Com|Pl|i|t DX

SAMPLE INFORMATION

Name:		**Date Sp. Extracted:**	-
Medical ID:		**Req. Physician:**	
Date Of Birth:		**Report No:**	
Material #1:	PARAFFIN EMBEDDED TISSUE-BLOCK	**Date Received:**	
Material #2:	-	**Date Of Report:**	
Sample #1 ID:		**Tumor type:**	LUNG CANCER

Com.Pl.i.t. Dx (73 genes, 18 fusions) | Comprehensive Panel for Individualized Treatment

Results and Interpretation*

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance	Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off-label therapies (Level C)	
KRAS	Exon 2 c.35G>T (p.G12V)		Daraxonrasib	Avutometinib+Defactinib	
KEAP1	Exon 2 c.299T>G (p.L100R)	-	-	-	-
STK11	Exon 8 c.963del (p.I322Sfs*14)				
Immunohistochemistry Biomarkers					
HER2 expression (IHC) (Table S1)	Negative (Score 1+)	-			-
c-MET expression (IHC)	Negative <50% (1%)	-			-
PD-L1 expression (Table S2)	TPS=60%	Pembrolizumab Atezolizumab Nivolumab Durvalumab Cemiplimab Nivolumab+Ipilimumab			-

Important Biomarkers			
Gene	**Finding (VAF)**	**Gene**	**Finding (VAF)**
EGFR (exons 18,19,20,21)	Not Detected	*ALK* rearrangement	Not Detected
*KRAS*_G12C	Not Detected	*ROS1* rearrangement	Not Detected
*BRAF*_V600E	Not Detected	*RET* rearrangement	Not Detected
MET ex14 skipping	Not Detected	*NTRK1/2/3* rearrangement	Not Detected
ERBB2	Not Detected		

In the Adjuvant/Neoadjuvant setting for non-metastatic NSCLC (stages I-III): consider the following biomarkers for possible treatment: EGFR, ALK and PD-L1. For all other findings, there are currently no approved therapies or established guidelines for patients with early-stage disease. However, these findings may become clinically relevant in the event of disease relapse or progression to metastatic disease.

*Note: Variants' Level of Evidence (LoE) (e.g. A, B, C etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

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Immune Checkpoint inhibitors biomarkers

Biomarker/Variant	Result	Clinical Interpretation
Treatment effect - positive correlation		
POLE mutation (driver)	Not detected	-
TP53 mutation	Not detected	-
KRAS mutation	**Detected**	**May increase the benefit rate of PD-1/PD-L1 inhibitors**
Biomarker/Variant	**Result**	**Clinical Interpretation**
Treatment effect - negative correlation		
PTEN inactivating mutation	Not detected	-
JAK2 inactivating mutation	Not detected	-
EGFR mutation (L858R/EX19del)	Not detected	-
ALK rearrangement	Not detected	-
STK11 inactivating mutation	**Detected**	**May decrease the benefit rate of PD-1/PD-L1 inhibitors**
KEAP1 inactivating mutation	**Detected**	**May decrease the benefit rate of PD-1/PD-L1 inhibitors**
MDM2 amplification	Not detected	-

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Genomic Alterations Identified								
KRAS: c.35G>T (p.G12V)	VAF*:31%	OncoKB		CIViC		PMKB		

Treatment information

Daraxonrasib is an investigational drug for cancers with RAS mutations, including NSCLC with KRAS G12V mutations, and it is not yet FDA-approved. In early trials, it showed a 38% overall response rate in patients with RAS-mutant NSCLC, with a median response duration of 15.1 months. It is being investigated in Phase 3 trials against docetaxel for patients with previously treated, RAS-mutant NSCLC. There are promising clinical data in patients with non-small cell lung cancer with a KRAS G12 mutation treated with the pan-RAS targeted inhibitor daraxonrasib. To date, most efforts to treat cancers with RAS mutations (with the exception of G12C), have focused on targeting downstream effectors of mutant RAS, such as RAF, MEK, or PI3K, each of which is druggable. MEK inhibitors have been the most widely investigated, typically as a combination therapy, despite the presence of multiple inhibitors that are being explored to target different KRAS-activated pathways (PMID: 33402199). The most common MEK inhibitors used in clinical practice are cobimetinib, binimetinib and trametinib. Cobimetinib is a kinase inhibitor, approved by the FDA, for use in combination with vemurafenib for the treatment of advanced melanoma with a BRAF V600E or V600K mutation (IMspire150, NCT02908672). An initial phase Ib study (NCT01988896) was conducted to investigate the safety and efficacy of cobimetinib plus atezolizumab for patients with solid tumors, 28 NSCLC patients included. Atezolizumab plus cobimetinib had manageable safety and clinical activity irrespective of KRAS/BRAF status (PMID: 30918950). Binimetinib is a potent and selective oral mitogen-activated protein kinase 1/2 (MEK 1/2) inhibitor, which is approved by the FDA in combination with encorafenib for patients with unresectable or metastatic melanoma with the BRAF V600E or V600K mutations (COLUMBUS; NCT01909453). The MEK inhibitor binimetinib has been examined in a number of clinical trials for patients with KRAS-mutated lung cancer, including studies looking at the agent in combination with chemotherapy (NCT02185690 PMID: 34052705, NCT02964689-completed/results non posted) and with palbociclib (NCT03170206-ongoing). Trametinib is a kinase inhibitor, approved by the FDA, for the treatment of melanoma, non-small cell lung cancer, thyroid cancer, and solid tumors with BRAF V600 mutations (METRIC study). The efficacy of MEK inhibitor trametinib, alone or in combination with docetaxel, has been evaluated in KRAS-mutant NSCLC. Trametinib plus docetaxel had encouraging results. Trametinib is being examined with the PD-1 inhibitor pembrolizumab in the phase Ib/II IM-BATTLE-2 trial (NCT03225664). Avutometinib is an inhibitor of Ras-Raf-MEK-ERK signaling being developed as a potential treatment for cancer. Defactinib is a small-molecule, oral focal adhesion kinase (FAK) inhibitor. It works by blocking FAK, a tyrosine kinase involved in cell adhesion and signaling pathways, including RAS/MEK/ERK and PI3K/Akt. Defactinib has been studied in various clinical trials for its potential anti-tumor and anti-angiogenic activities. In 2025 FDA approved defactinib in combination with avutometinib for the treatment of adult patients with recurrent low-grade serous ovarian cancer. A phase I clinical trial of RMC-6236 in patients with advanced refractory solid cancers harboring specific KRAS mutations is ongoing (NCT05379985).

