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Solid Tumor Profile Plus

Patient Name:		Ordered By	
Date of Birth:		Ordering Physician:	
Gender (M/F):		Physician ID:	
Client:		Accession #:	
Case #:		Specimen Type:	
Body Site:		Specimen ID:	

Ethnicity:				Family History:	
MRN:				Indication for Testing:	
Collected Date:		Time :		Reason for Referral:	Malignant Neoplasm of Lung
Received Date:		Time :		Tumor Type:	Lung
Reported Date:		Time :		Stage:	T2B

Test Description:

This is a next generation sequencing (NGS) test to identify molecular abnormalities in DNA of 434 genes and RNA in 55 genes implicated in solid tumors. Whenever possible, clinical relevance and implications of detected abnormalities are described below.

Detected Genomic Alterations				
Level 1 (FDA-Approved)	Level 2 (Standard of Care)	Level 3 (Clinical Evidence)	Level 4 (Biological Relevance)	Other
EGFR : L858	TMB (high)	BRAF: V600E	PTEN: Deletion	TP53: I255S
ALK: EML4-ALK Fusion	KIT: T670I			

Tumor Heterogeneity
BRAF and KIT mutations are detected in small subclones

Diagnostic Implications	
EGFR Mutation and ALK Rearrangement	The co-presence of these two abnormalities is extremely rare

Prognostic Implications	
ALk/EGFR	Good

FDA-Approved Therapeutics	
EGFR : L858	Afatinib, Osimertinib, Gefitinib, Erlotinib
ALK: EML4-ALK Fusion	Crizotinib, Ceritinib, Brigatinib, Alectinib
TMB*	Ipilimumab, Durvalumab, Avelumab, Atezolizumab, Nivolumab, Pembrolizumab,
* The drugs are approved, but the marker is not approved as a companion test	

FDA-Approved Therapeutics in Other Tumor Types	
BRAF: V600E	Dabrafenib, Trametinib, Vemurafenib, Binimetinib, Encorafenib, Cobimetinib, Tametinib
KIT: T670I	Regoraenib, Imatinib, Sunitinib

Relevant Alteration Associated with Resistance
NONE

Levels 2, 3 & 4 (Standard of Care and Clinical/Biological Evidence)	
BRAF: V600E	Afatinib, Osimertinib, Gefitinib, Erlotinib
KIT: T670I	Regoraenib, Imatinib, Sunitinib, Sorafnib
TP53: I255S	NONE

Relevant Genes with No Alteration		
KRAS	ROS1	ERBB2
RET	MET	Microsatellite

Results Summary

- There are mutations in the EGFR (EXON 21), BRAF, TP53, and KIT. In addition, fusion involving the ALK gene (EML4-ALK) and a deletion in PTEN are detected.
- Tumor mutation burden: high 14/mb (above median, but below upper third).
- EGFR mutation and ALK fusion in the same tumor is highly unusual and rare.
- The presence of EGFR mutation suggests response to EGFR inhibitors.
- The presence of ALK rearrangement suggests response to ALK inhibitors.
- The high TMB suggests possible response to immunotherapy.
- Heterogeniety 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 amplfied 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.).
- ALK amplifications, fusions and mutations have been shown to be driving events in non-small cell lung cancer. While crizontinib has demonstrated efficacy in treating the amplification, mutations in ALK have been shown to confer resistance to current tyrosine kinase inhibitors. Second-generation TKI's have seen varied success in treating these resistant cases, and the HSP90 inhibitor 17-AAG has been shown to be cytostatic in ALK-altered cell lines.
- 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. Germline 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 appoaches 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.

