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SAMPLE INFORMATION

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

PrIMe

Report Summary

1021	Unique Genes (38 Fusions) analyzed	**3**	Genomic alterations identified in tumor
6	Biomarker related approved therapies for indication	**7**	Biomarker related therapies with potential benefit
7	Biomarker related therapies with potential resistance	**30**	Biomarker related Clinical Trials

Results and Interpretation*

Biomarker	Result	Approved therapies for indication	Therapies with potential benefit	Therapies with potential resistance/toxicity	Clinical Trials
EGFR	Exon 19 c.2236_2250del (p.E746_A750del)	Erlotinib (1A.1) Afatinib (1A.1) Osimertinib (1A.1) Dacomitinib (1A.1) Gefitinib (1A.1) Erlotinib+Ramucirumab (1A.1)	-	-	yes
EGFR	Exon 20 c.2390G>C (p.C797S)	-	-	Osimertinib (1B)	yes
TP53	Exon 7 c.745A>G (p.R249G)	-	-	-	yes
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-
Loss of Heterozygosity (LOH)	Low 4.33 %	-	-	-	-
PD-L1 expression (Table S2)	Negative TPS<1%	-	-	-	-
Tumor Mutational Burden (TMB)	4.8 Muts/MB	-	-	-	-
ERCC1	High expression	-	-	Carboplatin Cisplatin Oxaliplatin	-

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RRM1	Low expression	-	Gemcitabine	-	-
BRCA1	Low expression	-	Carboplatin Cisplatin Oxaliplatin	Paclitaxel Docetaxel Vinorelbine	-
TYMS	Low expression	-	Capecitabine 5-Fluorouracil Pemetrexed	-	-

*Note: Variants' Level of Evidence (LoE) (e.g. 1A.1, 2C.1, 1B 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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Genomic Alterations Identified

EGFR: c.2236_2250del (p.E746A750del)	VAF*:41%	OncoKB	CIViC	PMKB

Patients with in-frame deletions in exon 19 of EGFR are sensitive to EGFR targeted therapies (PMID: 29075127). They lead to increased receptor dimerisation and increased kinase activity, when compared with the wild-type EGFR protein (PMID: 31562956). Thus, NSCLC patients carrying this type of mutations have shown responses to treatment with EGFR tyrosine kinase inhibitors (TKIs). Therefore the following treatment options have been approved for such patients: The TKI Erlotinib is approved 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, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. (PMID: 28017789, PMID: 22285168). The TKI Afatinib is approved for patients harboring EGFR mutations. The primary trial supporting approval was Study 1200.32 (LUX-3), a randomized, open-label, multicenter, multinational trial comparing the efficacy of afatinib to cisplatin/pemetrexed chemotherapy doublet for the first-line treatment of metastatic or unresectable, EGFR mutation-positive adenocarcinoma of the lung (PMID: 32559335, PMID: 28017789). The new label includes data on three additional EGFR mutations: L861Q, G719X and S768I. The third-generation EGFR TKI Osimertinib is approved for NSCLC patients with EGFR exon 19 deletions exon 21 L858R mutations as adjuvant therapy after tumor resection and first-line treatment of adult patients with metastatic NSCLC (PMID: 34301748, PMID: 32955177). The oral EGFR kinase inhibitor Dacomitinib is approved for the first-line treatment of patients with metastatic NSCLC and EGFR exon 19 deletion or exon 21 L858R substitution mutations, based on results from the ARCHER 1050 phase 3 clinical study, indicating the drug's potential as a significant treatment advance for this patient population (PMID: 28958502, PMID: 28958502). The kinase inhibitor Gefitinib is approved for the frontline treatment of patients with metastatic, EGFR-positive NSCLC with an exon 19 deletion or exon 21 (L858R) substitution. The FDA approval of Gefitinib is based on data from the Phase IV IFUM1 (IRESSA Follow-Up Measure) study, assessing Gefitinib as a first-line treatment for Caucasian patients with locally advanced or metastatic EGFR mutation-positive NSCLC. This was supported by results from the IPASS2 (IRESSA Pan-ASia Study) clinical trial (PMID: 24263064, PMID: 21670455). Finally, FDA approved ramucirumab in combination with erlotinib for first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations. Efficacy was evaluated in RELAY (NCT02411448), a multinational, randomized, double-blind, placebo-controlled, multicenter study, where ramucirumab plus erlotinib demonstrated superior progression-free survival compared with placebo plus erlotinib (PMID: 31591063, 33905962).