Gene information

The KRAS gene encodes the protein KRAS, which is a small GTPase that acts as a molecular switch for various cellular processes by coupling cell membrane growth factor receptors to intracellular signaling pathways and transcription factors. One KRAS mutation is present in up to 25% of all human tumors, and this is one of the most frequently activated oncogenes. Approximately 15-25% of patients with lung adenocarcinoma have tumor associated KRAS mutations. The role of KRAS as either a prognostic or predictive factor in NSCLC is unknown at this time. In clinical practice, conventional chemotherapy is widely used to treat patients with KRAS-mutant NSCLC. However, in a meta-analysis of nine clinical trials including 5633 participants with NSCLC, immune checkpoint inhibitors vs. chemotherapy showed improved OS (HR, 0.65; 95% CI) and PFS (HR, 0.49; 95% CI) in NSCLC patients harboring KRAS mutation (PMID: 36061356).

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Variant Information

G12V is located within exon 2 of KRAS gene and represents an alteration that predominantly occurs as a somatic variant in a wide range of cancers, including lung cancer. This variant has less intrinsic GTPase activity than wild-type KRAS, implicating an increase of KRAS in its activated GTP-bound state, and results in persistent signaling as well as a proliferative and transforming state (PMID: 8524100,PMID: 29533785, PMID: 24642870, PMID: 26037647). This alteration possesses more oncogenic potential and is associated with more aggressive cancer behavior than the G12D variant (PMID: 25359494, PMID: 16679305). One study reported that the G12V variant signals predominantly through the MAPK signaling cascade, and has lost the ability to signal through PI3K (PMID: 22247021).

KEAP1: **c.299T>G (p.L100R)** **VAF*:34%** OncoKB CIViC PMKB

Gene Information

KEAP1 encodes a substrate adaptor protein for the E3 ubiquitin ligase complex. This complex is formed by the proteins CUL3 and RBX1 and targets NRF2 for ubiquitination and subsequent proteasomal degradation (PMID: 15572695). NRF2 (encoded by the gene NFE2L2) is a master transcriptional regulator of the cellular antioxidant response (PMID: 21251164). Activation of NRF2 can provide a fitness advantage for cells by upregulating pathways for handling xenobiotic stress and detoxification (PMID: 21251164). KEAP1 and NFE2L2 mutations occur in approximately 20% of lung adenocarcinomas and 25% to 30% of lung squamous carcinomas (https://genie.cbioportal.org). Regardless of pathological subtype, KEAP1 and NFE2L2 alterations are mutually exclusive. The mutational pattern of KEAP1 is consistent with its tumor-suppressive function. Indeed, pathogenic mutations are scattered throughout the whole gene length,and approximately one-third of them are stop-gain variants (PMID: 33307193).

Variant Information

The KEAP1 L100R is identified in this case. This alteration is predicted to be likely pathogenic. (ACMG classification). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with KEAP1 L100R mutant non-small cell lung cancer. Preclinical and clinical studies in NSCLC revealed that loss-of-function (LOF) mutations in KEAP1 and gain-of-function mutations in NFE2L2 (the gene encoding for NRF2) confer resistance to chemotherapy, radiotherapy, and targeted agents (PMID: 33307193). More recently, KEAP1 mutations were connected to adverse survival outcomes in patients with advanced NSCLC treated with immunotherapy, particularly in the presence of specific co-occurring mutations (PMID: 32866624, 34450259, 34740862).

STK11: **c.963del (p.I322Sfs*14)** **VAF*:32%** OncoKB CIViC PMKB

Gene Information

STK11 encodes a member of the serine/threonine kinase family that functions as a tumor suppressor (PMID: 18439900). The protein controls the activity of AMP-activated protein kinases, thereby playing a role in cell metabolism, cell polarity, apoptosis and DNA damage response (PMID: 21396365). STK11 germline mutations are associated with Peutz-Jeghers syndrome. Loss of STK11 has been shown to lead to disorganized cell polarity and tumor growth in nutrient poor conditions. Activation of STK11 by ATM under conditions of DNA damage leads to downstream inhibition of the mTOR pathway (PMID: 20160076). Mutations in the STK11 gene are found in approximately 5-30% of NSCLC cases (PMID: 29191602, 12097271, 22980975).

Variant Information

This sequence change is a frameshift mutation, resulting in a premature translational stop signal (p.I322Sfs*14) in the STK11 gene. It is expected to result in an absent or disrupted protein product. For this reason, this variant is predicted to be likely pathogenic. Everolimus is an

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oral inhibitor of mTOR indicated for the treatment of patients with advanced HR+, HER2- breast cancer; progressive neuroendocrine tumors of pancreatic origin (PNET); progressive neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin; advanced renal cell carcinoma; and subependymal giant cell astrocytoma (SEGA) and renal angiomyolipomas associated with tuberous sclerosis. STK11 mutations have been associated with response to the mTOR inhibitor everolimus in different tumor types (PMID: 28550065, 21189378). Additionally, STK11 mutations are associated with an-immune cold - tumor microenvironment characterized by low or no PD-L1, low T-cell densities, high levels of granulocyte colony stimulating factor and IL-8 family cytokines, high density of neutrophil-like cells, and production of myeloid cell-recruiting chemokines such as IL-6 (PMID: 29773717, 26833127, 29764856). STK11 genomic alterations were shown to be significantly associated with poor outcomes with chemoimmunotherapy (PMID: 29773717) and have been identified as an important regulator of resistance to anti-PD-1/PD-L1 therapies (PMID: 29773717,28550065). The prognostic role of STK11m in combination with mutations in other genes and based on PD-L1 expression and TMB is being evaluated in various clinical trials.