Crizotinib

A selective c-Met/Alk tyrosine kinase inhibitor in clinical development as an anticancer agent.
An orally bioavailable agent belonging to the class of c-met/hepatocyte growth factor receptor (HGFR) tyrosine kinase inhibitors with potential antineoplastic activity. MET tyrosine kinase inhibitor PF-02341066 inhibits the membrane receptor MET and activation of the MET signaling pathway, which may block tumor cell growth, migration and invasion, and tumor angiogenesis in susceptible tumor cell populations.
XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test

Ceritinib

An anaplastic lymphoma kinase inhibitor.
ZYKADIA® is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

Brigatinib

An anaplastic lymphoma kinase inhibitor.
An orally available inhibitor of receptor tyrosine kinases anaplastic lymphoma kinase (ALK) and the epidermal growth factor receptor

(EGFR) with potential antineoplastic activity. Brigatinib binds to and inhibits ALK kinase and ALK fusion proteins as well as EGFR and mutant forms. This leads to the inhibition of ALK kinase and EGFR kinase, disrupts their signaling pathways and eventually inhibits tumor cell growth in susceptible tumor cells. In addition, brigatinib appears to overcome mutation-based resistance. ALK belongs to the insulin receptor superfamily and plays an important role in nervous system development; ALK dysregulation and gene rearrangements are associated with a series of tumors. EGFR is overexpressed in a variety of cancer cell types.
ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
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 a confirmatory trial.

Alectinib

An anaplastic lymphoma kinase (Alk) inhibitor
An orally available inhibitor of the receptor tyrosine kinase anaplastic lymphoma kinase (ALK) with antineoplastic activity. Upon administration, alectinib binds to and inhibits ALK kinase, ALK fusion proteins as well as the gatekeeper mutation ALKL1196M known as one of the mechanisms of acquired resistance to small-molecule kinase inhibitors. The inhibition leads to disruption of ALK-mediated signaling and eventually inhibits tumor cell growth in ALK-overexpressing tumor cells. ALK belongs to the insulin receptor superfamily and plays an important role in nervous system development. ALK dysregulation and gene rearrangements are associated with a series of tumors

ALECENSA is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

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 cell 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 cytotoxicity (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 cell 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 (CD274 ANTIGEN) 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
-are not eligible for 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

A genetically engineered, fully human immunoglobulin G4 (IgG4) monoclonal anti programmed death-1/PD-1 protein antibody.
-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.
OPDIVO as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive 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
-3 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

-OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with 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 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 pemetrexed 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 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, 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

Trial #	Status	Title	Disease	Drug	Sites
NCT02716311	Recruiting	Combination of Cetuximab With Afatinib for Patient With EGFR Mutated Lung Cancer	Non Small Cell Lung Cancer	Drug: Afatinib, Cetuximab	Centre Hospitalier du Pays d'Aix, Aix-en-Provence, France, Clinique de L'Europe, Amiens, France, Angers - CHU, (and 30 more...)
NCT03567642	Recruiting	A Study of the Combination of Osimertinib, Platinum and Etoposide for Patients With Metastatic EGFR Mutant Lung Cancers	Lung Cancer	Drug: Osimertinib, Platinum, Etoposide	Memoral Sloan Kettering Cancer Center, Basking Ridge, New Jersey, United States, Memorial Sloan Kettering Monmouth, Memorial Sloan Kettering Commack, Middletown, New Jersey, United States,
NCT03122717	Recruiting	Osimertinib and Gefitinib in EGFR Inhibitor naïve Advanced EGFR Mutant Lung Cancer	Non-Small Cell Lung Cancer	Drug: Gerfitinib, Osimetinib	Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States, Dana Farber Cancer Institute, Boston, Massachusetts, United States
NCT02804776	Recruiting	PRe-Operative Gefitinib in Resectable EGFR Mutation Positive Lung Cancer With Sector Sequencing for Biomarker Discovery	Non-small Cell Lung Cancer	Drug: Gefitinib	National Cancer Centre, Singapore, Singapore