EGFR is a member of the ErbB family of structurally related RTKs, consisting of the EGFR (ErbB1), as well as human epidermal growth factor receptor 2 (ErbB2; HER2), ErbB3 (HER3) and ErbB4 (HER4) (PMID: 11252954, 24269963). These proteins form an array of homo- or heterodimers at the cell surface and play a key role in the normal physiological regulation of cellular proliferation. Aberrant ErbB family signaling is implicated in the development and progression of many human cancers, including non-small cell lung cancer (NSCLC) (PMID: 15864276). Approximately 15% of NSCLC Caucasians patients and 35% of Asians patient populations harbor tumor associated EGFR mutations (PMID: 15118073, 15118125, 15329413) in exons 18-21, which code for a

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portion of the EGFR tyrosine kinase domain. There are approximately five types of mutations, including a point mutation in exon18, deletions in exon 19, insertions in exon 20, a point mutation in exon 20, and a point mutation (L858R) in exon 21.

The alteration detected in this patient occurs within exon 19 of the EGFR gene, and results from a 15-bp nucleotide deletion that leads to an in-frame deletion of 5 amino acids. EGFR E746_A750del is the second-most common EGFR mutation and occurs most commonly in lung adenocarcinoma (COSMIC).

***EGFR:* c.2390G>C (p.C797S)**	**VAF*:9%**	**OncoKB**	**CIViC**	**PMKB**

Multiple biological mechanisms of acquired resistance to osimertinib have been identified, thus confirming tumor heterogeneity and adaptability. These mechanisms include secondary resistance mutations, that interfere with drug binding, the most frequent being EGFR C797S, or the activation of alternative signaling pathway (PMID: 27252416). The analysis of cell free DNA (cfDNA) by NGS, performed in plasma from a subgroup of patients enrolled in the phase I AURA trial, who had progressed to osimertinib, revealed the presence of C797S mutation in the exon 20 of the EGFR gene in approximately 40% of the patients evaluated (PMID: 25939061). Osimertinib forms a covalent bond with the cysteine 797 located at the ATP binding pocket, and mutation at this site prevents the binding of the drug, thus conferring resistance. Preclinical findings demonstrate that the efficacy of first and second-generation TKIs is not affected by the cysteine at position 797 (PMID: 25964297, 30073261), thus suggesting that treatment with these drugs might be a strategy to overcome EGFR C797S resistance mutation acquired following Osimertinib (PMID: 32642198).

***TP53:* c.745A>G (p.R249G)**	**VAF*:18%**	**OncoKB**	**CIViC**	**PMKB**

The tumor suppressor gene P53 encodes a ubiquitous nuclear protein involved in the control of genome integrity by preventing cells from dividing before DNA damage is repaired. P53 mutations are universal across cancer types. Loss of tumor suppressors is most recognized by 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 variants, or missense mutations. These variants are also very broadly distributed throughout the gene, not localizing in any particular hotspot. Somatic TP53 mutations occur in almost every type of cancer at rates from 38%-50% in ovarian, esophageal, colorectal, head and neck, larynx, and lung cancers to about 5% in primary leukemia, sarcoma, testicular cancer, malignant melanoma, and cervical cancer (PMID: 20182602) While a large proportion of cancer genomics research is focused on somatic variants, TP53 mutations may be potential prognostic and predictive markers in some tumor types, as well as targets for pharmacological intervention in some clinical setting. Germline TP53 mutations are the hallmark of Li-Fraumeni syndrome, and many (both germline and somatic) have been found to have prognostic impact on patient outcomes (PMID: 14583457).

The TP53 R249G mutation is located in the DNA-binding domain of the protein. This mutation has been identified in breast cancer and is a statistically significant hotspot (PMID: 8673929). In vivo studies with yeast expressing TP53 R249G demonstrated that the mutation is inactivating as measured by the loss of transactivational activity as compared to wildtype (PMID: 27328919,

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12826609). In vitro studies with various human cancer cell lines expressing TP53 R249G also demonstrated the mutation is inactivating as measured by reduced growth suppression activity as compared to wildtype (PMID: 29979965, 30224644).