*VAF: Variant Allele Frequency

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Associated Treatments Information

Daraxonrasib

DrugBank

Daraxonrasib is an orally available, small-molecule RAS(ON) multi-selective noncovalent inhibitor. There are promising clinical data in patients with non-small cell lung cancer (NSCLC) harboring a KRAS G12 mutation treated with daraxonrasib. |In a clinical study of daraxonrasib in 39 patients with KRAS G12X-mutant NSCLC (n=3 KRAS G12A, n=17 KRAS G12D, n=17 KRAS G12V, n=2 KRAS G12S), the overall response rate was 38% (15/39), with one patient (3%) demonstrating complete response (n=1 KRAS G12V), fourteen patients (35%) demonstrating partial response (n=7 KRAS G12D, n=7 KRAS G12V), nineteen patients (48%) demonstrating stable disease (n=1 KRAS G12A, n=8 KRAS G12D, n=9 KRAS G12V, n=1 KRAS G12S) and five patients (13%) demonstrating progressive disease (n=2 KRAS G12A, n=2 KRAS G12D, n=1 KRAS G12S) (Abstract: Arbour, KC. et al., Abstract#6520, Annals of Oncol., 2023. https://www.annalsofoncology.org/article/S0923-7534%2823%2902675-3/fulltext). In a case report, a patient with NSCLC harboring KRAS G12V was treated with daraxonrasib and achieved a complete response with a 100% decrease in both target lesions (PMID: 38593348). In vitro studies with KRAS position 12 (G12X) mutated RAS-addicted cell lines demonstrated increased sensitivity to daraxonrasib as measured by increased inhibition of cellular proliferation compared to other RAS-mutated cell lines (Abstract: Singh et al. Abstract # 3597, AACR 2022. https://s3.us-west-2.amazonaws.com/rvmdpubs.revmed.com/2022/AACR_2022_Singh.pdf). In vivo human xenograft models with KRAS G12X mutant tumors demonstrated sensitivity to daraxonrasib as measured by dose-dependent tumor regression, anti-tumor immunity and RAS pathway inhibition (Abstract: Koltun et al. Abstract# 3597, AACR 2022. https://aacrjournals.org/cancerres/article/82/12_Supplement/3597/702320).

Avutometinib+Defactinib

DrugBank

Avutometinib, a RAF/MEK clamp inhibitor, and defactinib, a FAK inhibitor, are FDA-approved in combination for the treatment of adult patients with KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy. FDA approval was based on the results of the Phase II RAMP-201 (NCT04625270) trial of avutometinib plus defactinib in 109 patients with recurrent LGSOC.|In the Phase II RAMP-201 (NCT04625270) trial, patients with KRAS-mutated LGSOC (n=57) demonstrated an overall response rate (ORR) of 44% (n=25), with a 2% (n=2) complete response (CR) rate, 40% (n=23) partial response (PR) rate and 49% (n=28) stable disease (SD) rate, a median duration of response (DOR) of 31.0 months (95% CI=14.8-31.1) and a median progression-free survival (PFS) of 22.0 months (95% CI=11.1-36.6) (PMID: 40644648). Responders included patients with the following KRAS mutations: KRAS A146V, G12D, G12R, G12V and Q61H (PMID: 40644648). Of patients with KRAS wildtype LGSOC (n=52), the cohort demonstrated an ORR of 17% (n=9), with a 17% (n=9) PR rate and 65% (n=34) SD rate, and a median PFS of 9.2 months (95% CI=5.5-NE) (PMID: 40644648).

Pembrolizumab

DrugBank

Pembrolizumab is a highly selective IgG4-kappa humanized monoclonal antibody against PD-1 receptor. It was generated by grafting the variable sequences of a very high-affinity mouse antihuman PD-1 antibody onto a human IgG4-kappa isotype with the containing a stabilizing S228P Fc mutation. It contains 32 cysteine residues and the complete folded molecule includes 4 disulfide linkages as interchain bonds and 23 interchain bonds. It was firstly approved by the FDA on September 4, 2014, for the treatment of metastatic malignant melanoma. This is the first approved therapy against PD-1. Its approval in melanoma was extended to several countries such as Australia, Israel, Korea, Macau, the European Union and the United Arab Emirates. On June 12, 2018, Pembrolizumab was approved for the treatment of cervical cancer under the status of accelerated approval.

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Pembrolizumab is indicated for the treatment patients with unresectable or metastatic melanoma; as a single therapy, pembrolizumab is indicated for first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have high PD-L1 expression as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; as a single therapy, pembrolizumab is indicated for first-line treatment of patients with metastatic non-small cell lung cancer 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 treatment. The following indications present the status of accelerated approval based on tumor response rate and durability of the response and thus, the approval of this indications are contingent upon verification and description of clinical benefit in confirmatory trials; 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; in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic non squamous non-small cell lung cancer ;patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy ;treatment of adults and pediatric patients with refractory classical Hodgkin lymphoma or who have relapsed after 3 or more prior lines of therapy ;treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma or who have relapsed after 2 or more prior lines of therapy ;treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy ;patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy ;treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient with solid tumors that have progressed following previous treatment and colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan ;patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (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.

