Boston, Massachusetts, United States,</td>
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<tr>
<td>NCT02804776</td>
<td>Recruiting</td>
<td>PRe-Operative Gefitinib in Resectable EGFR Mutation Positive Lung Cancer With Sector Sequencing for Biomarker Discovery</td>
<td>Non-small Cell Lung Cancer</td>
<td>Drug: Gefitinib</td>
<td>National Cancer Centre, Singapore, Singapore</td>
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<tr>
<td>NCT03392246</td>
<td>Recruiting</td>
<td>A Phase 2 Study of Osimertinib in Combination With Selumetinib in Non-small Cell Lung Cancer</td>
<td>Drug: Osimertinib, Selumetinib</td>
<td>Massachusetts General Hospital, Boston, Massachusetts,</td>
<td></td>
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The professional and technical components of this assay were performed at Genomic Testing Cooperative, LCA, 27 Technology Drive, Suite 100, Irvine, CA 92618 (CLIA ID: 05D211917).

The assay is FDA cleared and the performance characteristics were established at this location and are approved by the FDA for this laboratory.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Status</th>
<th>Treatment</th>
<th>Condition</th>
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<tbody>
<tr>
<td>NCT02803203</td>
<td>Recruiting</td>
<td>Osimertinib and Bevacizumab as Treatment for EGFR-mutant Lung Cancers</td>
<td>Non-small Cell Lung Cancer</td>
<td>United States, Beth Israel Deaconess Medical Center, Boston, Dana, Boston, Massachusetts, United States Farber Cancer Institute, Massachusetts, United States</td>
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<tr>
<td>NCT03066206</td>
<td>Recruiting</td>
<td>Pozotinib in EGFR Exon 20 Mutant Advanced Non-Small Cell Lung Cancer (NSCLC) and HER2 Exon 20 Mutant NSCLC</td>
<td>Malignant Neoplasm of Respiratory and Intrathoracic Organ</td>
<td>University of Texas MD Anderson Cancer Center</td>
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<tr>
<td>NCT02954523</td>
<td>Recruiting</td>
<td>Dasatinib and Osimertinib (AZD9291) in Advanced Non-Small Cell Lung Cancer With EGFR Mutations</td>
<td>EGFR Gene Mutation, NSCLC</td>
<td>Georgetown Lombardi Comprehensive Cancer Center, John Theurer Cancer Center at Hackensack University Medical Center</td>
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<td>NCT03396185</td>
<td>Recruiting</td>
<td>Icotinib as Consolidation Therapy After Chemoradiotherapy in EGFR-Mutant Stage IIA-IIIB Non-Small Cell Lung Cancer</td>
<td>EGFR Gene Mutation</td>
<td>Cancer Hospital, Chinese Academy of Medical Science</td>
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<tr>
<td>NCT03292133</td>
<td>Recruiting</td>
<td>A Study of EGF816 and Gefitinib in TKI-naïve EGFR-mutant Non-Small Cell Lung Cancer</td>
<td>Lung Cancer</td>
<td>Massachusetts General Hospital</td>
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<tr>
<td>NCT02335944</td>
<td>Recruiting</td>
<td>Study of Safety and Efficacy of EGFR-TKI EGF816 in Combination With cMET Inhibitor INC280 in Non-Small Cell Lung Cancer Patients With EGFR Mutation.</td>
<td>Non Small Cell Lung Cancer</td>
<td>City of Hope National Medical Center SC, H. Lee Moffitt Cancer Center &amp; Research Institute H Lee Moffitt, Massachusetts, General Hospital Mass General, (and 19 more...)</td>
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<tr>
<td>NCT02714010</td>
<td>Recruiting</td>
<td>EGFR-TKI Concurrent With/Without WBRT in Brain Metastasis From NSCLC</td>
<td>Non-Small Cell Lung Cancer</td>
<td>Drug: EGFR-TKI, Radiation: Whole brain</td>
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<tr>
<td>NCT03455829</td>
<td>Recruiting</td>
<td>G1T38, a CDK 4/6 Inhibitor, in Combination With Osimertinib in EGFR-Mutant Non-Small Cell Lung Cancer</td>
<td>Carcinoma, Non-Small-Cell Lung</td>
<td>Drug: G1T38, Osimertinib</td>
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<tr>
<td>NCT02633189</td>
<td>Recruiting</td>
<td>Study Comparing Bevacizumab + Erlotinib vs Erlotinib Alone as First Line Treatment of Patients With EGFR Mutated Advanced Non Squamous Non Small Cell Lung Cancer</td>
<td>Non-squamous Non-small Cell Lung Cancer</td>
<td>Drug: Erlotinib, Bevacizumab</td>
</tr>
<tr>
<td>NCT02468661</td>
<td>Recruiting</td>
<td>A Safety and Efficacy Study of INC280 Alone, and in Combination With Erlotinib, Compared to Chemotherapy, in Advanced/Metastatic Non-small Cell Lung Cancer Patients With EGFR Mutation and cMET Amplification</td>
<td>Non-Small Cell Lung Cancer</td>
<td>Drug: INC280 single agent; INC280 in combination with erlotinib; Platinum/pe metrexed</td>
</tr>
</tbody>
</table>