NCT03392246	Recruiting	A Phase 2 Study of Osimertinib in Combination With Selumetinib in EGFR Inhibitor naïve Advanced EGFR Mutant Lung Cancer	Non-small Cell Lung Cancer	Drug: Osimertinib, Selumetinib	Massachusetts General Hospital, Boston, Massachusetts, United States, Beth Israel Deaconess Medical Center, Boston, Dana, Boston, Massachusetts, United States Farber Cancer Institute, Massachusetts, United States,
NCT02803203	Recruiting	Osimertinib and Bevacizumab as Treatment for EGFR-mutant Lung Cancers	Non-small Cell Lung Cancer	Drug: osimertinib, Bevacizumab	Memoral Sloan Kettering Cancer Center
NCT03066206	Recruiting	Poziotinib in EGFR Exon 20 Mutant Advanced Non-Small Cell Lung Cancer (NSCLC) and HER2 Exon 20 Mutant NSCLC	Malignant Neoplasm of Respiratory and Intrathoracic Organ	Drug: Poziotinib	University of Texas MD Anderson Cancer Center
NCT02954523	Recruiting	Dasatinib and Osimertinib (AZD9291) in Advanced Non-Small Cell Lung Cancer With EGFR Mutations	EGFR Gene Mutation, NSCLC	Drug: Dasatinib, Osimertinib	Georgetown Lombardi Comprehensive Cancer Center, John Theurer Cacner Center at Hackensack University Medical Center
NCT03396185	Recruiting	Icotinib as Consolidation Therapy After Chemoradiotherapy in EGFR-Mutant Stage IIIA-IIIB Non-small Cell Lung Cancer	EGFR Gene Mutation	Drug: Icotinib	Cancer Hospital, Chinese Academy of Medical Science
NCT03292133	Recruiting	A Study of EGF816 and Gefitinib in TKI-naïve EGFR-mutant Non-Small Cell Lung Cancer	Lung Cancer	Drug: (EGF816) Gefitinib	Massachusetts General Hospital
NCT02335944	Recruiting	Study of Safety and Efficacy of EGFR-TKI EGF816 in Combination With cMET Inhibitor INC280 in Non-small Cell Lung	Non Small Cell Lung Cancer	Drug: INC280 (EGF816)	City of Hope National Medical Center SC, H. Lee Moffitt Cancer Center & Research Institute H Lee Moffitt,

		Cancer Patients With EGFR Mutation.			Massachusetts, General Hospital Mass General, (and 19 more...)
NCT02714010	Recruiting	EGFR-TKI Concurrent With/Without WBRT in Brain Metastasis From NSCLC	Non-Small Cell Lung Cancer	Drug: EGFR-TKI, Radiation: Whole brain	Sun Yat-sen University of cancer center, Guangzhou, Guangdong, China
NCT03455829	Recruiting	G1T38, a CDK 4/6 Inhibitor, in Combination With Osimertinib in EGFR-Mutant Non-Small Cell Lung Cancer	Carcinoma, Non-Small-Cell Lung	Drug: G1T38, Osimertnib	Beverly Hills Cancer Center, St Joseph Heritage Healthcare
NCT02633189	Recruiting	Study Comparing Bevacizumab + Erlotinib vs Erlotinib Alone as First Line Treatment of Patients With EGFR Mutated Advanced Non Squamous Non Small Cell Lung Cancer	Non-squamous Non-small Cell Lung Cancer	Drug: Erlotinib, Bevacizumab	Ospedale Ramazzini, Day Hospital Oncologico, Carpi, MO, Italy, Casa di Cura La Maddalena S.p.A., Dipartimento Oncologico,
NCT02468661	Recruiting	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	Non-Small Cell Lung Cancer	Drug: INC280 single agent; INC280 in combination with erlotinib; Platinum/pemetrxed	Los Angeles Hematology/Oncology Medical Group, University of California Irvine Medical Center Chao Family SC, Orange, California, United States, Yale School of Medicine, New Haven, Connecticut, United States

Detailed Results

Single Nucleotide Variant (SNV)

Gene name	Hgvsp	Hgvsc	Aminoacids	Codons	Consequence	Allele frequency	Read depth	Predicted effect on protein
EGFR	NP_005219.2:p.Leu858Arg	NM_005228.3:c.2573T>G	L/R	cTg/cGg	missense_variant	37.8	411	deleterious (0)
TP53	NP_000537.3:p.Ile255Asn	NM_000546.5:c.764T>A	I/N	aTc/aAc	missense_variant	34.2	268	deleterious (0)
BRAF	NP_004324.2:p.Val600Glu	NM_004333.4:c.1799T>A	V/E	gTg/gAg	missense_variant	27.6	468	deleterious (0)
KIT	NP_000213.1:p.Trp557Arg	NM_000222.2:c.1669T>C	W/R	Tgg/Cgg	missense_variant	37.4	401	deleterious (0)