Atezolizumab

DrugBank

Atezolizumab is a humanized monoclonal antibody used to prevent the interaction of PD-L1 and PD-1, removing inhibition of immune responses seen in some cancers. This medication is reserved for patients whose tumors express PD-L1, cannot receive platinum based chemotherapy, or whose tumors do not respond to platinum based chemotherapy. Atezolizumab was granted FDA approval on 18 October 2016.

Atezolizumab is indicated to treat locally or advanced metastatic urothelial carcinoma in patients ineligible for cicplatin-containing chemotherapy with tumors expressing PD-L1, in patients ineligible for cisplatin-containing chemotherapy irrespective of PD-L1, have disease progression following platinum containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant chemotherapy. Atezolizumab is also indicated first line for non small cell lung cancer in combination with bevacizumab, paclitaxel, and carboplatin with no EGFR or ALK genomic abnormalities. It can be used in patients with disease progression during or after platinum containing chemotherapy even if they have EGFR and ALK abnormalities. Atezolizumab is indicated in combination with paclitaxel protein-bound to treat locally advanced or metastatic triple negative breast cancer expressing PD-L1. Finally, atezolizumab is indicated in combination with carboplatin and etoposide as first line treatment for extensive stage small cell lung cancer.

Nivolumab

DrugBank

Nivolumab is a fully human IgG4 antibody targeting the immune checkpoint programmed death receptor-1 (PD-1). This molecule was produced entirely on mice and grafted onto human kappa and IgG4 Fc region with the mutation S228P for additional stability and reduced

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variability. It was originally FDA approved on December 22, 2014. Since this approval, nivolumab has been approved for a variety of other uses related to cancer therapy. On 2017, was notably approved for the treatment of hepatocellular carcinoma and on July 11, 2018, the FDA approved this agent in combination with low doses of for the treatment of MSI-H/dMMR metastatic colorectal cancer.

Nivolumab is indicated to treat unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic non-small cell lung cancer, small cell lung cancer, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, and hepatocellular carcinoma.

Durvalumab DrugBank

Durvalumab is a human monoclonal antibody that blocks programmed death ligand 1 (PD-L1), or CD 274. In May, 2017 it received FDA approval for previously treated patients with locally advanced or metastatic cancer in the urinary system (as Imfinzi). It is shown to be effective in patients with continued disease progression after the platinum-based chemotherapy. This drug has a relatively tolerable safety profile and its structural modification advantageously prevents the induction of antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

Durvalumab is indicated for patients with urothelial carcinoma, such as urinary bladder, urethra or ureter cancer. Patients with prolonged disease progression due to failed platinum-based chemotherapy such as cisplatin and carboplatin are most likely to benefit from durvalumab treatment. Its clinical effectiveness is especially enhanced in PD-L1-positive patient groups.

Cemiplimab DrugBank

Cemiplimab is a fully human monoclonal antibody that works against programmed death receptor-1 (PD-1), which is a negative regulator of T cell function. By blocking PD-1, cemiplimab works to enhance T cell-mediated antitumour responses. Cemiplimab was first approved by the FDA on September 28, 2018, as the first FDA-approved treatment for advanced cutaneous squamous cell carcinoma (CSCC). It was later approved to be used in basal cell carcinoma and non-small non-small cell lung cancer. Cemiplimab was also approved by the European Commission on June 28, 2019. In October 2022, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended cemiplimab be granted marketing authorization for the treatment of cervical cancer. Cemiplimab is indicated to treat:

- Locally advanced or metastatic cutaneous squamous cell carcinoma (mCSCC) in patients who are not candidates for curative surgery or curative radiation.
- Locally advanced basal cell carcinoma (laBCC) in previously treated patients with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
- Metastatic basal cell carcinoma (mBCC) in patients who were previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. This indication is approved under accelerated approval based on tumour response rate and durability of response. Continued approval for mBCC may be contingent upon verification and description of clinical benefit.
- Locally advanced non-small cell lung cancer (NSCLC) in combination with platinum-based chemotherapy for the first-line treatment of adults with no EGFR, ALK or ROS1 aberrations, who are not candidates for surgical resection or definitive chemoradiation. It is also indicated to treat metastatic NSCLC in combination with platinum-based chemotherapy as first-line treatment in adults.
- Locally advanced or metastatic NSCLC as monotherapy for the first-line treatment of adults whose tumours have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations. Patients with locally

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advanced NSCLC must not be candidates for surgical resection or definitive chemoradiation.
- Recurrent or metastatic cervical cancer in adults with disease progression on or after platinum-based chemotherapy.

Ipilimumab DrugBank

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody used to treat metastatic or unresectable melanoma. On April 8, 2025, the Food and Drug Administration approved nivolumab with ipilimumab for adult and pediatric patients 12 years of age and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). The FDA also converted the accelerated approval to regular approval for single agent nivolumab for adult and pediatric patients 12 years of age and older with MSI-H or dMMR metastatic CRC, that has progressed following fluoropyrimidine, oxaliplatin, and irinotecan. Efficacy of nivolumab with ipilimumab was evaluated in CHECKMATE-8HW (NCT04008030), a randomized, three-arm, open-label trial in immunotherapy-naive patients with unresectable or metastatic CRC with known MSI-H or dMMR status. Median PFS was NR in the nivolumab + ipilimumab arm and 39.3 months in the nivolumab arm. ORR was 71% in the nivolumab + ipilimumab arm and 58% in the nivolumab arm.