*VAF: Variant Allele Frequency

Associated Treatments Information

Erlotinib

DrugBank

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that is used in the treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. Erlotinib binds to the epidermal growth factor receptor (EGFR) tyrosine kinase in a reversible fashion at the adenosine triphosphate (ATP) binding site of the receptor. Recent studies demonstrate that erlotinib is also a potent inhibitor of JAK2V617F, which is a mutant form of tyrosine kinase JAK2 found in most patients with polycythemia vera (PV) and a substantial proportion of patients with idiopathic myelofibrosis or essential thrombocythemia. This finding introduces the potential use of erlotinib in the treatment of JAK2V617F-positive PV and other myeloproliferative disorders.

Erlotinib is indicated for: - The treatment of metastatic non-small cell lung cancer (NSCLC) with tumors showing epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. - In combination with first-line treatment for patients diagnosed with locally advanced, unresectable or metastatic pancreatic cancer. The safety and efficacy of erlotinib have not been established for patients with NSCLC whose tumors show other EGFR mutations. Additionally it is not recommended for use in combination with platinum-based chemotherapy

Afatinib

DrugBank

Afatinib is a 4-anilinoquinazoline tyrosine kinase inhibitor in the form of a dimaleate salt. For oral use, afatinib tablets are a first-line (initial) treatment for patients with metastatic non-small cell lung cancer (NSCLC) with common epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.

Afatinib is a kinase inhibitor indicated as monotherapy for the first-line treatment of (a) Epidermal Growth Factor Receptor (EGFR) TKI (tyrosine kinase inhibitor)-naive adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have non-resistant EGFR mutations as detected by an FDA-approved test, and (b) adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy . Recently, as of January 2018, the US FDA approved a supplemental New Drug Application for afatinib 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 . The new label includes data on three additional EGFR mutations: L861Q, G719X and S768I .

Osimertinib

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Osimertinib is an oral, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) drug. Its use is indicated for the treatment of metastatic non-small cell lung cancer (NSCLC) in cases where tumour EGFR expression is positive for the T790M mutation as detected by FDA-approved testing and which has progressed following therapy with a first-generation EGFR tyrosine kinase inhibitor. Approximately 10% of patients with NSCLC have a rapid and clinically effective response to EGFR-TKIs due to the presence of specific activating EGFR mutations within the tumour cells. More specifically, deletions around the LREA motif in exon 19 and exon 21 L858R point mutations are correlated with response to therapy. Development of third-generation EGFR-TKIs, such as osimertinib, has been in response to altered tumour resistance patterns following treatment and toxic side effects that impact patient quality of life. Treatment with first-generation EGFR-TKIs (gefitinib and erlotinib) has been associated with the development of resistance through activating mutations in the EGFR gene. Second-generation EGFR-TKIs (afatinib and dacomitinib) were then developed to be more potent inhibitors, although their use is associated with increased toxicity through nonspecific targeting of wild-type EGFR. In contrast, third-generation inhibitors are specific for the gate-keeper T790M mutations which increases ATP binding activity to EGFR and result in poor prognosis for late-stage disease. Furthermore, osimertinib has been shown to spare wild-type EGFR during therapy, thereby reducing non-specific binding and limiting toxicity.

Osimertinib is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA- approved test, who have progressed on or after EGFR-TKI therapy.

Dacomitinib

DrugBank

Dacomitinib, designed as (2E)-N-16-4-(piperidin-1-yl) but-2-enamide, is an oral highly selective quinazalone part of the second-generation tyrosine kinase inhibitors which are characterized by the irreversible binding at the ATP domain of the epidermal growth factor receptor family kinase domains. Dacomitinib was approved by the FDA on September 27, 2018. Some evidence in the literature suggests the therapeutic potential of dacomitinib in the epithelial ovarian cancer model, although further investigations are needed.