Copy Number Variant

None

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Fusion (traslocation)	
Gene Name	Fusion Reads (%)
EML4-ALK	51%

Heterogeneity within the Tumor

The most dominant clone caries the STK11 mutation and KRAS mutations. SMARCA4 and TGFBR2 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.
In addition to DNA analysis, targeted RNA NGS analysis was performed. This analyzes targeted RNA with a focus on 55 genes. It is based on hybrid capture of targeted RNA. Duplicates are excluded for levels measurements. While the major focus of the analysis is the detection of fusion mRNA, mutations in the expressed RNA of the analyzed genes are also analyzed and reported. mRNA expression levels are evaluated, and only significant high expression of specific genes are relatively reported. CD274 (PD-L1) mRNA levels are reported when they are significantly elevated. If requested, detailed expression levels will be provided as a research data and not for clinical use. All detect fusion transcripts are reported. This test specifically covers translocations that lead to the expression of fusion RNA. Translocations that lead to deregulation of expression can be addressed by this test if compared to the expression proper normal control. The sensitivity of this assay in detecting fusion mRNA is between 1% and 5%. This assay is not designed to detect minimal residual disease and should be used for diagnosis when neoplastic cells are >10% of the analyzed cells. The Universal Human Reference (UHR) RNA is used as control.

Tested genes

Genes Tested for Abnormalities in coding sequence															
ABCB7	AURKB	C15ORF41	CEBPA	DICER1	FANCC	FLT3	GRIN2A	IRF2	LMO1	MSH2	NTRK1	POLE	RANBP2	SETD2	STAT4	TSC2
ABL1	AURKC	CALR	CHD2	DOT1L	FANCD2	FLT4	GRM3	IRF4	LPIN2	MSH6	NTRK2	POT1	RARA	SF3B1	STAT6	TSHR
ABL2	AXIN1	CARD11	CHD4	EED	FANCE	FOXL2	GSK3B	IRS2	LRP1B	MTOR	NTRK3	PPM1D	RB1	SLIT2	STK11	U2AF1
ACD	AXIN2	CBFB	CHEK1	EGFR	FANCF	FOXP1	GSKIP	JAGN1	LYN	MUTYH	NUP93	PPP2R1A	RBBP6	SLX4	SUFU	U2AF2
ACVR1B	AXL	CBL	CHEK2	EGLN1	FANCG	FRS2	H3F3A	JAK1	LYST	MVK	PAK3	PRDM1	RBM10	SMAD2	SUZ12	VEGFA
ADA	B2M	CBLB	CIC	ELANE	FANCI	FUBP1	HAX1	JAK2	LZTR1	MYC	PALB2	PREX2	RBM8A	SMAD3	SYK	VHL
AK2	BAP1	CBLC	CREBBP	EP300	FANCL	G6PC3	HGF	JAK3	MAGI2	MYCL	PARK2	PRKAR1A	RET	SMAD4	TAF1	WAS
AKT1	BARD1	CCND1	CRKL	EPAS1	FANCM	GABRA6	HIST1H3B	JUN	MAP2K1	MYCN	PAX5	PRKCI	RHEB	SMAD9	TAL1	WHSC1
AKT2	BCL2	CCND2	CRLF2	EPCAM	FAS	GALNT12	HNF1A	KAT6A	MAP2K2	MYD88	PBRM1	PRKDC	RHOA	SMAD9L	TBX3	WISP3
AKT3	BCL2L1	CCND3	CSF1R	EPHA3	FAT1	GATA1	HOXA11	KDM5A	MAP2K4	NBN	PDCD1LG2	PRSS1	RICTOR	SMARCA4	TCF3	WT1
ALK	BCL2L2	CCNE1	CSF3R	EPHA5	FBXW7	GATA2	HOXB13	KDM5C	MAP3K1	NF1	PDGFRA	PRSS8	RIT1	SMARCB1	TCIRG1	XPO1
AMER1	BCL6	CD274	CTC1	EPHA7	FGF10	GATA3	HRAS	KDM6A	MAP3K14	NF2	PDGFRB	PSTPIP1	RNF168	SMC1A	TERC	XRCC2
ANKRD26	BCOR	CD79A	CTCF	EPHB1	FGF14	GATA4	HSD3B1	KDR	MAPK1	NFE2L2	PDK1	PTCH1	RNF43	SMC3	TERF1	XRCC3
APC	BCORL1	CD79B	CTNNA1	ERBB2	FGF19	GATA6	HSP90AA1	KEAP1	MCL1	NFKBIA	PHF6	PTEN	ROS1	SMO	TERF2	ZBTB2
AR	BCR	CDAN1	CTNNB1	ERBB3	FGF23	GEN1	ID3	KEL	MDM2	NHP2	PIK3C2B	PTPN11	RPTOR	SNCAIP	TERF2IP	ZNF217
ARAF	BIRC3	CDC73	CUL3	ERBB4	FGF3	GFI1	IDH1	KIF23	MDM4	NKX2-1	PIK3CA	QKI	RTEL1	SOCS1	TERT	ZNF703
ARFRP1	BLM	CDH1	CUX1	ERCC4	FGF4	GFI1B	IDH2	KIT	MED12	NLRP3	PIK3CB	RAB27A	RUNX1	SOX10	TET2	ZRSR2
ARID1A	BMPR1A	CDK12	CXCR4	ERG	FGF6	GID4	IGF1R	KLF1	MEF2B	NME1	PIK3CG	RAC1	RUNX1T1	SOX2	TGFBR2	
ARID1B	BRAF	CDK4	CYLD	ERRFI1	FGFR1	GLI1	IGF2	KLHL6	MEFV	NOP10	PIK3R1	RAD21	SBDS	SOX9	TNFAIP3	
ARID2	BRCA1	CDK6	DAXX	ESR1	FGFR2	GLI2	IKBKE	KLLN	MEN1	NOTCH1	PIK3R2	RAD50	SBF2	SPEN	TNFRSF14	
ASXL1	BRCA2	CDK8	DDR2	ETV6	FGFR3	GNA11	IKZF1	KMT2A	Merged	NOTCH2	PIM1	RAD51	SDHA	SPOP	TNFRSF1A	
ATG2B	BRD4	CDKN1A	DDX11	EXO1	FGFR4	GNA13	IKZF3	KMT2B	MET	NOTCH3	PLCG1	RAD51B	SDHB	SPTA1	TOP1	
ATM	BRIP1	CDKN1B	DDX41	EZH2	FH	GNAQ	IL2RG	KMT2C	MITF	NPM1	PLCG2	RAD51C	SDHC	SRC	TOP2A	