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Clinical Trials to consider

STK11 associated clinical trials

NCT07207395	Phase 2
Title	A Study of Orally Administered JBI-802 Alone or in Combination With Pembrolizumab for Patients With Non-small Cell Lung Cancer With an STK11 Mutation.
Treatment	JBI-802| Pembrolizumab
Location	United States

NCT06331650	Phase 2
Title	A Single-arm Pilot Study of First-line Treatment With Carbognilumab Combined With Chemotherapy in Patients With STK11-mutated Advanced or Postoperative Recurrent Non-small Cell Lung Cancer
Treatment	cadonilimab
Location	China

NCT03297606	Phase 2
Title	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)
Treatment	Olaparib| Dasatinib| Nivolumab plus Ipilimumab| Axitinib| Bosutinib| Crizotinib| Palbociclib| Sunitinib| Temsirolimus| Erlotinib| Trastuzumab plus Pertuzumab| Vemurafenib plus Cobimetinib| Vismodegib| Tucatinib
Location	Canada

NCT07017829	Phase 2
Title	GT103 in Combination With Pembrolizumab for the Treatment of Advanced or Metastatic STK11 Mutant Non-Small Cell Lung Cancer
Treatment	Anti-CFH Monoclonal Antibody GT103| Biopsy Procedure| Biospecimen Collection| Computed Tomography| Echocardiography Test| Magnetic Resonance Imaging| Pembrolizumab
Location	United States

NCT05807048	Phase 2
Title	Daratumumab in STK11 Mutated NSCLC
Treatment	Daratumumab and Hyaluronidase-fihj| Pre-Intervention Medication| Post-Intervention Medication
Location	United States

NCT06341660	Phase 2

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Title	To Evaluate the Safety and Tolerability of Carbognilumab Combined With Chemotherapy as the First-line Treatment for Patients With KEAP1 Mutated Advanced or Postoperative Recurrent Non-small Cell Lung Cancer (NSCLC)
Treatment	cadonilimab
Location	China

NCT05887492	**Phase 1|Phase 2**
Title	Study of TNG260 and an Anti-PD Antibody in STK11 Mutated Solid Tumors
Treatment	TNG260| Pembrolizumab
Location	United States

Press here for a live search of clinical trials for STK11

KRAS associated clinical trials

NCT05067283	**Phase 1**
Title	A Study of MK-1084 in KRAS Mutant Advanced Solid Tumors (MK-1084-001)
Treatment	MK-1084| Pembrolizumab| carboplatin| pemetrexed| cetuximab| oxaliplatin| leucovorin| 5-fluorouracil
Location	United States, Australia, Canada, Chile, China, Denmark, Israel, Italy, Japan, Lithuania, Malaysia, New Zealand, Panama, Poland, South Korea, Spain, Switzerland, Taiwan, Turkey (TÃƒÂ¼rkiye), Ukraine

Press here for a live search of clinical trials for KRAS

KEAP1 associated clinical trials

NCT06008093	**Phase 3**
Title	A Study to Investigate the Efficacy of Durvalumab Plus Tremelimumab in Combination With Chemotherapy Compared With Pembrolizumab in Combination With Chemotherapy in Metastatic NSCLC Patients With Non-squamous Histology Who Have Mutations and/or Co-mutations in STK11, KEAP1, or KRAS
Treatment	Durvalumab| Tremelimumab| Pemetrexed| Pembrolizumab| Carboplatin| Cisplatin
Location	United States

NCT06341660	**Phase 2**
Title	To Evaluate the Safety and Tolerability of Carbognilumab Combined With Chemotherapy as the First-line Treatment for Patients With KEAP1 Mutated Advanced or Postoperative Recurrent Non-small Cell Lung Cancer (NSCLC)
Treatment	cadonilimab
Location	China

Press here for a live search of clinical trials for KEAP1

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Variants of Uncertain Significance (VUS)

The clinical significance of the variants listed in the below table is uncertain at this time. Until the uncertainty is resolved, these variants should not be used in clinical management decisions.

Gene	Variant	Predicted effect*
APC	c.6853G>T, p.V2285F	Loss of Function

* Prediction based on in silico analysis

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Methodology

NGS analysis

DNA is extracted from the sample under investigation using the Qiamp DNA FFPE Kit (Qiagen). RNA was extracted using the RNeasy FFPE Kit (Qiagen). A total of 79 unique genes is analyzed, including the entire coding sequences of 73 genes and 18 RNA fusions, using the Pan Cancer Panel NGS Assay (Genes2Me). This is a CE-IVD hybrid capture-based assay, in which target genomic regions are enriched through probe hybridization technology. The assay enables the detection of single nucleotide variants (SNVs), insertions/deletions (indels), copy number variations (CNVs), and RNA fusions (Table 1).

Sequencing is performed on the DNBSEQ-T7 next-generation sequencing platform (MGI). Raw sequencing data are processed and analyzed using the CliSeq Interpreter, a companion software for automated, cloud-based analysis. In addition, the SeqPilot software (Version 4.4, Build 505; JSI Medical Systems) is used for independent variant calling and result confirmation.

Alteration- and tumor type-specific therapeutic implications are classified using the OncoKB Levels of Evidence system, which assigns clinical actionability to individual mutational events. For additional details about the OncoKB curation process, please refer to the version-controlled OncoKB Curation Standard Operating Procedure.

Sensitivity: Positive reference standards were tested with the assay. All corresponding mutation sites were accurately detected, with an analytical sensitivity of 96% and a positive percent agreement (PPA) of 96% across all variant types, including SNVs, indels, fusions, and CNVs.

Specificity: Negative reference standards were tested with the assay. The analytical specificity and negative percent agreement (NPA) for SNVs, indels, fusions, and CNVs were both 100%, confirming a very low false-positive rate.

Precision and Reproducibility: The assay demonstrated a precision of >96% and reproducibility of 97%, ensuring robust and consistent results across multiple runs and samples.

Limit of Detection (LoD): The detection limit of the method is 1-2% of mutant allelic content, depending on the genomic region. DNA variations detected at frequencies of less than 5% are confirmed using NGS or an alternative method (Real-Time PCR). All fusions detected are confirmed with an alternative method (Real-Time PCR or FISH).