Dacomitinib is indicated as the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as verified by an FDA-approved test. Lung cancer is the leading cause of cancer death and NSCLC accounts for 85% of lung cancer cases. From the cases of NSCLC, approximately 75% of the patients present a late diagnosis with metastatic and advanced disease which produces a survival rate of 5%. The presence of a mutation in EGFR accounts for more than the 60% of the NSCLC cases and the overexpression of EGFR is associated with frequent lymph node metastasis and poor chemosensitivity.

Gefitinib

DrugBank

Gefitinib (originally coded ZD1839) is a drug used in the treatment of certain types of cancer. Acting in a similar manner to erlotinib, gefitinib selectively targets the mutant proteins in malignant cells.

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Gefitinib is indicated for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of either platinum-based or docetaxel chemotherapies.

Ramucirumab

DrugBank

Ramucirumab is a VEGFR2 antagonist that specifically binds VEGFR2 and blocks binding of VEGFR ligands VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab blocks ligand-stimulated activation of VEGFR2, thereby inhibiting ligand-induced proliferation and migration of human endothelial cells. Ramucirumab inhibits angiogenesis in animal models. On May 29, 2020, the Food and Drug Administration approved ramucirumab in combination with erlotinib for first-line treatment of metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.

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Clinical Trials to consider

EGFR associated clinical trials

NCT05388669	Phase 3
Title	A Study of Lazertinib With Subcutaneous Amivantamab Compared With Intravenous Amivantamab in Participants With Epidermal Growth Factor Receptor (EGFR)-Mutated Advanced or Metastatic Non-small Cell Lung Cancer
Treatment	Lazertinib| Amivantamab Subcutaneous and Co-Formulated with Recombinant Human Hyaluronidase (SC CF)| Amivantamab Intravenous
Location	United States, Argentina, Australia, Brazil, Canada, China, France, Germany, Israel, Italy, Japan, Korea, Republic of, Malaysia, Poland, Portugal, Spain, Taiwan, Thailand, Turkey, United Kingdom

NCT04988295	Phase 3
Title	A Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non- Small Cell Lung Cancer After Osimertinib Failure
Treatment	Lazertinib| Amivantamab| Pemetrexed| Carboplatin
Location	United States, Argentina, Belgium, Brazil, Bulgaria, Canada, China, Czechia, Denmark, France, Germany, Hong Kong, India, Israel, Italy, Japan, Korea, Republic of, Malaysia, Mexico, Netherlands, Poland, Portugal, Puerto Rico, Russian Federation, Spain, Sweden, Taiwan, Turkey, United Kingdom

NCT03833154	Phase 3
Title	Durvalumab vs Placebo With Stereotactic Body Radiation Therapy in Early Stage Unresected Non-small Cell Lung Cancer (NSCLC) Patients / Osimertinib Following SBRT in Patients With Early Stage Unresected NSCLC Harboring an EGFR Mutation
Treatment	Durvalumab| Placebo| Osimertinib (single-arm, open-label)
Location	United States, Australia, Belgium, Brazil, Canada, China, France, Germany, Greece, Israel, Italy, Japan, Korea, Republic of, Netherlands, Poland, Puerto Rico, Russian Federation, Spain, Turkey, United Kingdom

NCT05261399	Phase 3
Title	Savolitinib Plus Osimertinib Versus Platinum-based Doublet Chemotherapy in Participants With Non-Small Cell Lung Cancer Who Have Progressed on Osimertinib Treatment
Treatment	Savolitinib| Osimertinib| Pemetrexed| Cisplatin| Carboplatin
Location	United States, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, France, Germany, Greece, Israel, Italy, Japan, Korea, Republic of, Malaysia, Netherlands, Poland, Russian Federation, Spain, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, Vietnam

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NCT04928846	Phase 3
Title	A Study to Assess Disease Activity and Adverse Events of Intravenous (IV) Telisotuzumab Vedotin Compared to IV Docetaxel in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
Treatment	Telisotuzumab Vedotin| Docetaxel
Location	United States, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Chile, China, Czechia, Denmark, France, Germany, Greece, Israel, Italy, Japan, Korea, Republic of, Netherlands, Poland, Romania, Slovakia, South Africa, Spain, Sweden, Taiwan, Turkey, United Kingdom