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ATR	BTG1	CDKN2A	DKC1	FAM175A	FLCN	GNAS	IL7R	KMT2D	MLH1	NRAS	PMS1	RAD51D	SDHD	SRSF2	TP53	
ATRX	BTK	CDKN2B	DNM2	FAM46C	FLI1	GPR124	INHBA	KRAS	MPL	NROB1	PMS2	RAD54L	SEC23B	STAG2	TRAF3	
* Microsatellite markers BAT25, BAT26, D2S123, D5S346, and D17S250 are included.																

Add-on RNA Fusions/Expression

Fusion/Expression													
ABL1	ALK	BRAF	CREBBP	EPOR	ETV5	FGFR2	FOXO1	JAK2	MAP3K1	NOTCH1	NUP214	PCM1	PICALM
ABL2	BCL1	CBFB	CRLF2	ERG	ETV6	FGFR3	FUS	KMT2A	MECOM	NTRK1	NUP98	PDGFRA	PML
AKT3	BCL2	CBL	CSF1R	ETV1	EWSR1	FIP1L1	GLI1	KRT18P6	MYC	NTRK2	P2RY8	PDGFRB	PTK2B
ALK	BCL6	CIC	EGFR	ETV4	FGFR1	FLT3	IKZF3	LYN	MYH9	NTRK3	PBX1	PD-L1	RARA

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Electronic Signature

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The Technical Component Processing, Analysis and Professional Component of this test was completed at GTC Laboratories, 21 Technology Dr. #100, Irvine, CA / 92618/ Medical Director: Maher Albitar, M.D. .

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.