The performance characteristics of the assay are summarized in the following table:

Feature	Performance
Precision (%)	>96
Reproducibility (%)	97
On-Target Ratio (%)	85-95
Analytical Sensitivity (%)	96
Analytical Specificity (%)	100
Repeatability (%)	96
Limit of Detection (LoD, VAF)	≥ 1%

Disclaimer

1.This test is mainly used to assist clinical decision-making, and the result does not represent clinical decision.

2.The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.

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3.The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: https://clinicaltrials.gov/.

4.As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.

5.Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follows guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).

6.Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

Limitations

1.Limited tissue detection may not represent the whole DNA/RNA variations of lesions because of tumor heterogeneity.

2.Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.

3.Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.

4.The detection could not distinguish between somatic mutations and germline mutations effectively without control sample analysis.

5.Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.

Quality Control Results

Quality Control Index	Result	Criterion
Average effective sequencing depth	571	≥ 500
Tumor cell content	40%	>20%
Overall Assessment	PASS	

Note：

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. Overall A tumor cell content percentage of ≥ 20% is recommended for the efficient detection of somatic alterations in the sample analyzed.
3. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.

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PD-L1 expression by IHC

PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. This assay is indicated as an aid in identifying NSCLC patients for treatment with immunotherapeutic agents.

VENTANA SP263 by IHC (CE IVD) is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone SP263, intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissue, using VENTANA BenchMark Series automated staining instrument. The specimen submitted for testing should contain at least 100 viable tumor cells to be considered adequate for evaluation. For cut-off values please refer to table S2.

ERBB2 (HER2) expression by IHC

ERBB2 staining is performed in a VENTANA BenchMark Series automated staining instrument using the ERBB2 clone 4B5, on formalin-fixed, paraffin-embedded (FFPE) tissue. The IHC test gives a score of 0 to 3+ that measures the amount of HER2 receptor protein on the surface of cancer cells. Scoring interpretation is as follows:

HER2 IHC positive (score 3+)
HER2 IHC equivocal (score 2+)
HER2 IHC negative (score 0 or 1+)
Scoring is based on the ASCO-CAP HER2 testing guidelines (PMID: 27841667, 37303228).
For mCRC the HERACLES criteria are also used (PMID: 26449765).

c-MET expression by IHC

The immunohistochemical investigation of c-Met protein overexpression is a recommended CE-IVD test, performed on formalin-fixed, paraffin-embedded (FFPE) tissue using the monoclonal antibody VENTANA MET, clone SP44, on the automated Ventana BenchMark Ultra platform.
According to the LUMINOSITY study data, c-Met protein overexpression in non-squamous (NSQ), EGFR-wild type, non-small cell lung carcinomas (NSCLC) is defined as the presence of strong membranous and/or cytoplasmic staining (3+) in > 25% of tumor cells. c-Met expression is further categorized as follows:
- High expression: 3+ staining in ≥ 50% of tumor cells **- Intermediate expression**: 3+ staining in ≥ 25% and < 50% of tumor cells
In clinical practice, high c-Met expression serves as a predictive marker of response to targeted therapy against c-Met, using the antibody-drug conjugate Telisotuzumab vedotin (Teliso-V).

FISH ALK

FISH analysis was carried out for the detection of rearrangements involving the ALK gene, using the ZytoLight FISH Tissue Implementation Kit (ZytoLight). Microtome sections (3μm) of the sample were hybridized with the ZytoLight SPEC ALK Dual Color Break Apart Probe using Thermobrite (Abbott Molecular) and evaluated microscopically. Signals from 50 nuclei from at least 5 different areas of the sections were microscopically analyzed. Imaging analysis was carried out using the ISIS FISH Imaging System, Metasystems.

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Genes Analyzed

73 DNA genes									
ABL1	*AKT1*	*ALK*	*APC*	*ARAF*	*ATM*	*BRAF*	*BRCA2*	*CCNE1*	*CDH1*
CDKN2A	*CSF1R*	*CTNNB1*	*DDR2*	*DICER1*	*EGFR*	*EIF1AX*	*ERBB2*	*ERBB3*	*ERBB4*
EZH1	*EZH2*	*FBXW7*	*FGFR1*	*FGFR2*	*FGFR3*	*FLT3*	*FOXL2*	*GNA11*	*GNAQ*
GNAS	*HNF1A*	*HRAS*	*IDH1*	*IDH2*	*JAK2*	*JAK3*	*KDR*	*KEAP1*	*KIT*
KRAS	*MAP2K1*	*MDM2*	*MET*	*MLH1*	*MPL*	*MYC*	*NOTCH1*	*NPM1*	*NRAS*
NTRK1	*NTRK2*	*NTRK3*	*PDGFRA*	*PIK3CA*	*POLE*	*PTEN*	*PTPN11*	*RAC1*	*RAF1*
RB1	*RET*	*ROS1*	*SMAD4*	*SMARCB1*	*SMO*	*SOS1*	*SPOP*	*STK11*	*SRC*
TERT	*TP53*	*VHL*							
18 RNA genes									
ALK	*BRAF*	*EGFR*	*ERG*	*FGFR2*	*FGFR3*	*MET*	*NRG1*	*NTRK1*	*NTRK2*
NTRK3	*PBX1*	*PPARG*	*PRKACA*	*RAF1*	*RET*	*ROS1*	*TFE3*		