NCT05120349	Phase 3
Title	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection
Treatment	Osimertinib| Placebo
Location	United States, Argentina, Brazil, Canada, China, Germany, Italy, Japan, Korea, Republic of, Malaysia, Poland, Romania, Russian Federation, Singapore, Spain, Taiwan, Thailand, Turkey, United Kingdom, Vietnam

NCT04351555	Phase 3
Title	A Study of Osimertinib With or Without Chemotherapy Versus Chemotherapy Alone as Neoadjuvant Therapy for Patients With EGFRm Positive Resectable Non-Small Cell Lung Cancer
Treatment	Osimertinib| Cisplatin| Carboplatin| Placebo| Pemetrexed
Location	United States, Austria, Brazil, Bulgaria, Canada, Chile, China, France, Germany, India, Israel, Italy, Japan, Korea, Republic of, Mexico, Peru, Poland, Russian Federation, Singapore, Spain, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, Vietnam

NCT05785208	Phase 4
Title	Efficacy Study of Osimertinib in Treatment-naÃ¯ve Patients With EGFR Mutant NSCLC According to TP53 Mutational Status.
Treatment	Osimertinib
Location	Italy

NCT04401059	Phase 4
Title	Synergistic Effect of Elemene Plus TKIs Compared With TKIs in EGFR-mutated Advanced NSCLCï¼šProspective Study
Treatment	Elemene plus first or third generation EGFR-TKIs| First or third generation EGFR-TKIs
Location	China

NCT05219162	Phase 4

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Title	Real-World Study on Gene Profile in Patients With Advanced NSCLC Who Progressed on First-Line Osimertinib Therapy(GPS).
Treatment	Gene Profile explore
Location	China

NCT03992885	**Phase 3**
Title	Clinical Study of Combination Therapy With Ectiecinib, Pemetrexed and Platinum in Patients With Metastatic Non-squamous Non-small Cell Lung Cancer With EGFR Mutations.
Treatment	Icotinib
Location	China

NCT04923906	**Phase 3**
Title	Aumolertinib With or Without Chemotherapy as 1st Line Treatment in Locally Advanced or Metastatic Non-Small Cell Lung Cancer With Sensitizing EGFR Mutations
Treatment	Aumolertinib| Placebo Aumolertinib
Location	China

NCT05445791	**Phase 3**
Title	Metformin Plus Tyrosine Kinase Inhibitors for Treatment of Patients With Non-small Cell Lung Cancer With EGFR Mutations
Treatment	Metformin Hydrochloride| Placebo
Location	Mexico

NCT03924050	**Phase 3**
Title	Toripalimab Plus Pemetrexed+Platinus in Advanced Non-small-cell Lungcancer Patients Previsouly Treated EGFR-TKI
Treatment	TORIPALIMAB INJECTION(JS001)
Location	China

NCT05388669	**Phase 3**
Title	A Study of Lazertinib With Subcutaneous Amivantamab Compared With Intravenous Amivantamab in Participants With Epidermal Growth Factor Receptor (EGFR)-Mutated Advanced or Metastatic Non-small Cell Lung Cancer
Treatment	Lazertinib| Amivantamab Subcutaneous and Co-Formulated with Recombinant Human Hyaluronidase (SC CF)| Amivantamab Intravenous

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Location	United States, Argentina, Australia, Brazil, Canada, China, France, Germany, Israel, Italy, Japan, Korea, Republic of, Malaysia, Poland, Portugal, Spain, Taiwan, Thailand, Turkey, United Kingdom

NCT01951469	**Phase 3**
Title	Gefitinib With or Without Chemotherapy in Brain Metastases From Non-small Cell Lung Cancer
Treatment	Gefitinib and Pemetrexed/platinum| Gefitinib mono-therapy
Location	China

NCT05338970	**Phase 3**
Title	HERTHENA-Lung02: A Study of Patritumab Deruxtecan Versus Platinum-based Chemotherapy in Metastatic or Locally Advanced EGFRm NSCLC After Failure of EGFR TKI Therapy
Treatment	Patritumab Deruxtecan| Platinum-based chemotherapy
Location	United States, Australia, Austria, Belgium, Canada, China, France, Germany, Hong Kong, Italy, Japan, Korea, Republic of, Netherlands, Norway, Poland, Portugal, Singapore, Spain, Switzerland, Taiwan, United Kingdom