**Detailed Results**

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Hgvsp</th>
<th>HgvsC</th>
<th>Aminoacids</th>
<th>Codons</th>
<th>Consequence</th>
<th>Allele frequency</th>
<th>Read depth</th>
<th>Predicted effect on protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>NP_005219.2:p.Leu858Arg</td>
<td>NM_005228.3:c.2573T&gt;G</td>
<td>L/R</td>
<td>cTg/cGg</td>
<td>missense_variant</td>
<td>37.8</td>
<td>411</td>
<td>deleterious (0)</td>
</tr>
<tr>
<td>TP53</td>
<td>NP_000537.3:p.Ile255Asn</td>
<td>NM_000546.5:c.764T&gt;A</td>
<td>I/N</td>
<td>aTc/aAc</td>
<td>missense_variant</td>
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<td>268</td>
<td>deleterious (0)</td>
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<tr>
<td>BRAF</td>
<td>NP_004324.2:p.Val600Glu</td>
<td>NM_004333.4:c.1799T&gt;A</td>
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<td>gTg/gAg</td>
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<td>deleterious (0)</td>
</tr>
<tr>
<td>KIT</td>
<td>NP_000213.1:p.Trp557Arg</td>
<td>NM_000222.2:c.1669T&gt;C</td>
<td>W/R</td>
<td>Tgg/Cgg</td>
<td>missense_variant</td>
<td>37.4</td>
<td>401</td>
<td>deleterious (0)</td>
</tr>
</tbody>
</table>

**Copy Number Variant**

None
Heterogeneity within the Tumor

The most dominant clone carries the STK11 mutation and KRAS mutations. SMARCA4 and TGFB2 mutations appear to be in subclones.

Methodology and Test Background

This is a next generation sequencing (NGS) test that analyzes DNA for abnormalities in 434 genes that are reported to be altered in various types of tumors. Nucleic acid is isolated from paraffin-embedded tissue. Testing is performed using massive parallel sequencing of the coding DNA of the listed genes. This includes sequencing of all the exons as well as 50 nucleotides at the 5’ and 3’ ends of each coding exon. Our sequencing method has a typical sensitivity of 3% for detecting common specific mutations and 5% for other mutations. Known hot spots in specific genes such as IDH1/2, NRAS, and KRAS are reported at levels of 1% and higher. Performance of the assay may vary dependent on the quantity and quality of nucleic acid, sample preparation and sample age. The assay is designed to detect significant gene amplification and deletion in addition to various single nucleotide variations (SNV) and indels.

Tested genes

Genes Tested for Abnormalities in coding sequence

<table>
<thead>
<tr>
<th>Genes Tested for Abnormalities in coding sequence</th>
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</thead>
<tbody>
<tr>
<td>ABC2B</td>
</tr>
<tr>
<td>ACL2</td>
</tr>
<tr>
<td>ALI2</td>
</tr>
<tr>
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<td>ALK1</td>
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</tr>
<tr>
<td>ALK6</td>
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Add-on RNA Fusions/Expression

Fusion/Expression

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>ABL1</td>
</tr>
<tr>
<td>ACL2</td>
</tr>
<tr>
<td>ALK1</td>
</tr>
<tr>
<td>AKT3</td>
</tr>
<tr>
<td>ALK1</td>
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</table>

The professional and technical components of this assay were performed at Genomic Testing Cooperative, LCA, 27 Technology Drive, Suite 100, Irvine, CA 92618 (CLIA ID: 05D211917). The assay is FDA cleared and the performance characteristics were established at this location.
The professional and technical components of this assay were performed at Genomic Testing Cooperative, LCA, 27 Technology Drive, Suite 100, Irvine, CA 92618 (CLIA ID: 05D211197). The genomics lab and the performance characteristics were established at this location and are

References


52. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.


Electronic Signature
Maher Albitar, M.D., Pathologist - GTC Laboratories
The Technical Component Processing, Analysis and Professional Component of this test was completed at GTC Laboratories, 21 Technology Dr. #100, Irvine, CA 92618. The Performance Characteristics of this test have been determined by GTC Laboratories. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity clinical testing.