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Appendix

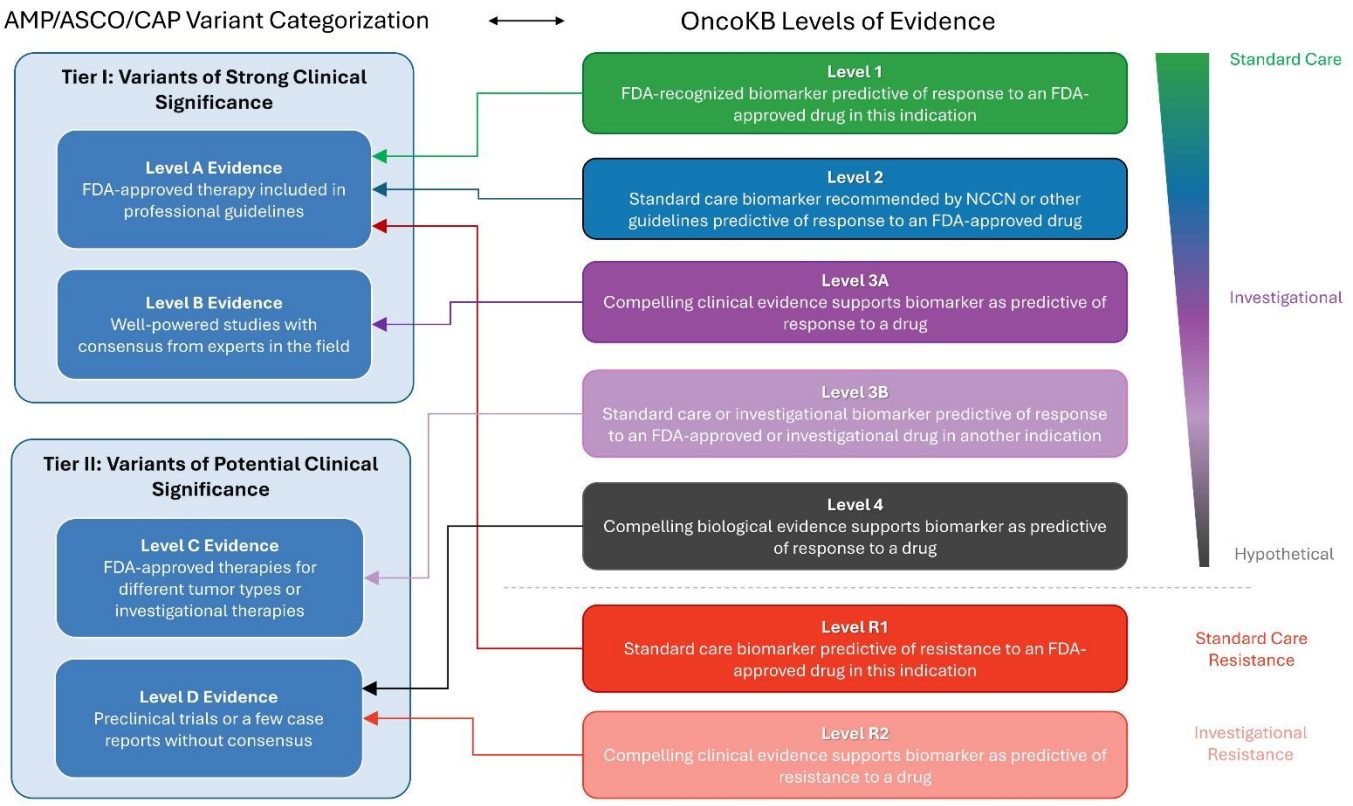

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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Table S1. ERBB2 Biomarkers associated with treatment response (LoE)

Cancer Type	3+ IHC	2+ IHC & ≥2 FISH	ERBB2 amplification by NGS	IHC 1+ or IHC 2+/ISH -ve
Breast Cancer	Trastuzumab Deruxtecan (1A.1) Trastuzumab (1A.1) Ado-Trastuzumab Emtansine (1A.1) Lapatinib + Capecitabine (1A.1) Lapatinib + Letrozole (1A.1) Margetuximab + Chemotherapy (1A.1) Neratinib (1A.1) Neratinib + Capecitabine (1A.1) Trastuzumab + Tucatinib + Capecitabine (1A.1) Trastuzumab + Chemotherapy (1A.1) Trastuzumab + Pertuzumab + Chemotherapy (1A.1)	Trastuzumab Deruxtecan (1A.1) Ado-Trastuzumab Emtansine (1A.1) Lapatinib + Capecitabine (1A.1) Lapatinib + Letrozole (1A.1) Margetuximab + Chemotherapy (1A.1) Neratinib (1A.1) Neratinib + Capecitabine (1A.1) Trastuzumab + Tucatinib + Capecitabine (1A.1) Trastuzumab + Chemotherapy (1A.1) Trastuzumab + Pertuzumab + Chemotherapy (1A.1) Trastuzumab (2C.1)	Trastuzumab Deruxtecan (2C.1) Trastuzumab (2C.1) Ado-Trastuzumab Emtansine (2C.1) Lapatinib + Capecitabine (2C.1) Lapatinib + Letrozole (2C.1) Margetuximab + Chemotherapy (2C.1) Neratinib (2C.1) Neratinib + Capecitabine (2C.1) Trastuzumab + Tucatinib + Capecitabine (2C.1) Trastuzumab + Chemotherapy (2C.1) Trastuzumab + Pertuzumab + Chemotherapy (2C.1)	Trastuzumab Deruxtecan (1A.1)
Colorectal Cancer	Trastuzumab Deruxtecan (1A.1) Tucatinib + Trastuzumab (1A.1) Lapatinib + Trastuzumab (1A.2) Trastuzumab + Pertuzumab (1A.2)	Tucatinib + Trastuzumab (1A.1) Lapatinib + Trastuzumab (1A.2) Trastuzumab + Pertuzumab (1A.2) Trastuzumab Deruxtecan (2C.1)	Tucatinib + Trastuzumab (1A.1) *(RAS/BRAF wild type)* Trastuzumab Deruxtecan (2C.1) Lapatinib + Trastuzumab (2C.1) *(RAS/BRAF wild type)* Trastuzumab + Pertuzumab (2C.1) *(RAS/BRAF wild type)*	N/A
Gastric/GEJ	Trastuzumab Deruxtecan (1A.1) Trastuzumab + Chemotherapy (1A.1) Pembrolizumab + Trastuzumab + Chemotherapy (1A.1) *(PD-L1 with CPS>1% required)*	Pembrolizumab+ Trastuzumab + Chemotherapy (1A.1) *(PD-L1 with CPS>1% required)* Trastuzumab + Chemotherapy (1A.1) Trastuzumab Deruxtecan (1A.1)	Pembrolizumab+ Trastuzumab + Chemotherapy (2C.1) *(PD-L1 with CPS>1% required)* Trastuzumab + Chemotherapy (2C.1) Trastuzumab Deruxtecan (2C.1)	N/A
Billiary Tract	Trastuzumab Deruxtecan (1A.1) Zanidatamab-hrii (1A.1) Trastuzumab + Pertuzumab (1A.2) Tucatinib + Trastuzumab (1A.2)	Trastuzumab Deruxtecan (2C.1) Zanidatamab-hrii (2C.1) Trastuzumab + Pertuzumab (1A.2) Tucatinib + Trastuzumab (1A.2)	Trastuzumab Deruxtecan (2C.1) Zanidatamab-hrii (2C.1) Trastuzumab + Pertuzumab (2C.1) Tucatinib + Trastuzumab (2C.1)	N/A
Uterine Serous Carcinoma/ Papillary Serous	Trastuzumab Deruxtecan (1A.1) Trastuzumab + Carboplatin-Taxol Regimen (1A.2)	Trastuzumab Deruxtecan (2C.1) Trastuzumab + Carboplatin-Taxol Regimen (2C.1)	Trastuzumab Deruxtecan (2C.1) Trastuzumab + Carboplatin-Taxol Regimen (2C.1)	N/A
Lung Cancer	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab Deruxtecan (2C.1)	N/A
All tumors	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab Deruxtecan (2C.1)	N/A