NCT03802240	**Phase 3**
Title	Sintilimab Â± IBI305 Plus Chemotherapy (Pemetrexed + Cisplatin) for EGFRm + Locally Advanced or Metastasis Non-Squamous NSCLC Patients After EGFR-TKI Treatment Failure
Treatment	Sintilimab| IBI305| Pemetrexed| Cisplatin| Placebo1| Placebo2
Location	China

NCT05104281	**Phase 3**
Title	Osimertinib Combined With Bevacizumab in Patients With Brain Metastasis Epidermal Growth Factor Receptor (EGFR) Mutation Positive Metastatic Non-Small Cell Lung Cancer
Treatment	osimertinib oral and bevazizumab intravenously
Location	China

NCT04988295	**Phase 3**
Title	A Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non- Small Cell Lung Cancer After Osimertinib Failure
Treatment	Lazertinib| Amivantamab| Pemetrexed| Carboplatin
Location	United States, Argentina, Belgium, Brazil, Bulgaria, Canada, China, Czechia, Denmark, France, Germany, Hong Kong, India, Israel, Italy, Japan, Korea, Republic of, Malaysia, Mexico, Netherlands, Poland, Portugal, Puerto Rico, Russian Federation, Spain, Sweden, Taiwan, Turkey, United Kingdom

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NCT02824458	Phase 3
Title	A Study of Gefitinib With or Without Apatinib in Patients With Advanced Non-squamous Non-Small-Cell Lung Cancer Harboring EGFR Mutations
Treatment	Apatinib| Gefitinib| Placebo
Location	China

NCT03833154	Phase 3
Title	Durvalumab vs Placebo With Stereotactic Body Radiation Therapy in Early Stage Unresected Non-small Cell Lung Cancer (NSCLC) Patients / Osimertinib Following SBRT in Patients With Early Stage Unresected NSCLC Harboring an EGFR Mutation
Treatment	Durvalumab| Placebo| Osimertinib (single-arm, open-label)
Location	United States, Australia, Belgium, Brazil, Canada, China, France, Germany, Greece, Israel, Italy, Japan, Korea, Republic of, Netherlands, Poland, Puerto Rico, Russian Federation, Spain, Turkey, United Kingdom

NCT05261399	Phase 3
Title	Savolitinib Plus Osimertinib Versus Platinum-based Doublet Chemotherapy in Participants With Non-Small Cell Lung Cancer Who Have Progressed on Osimertinib Treatment
Treatment	Savolitinib| Osimertinib| Pemetrexed| Cisplatin| Carboplatin
Location	United States, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, France, Germany, Greece, Israel, Italy, Japan, Korea, Republic of, Malaysia, Netherlands, Poland, Russian Federation, Spain, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, Vietnam

NCT04351555	Phase 3
Title	A Study of Osimertinib With or Without Chemotherapy Versus Chemotherapy Alone as Neoadjuvant Therapy for Patients With EGFRm Positive Resectable Non-Small Cell Lung Cancer
Treatment	Osimertinib| Cisplatin| Carboplatin| Placebo| Pemetrexed
Location	United States, Austria, Brazil, Bulgaria, Canada, Chile, China, France, Germany, India, Israel, Italy, Japan, Korea, Republic of, Mexico, Peru, Poland, Russian Federation, Singapore, Spain, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, Vietnam

NCT04181060	Phase 3
Title	Osimertinib With or Without Bevacizumab as Initial Treatment for Patients With EGFR-Mutant Lung Cancer
Treatment	Bevacizumab| Biospecimen Collection| Computed Tomography| Echocardiography| Magnetic Resonance Imaging| Multigated Acquisition Scan| Osimertinib
Location	United States

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NCT04294810	Phase 3
Title	A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer
Treatment	Atezolizumab| Tiragolumab| Matching Placebo
Location	United States, Argentina, Australia, Austria, Brazil, China, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, Republic of, Mexico, Netherlands, Peru, Poland, Russian Federation, Serbia, Spain, Switzerland, Taiwan, Thailand, Turkey, Ukraine