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Table S2. PD-L1 interpretation and cut-offs.

Cancer type	Therapy	PD-L1	Cut-off	We report
Non-Small Cell Lung Cancer (NSCLC)	Anti-PD-1 [1-4]	VENTANA (SP263)	1L TPS ≥ 50% 2L TPS ≥ 1%	%TPS
	Anti-PD-L1 [5-7]	VENTANA (SP263)	2L TPS ≥ 1%	%TPS
		VENTANA (SP263)	1L TPS ≥ 50%	%TPS
		VENTANA (SP142)	1L TC ≥ 50% or IC ≥ 10%	%TC/%IC
	Anti-PD-1 + Anti-CTLA-4 [8]	VENTANA (SP263)	1L TPS ≥ 1%	%TPS
Urothelial Cancer (UC)	Anti-PD-1 [9]	Dako 22C3	1L CPS ≥ 10	CPS
	Anti-PD-1(19)	VENTANA (SP263)	1L TC≥ 1%	%TC
	Anti-PD-L1 [10]	VENTANA (SP142)	2L IC ≥ 5%	%IC
Triple Negative Breast Cancer (TNBC)	Anti-PD-L1 [11]	VENTANA (SP142)	1L IC ≥ 1%	%IC
	Anti-PD-1 [12] + chemotherapy	Dako 22C3	1L CPS ≥ 10	CPS
Cervical cancer	Anti-PD-1 [16]	Dako 22C3	2L CPS ≥ 1	CPS
Head and Neck Squamous Cell Carcinoma (HNSCC)	Anti-PD-1 [14,15]	Dako 22C3	1L CPS ≥ 1 2L TPS ≥ 50%	CPS and %TPS
Gastric cancer (adenocarcinoma) (HER-2 Positive)	Anti-PD-1 [13,20]	Dako 22C3	1L CPS ≥ 1	CPS
Gastric cancer (adenocarcinoma) (HER-2 Negative)	Anti-PD-1 18, 20)	Dako 22C3	1L CPS ≥5	CPS
Oesophageal (Adenocarcinoma and squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 10	CPS
Oesophageal (squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L TC ≥ 1%	%TC
Oesophageal (Adenocarcinoma) (HER-2 Negative)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 5	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Negative)	Anti-PD-1 [17,20] *Depending on PD-L1 inhibitor	Dako 22C3	1L CPS ≥ 5 or* 1L CPS ≥ 10	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Positive)		Dako 22C3	1L CPS ≥ 1	

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TPS: Tumor Proportion Score = $\frac{\#\text{PD-L1 positive tumor cells}}{Total\ \#PD\text{-}L1\ positive + PD\text{-}L1\ negative\ tumor\ cells} \times 100$

TC: tumor cell

CPS: Combined Positive Score = $\frac{\#\text{PD-L1 staining cells (tumor cells,lymphocytes,macrophages)}}{Total\ \#\ of\ viable\ tumor\ cells} \times 100$

IC: immune cell

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Biomarker Result	Therapies with strong clinical significance		Therapies with potential significance		Therapies with potential resistance
	Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off-label/investigational therapies (Level C)	Therapies in pre-clinical trials (Level D)	
KRAS	-	Daraxonrasib	Avutometinib+Defactinib	Cobimetinib Binimetinib Trametinib	-
KEAP1	-	-	-	-	-
STK11	-	-	-	-	-

Treatment Table for NSCLC non metastatic setting based on the NCCN guidelines (accessed June 2025)		
Phase	**Indication**	**Treatment**
Neoadjuvant	Patients with tumors ≥4 cm or node positive should be evaluated for preoperative therapy, with strong consideration for an immune checkpoint inhibitor + chemotherapy EGFR wild-type ALK wild-type	Eligible for immunotherapy
Adjuvant	EGFR (Exon 19 Del/L858R)	Osimertinib (A)
	ALK rearrangement	Alectinib (A)

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