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TP53 associated clinical trials

NCT05785208	Phase 4
Title	Efficacy Study of Osimertinib in Treatment-naÃ¯ve Patients With EGFR Mutant NSCLC According to TP53 Mutational Status.
Treatment	Osimertinib
Location	Italy

NCT04869475	Phase 2
Title	Arsenic Trioxide in Refractory Solid Tumors With Rescuable p53 Mutation
Treatment	Arsenic trioxide
Location	China

NCT03574402	Phase 2
Title	Phase II Umbrella Study Directed by Next Generation Sequencing
Treatment	Avitinib Maleate| Afatinib| Crizotinib| X-396| Chidamide| Pyrotinib Maleate| AZD3759| Pirotinib| Nimotuzumab| Pemetrexed| Cisplatin| Sintilimab| Gemcitabine| Gemcitabine| Carboplatin
Location	China

NCT03560882	Phase 1
Title	A Pilot Trial of Atorvastatin in Tumor Protein 53 (p53) -Mutant and p53 Wild-Type Malignancies
Treatment	Atorvastatin
Location	United States

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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*
FGFR4	c.1211C>G p.A404G	Normal Function

* Prediction based on in silico analysis

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Methodology

DNA was extracted from the sample under investigation using the Qiasymphony DSP DNA Mini Kit (Qiagen). A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology Multi-Gene Variant Assay (GenePlus) which is a qualitative in vitro diagnostic test that detects variants in 1021 tumor-related genes and gene rearrangements / fusions in 38 genes. Sequencing was carried out on an MGI sequencing platform (DNBSEQ-G400). The analysis includes the entire exon regions of 312 genes, introns/promoters/fusion breakpoint regions of 38 genes and partial coding exons of 709 genes. The test also reports 30+ immune response biomarkers, including Tumor Mutational Burden (TMB) score and Microsatellite Instability (MSI) status.

Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system.

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 100%. Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 100%.

Limit of Detection (LoD): The limit of detection (LoD) of this assay is listed in the table below. The LoD is based on as low as 50 ng of gDNA input for library preparation. The assay can also be used to test the microsatellite instability (MSI) with a tumor cell content as low as 10%.

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Insertions/deletions (Indel)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Fusion (or rearrangement)	VAF ≥2%

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.
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.

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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. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Limited tissue detection may not represent the whole DNA variations of lesions because of tumor heterogeneity.
3. 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.
4. 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.
5. The detection could not distinguish between somatic mutations and germline mutations effectively without control sample analysis.
6. This test does not replace germline testing and provides information on cancer susceptibility.
7. 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.

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.

Loss of Heterozygosity (LOH)

Homologous recombination deficiency (HRD), identified by homologous recombination (HR) gene alterations or high percentage of loss of heterozygosity (LOH), is associated with improved prognosis, platinum sensitivity (PS), and poly (ADP-ribose) polymerase inhibitor response in high-grade ovarian cancer (PMID: 33004253, PMID: 34015643).

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The assay measures genomic instability using sample-level LOH in addition to the analysis for HR gene alterations. The Ion ReporterTM Software OncomineTM Comprehensive Assay Plus DNA analysis workflow utilizes heterozygous population SNPs covered by the assay to determine the ploidy levels of genomic segments. The genome is divided into contiguous segments of similar ploidy levels. Log odds ratios for variant allele frequency of observed population SNPs (by TVC) and copy number (CN) ratios (by VCIB CNV pipeline) for each segment are calculated. Log odds ratio and CN ratios are then used to infer tumor cellularity (i.e., percentage of the tumor cells in the sample) and Loss-of-heterozygosity (LOH) for each genomic segment. Segment level LOH events are intersected with targeted gene boundaries to determine LOH events in selected genes. Segment level LOH events are also aggregated to determine sample level % LOH. Furthermore, exon-level copy number alterations are calculated for selected genes.

Gene Expression analysis by Real Time RT-PCR

RNA is reverse transcribed to cDNA, followed by Real Time PCR for the detection of mRNA levels of ERCC1,BRCA1, RRM1 and TYMS genes. The relative expression value of the genes under investigation is determined using β-actin as a reference gene.

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Genes Analyzed

312 genes including all exon regions and available for detecting SNV / Indel / CNV									
ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	APC	AR	ARAF	ARID1A
ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2
AXL	B2M	BAP1	BARD1	BCL2	BCL2L1	BCOR	BLM	BMPR1A	BRAF
BRCA1	BRCA2	BRD4	BRIP1	BTK	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD274	CDC73	CDH1	CDK12	CDK4	CDK6	CDK8
CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP
CRKL	CSF1R	CTCF	CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDR1	DDR2
DICER1	DNMT3A	DOT1L	EGFR	EIF1AX	EMSY	EP300	EPAS1	EPCAM	EPHA2
EPHA3	EPHA5	EPHB1	EPHB6	ERBB2	ERBB3	ERBB4	ERCC1	ERCC3	ERCC4
ERCC5	ERG	ERRFI1	ESR1	EXT1	EXT2	EZH2	FAM123B	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FANCM	FAS	FAT1	FAT2
FBXW7	FGF19	FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN
FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXP1	FUBP1	GALNT12	GATA3	GNA11
GNAQ	GNAS	GRIN2A	GRM3	HDAC1	HGF	HNF1A	HOXB13	HRAS	IDH1
IDH2	IFNG	IFNGR1	IGF1R	IKBKE	IKZF1	IL7R	INPP4B	IRF2	IRS2
JAK1	JAK2	JAK3	JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT
KRAS	LRP1B	MAF	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAPK1	MAX	MCL1
MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLH3	MLL
MLL2	MLL3	MPL	MRE11A	MS4A1	MSH2	MSH3	MSH6	MST1R	MTOR
MUTYH	MYC	MYCL1	MYCN	MYD88	NBN	NCOR1	NF1	NF2	NFE2L2
NFKB1A	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NSD1	NTHL1	NTRK1
NTRK2	NTRK3	PALB2	PARK2	PARP1	PAX5	PBRM1	PCK1	PDCD1	PDCD1LG2
PDGFRA	PDGFRB	PDK1	PIK3CA	PIK3CB	PIK3CG	PIK3R1	PIK3R2	PMS1	PMS2
POLD1	POLE	POT1	PPP2R1A	PRDM1	PRKAR1A	PTCH1	PTCH2	PTEN	PTPN11
PTPRD	RAC1	RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1
RARA	RB1	RBM10	RECQL	RECQL4	RET	RHOA	RICTOR	RINT1	RNF43
ROS1	RPTOR	RUNX1	SDHA	SDHAF2	SDHB	SDHC	SDHD	SERPINB3	SERPINB4
SETD2	SF3B1	SLX4	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1
SOX2	SOX9	SPOP	SRC	STAG2	STAT3	STK11	SUFU	SYK	TBX3
TCF7L2	TERC	TET2	TGFBR2	TMEM127	TMPRSS2	TNFAIP3	TNFRSF14	TOP1	TOP2A
TP53	TSC1	TSC2	TSHR	U2AF1	VEGFA	VHL	WRN	WT1	XPO1

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XRCC2	ZMAT3								
38 genes including specific intron, promoter and fusion breakpoint regions and available for detecting gene rearrangement or fusion									
ALK	BCL2L11	BRAF	BRCA1	BRD4	CD74	EGFR	EML4	ERG	ETV6
EZR	FGFR1	FGFR2	FGFR3	KIF5B	KIT	MAML2	MET	MSH2	MYC
MYCL1	NCOA4	NOTCH2	NTRK1	NTRK2	NTRK3	PDGFRA	RAF1	RET	ROS1
RSPO2	SDC4	SLC34A2	TERT	TFE3	TMPRSS2	TPM3	PMS2		
709 genes including partial exon regions and available for detecting SNV / Indel									
ABCA13	ABCB1	ABCC1	ABCC11	ABCC2	ABCG2	ABL2	ACACA	ACIN1	ACTB
ACTG1	ACTG2	ACVR2A	ACVRL1	ADAM29	ADAMTS5	ADCY1	AFF1	AFF2	AFF3
AHNAK	AKAP9	ALB	AMOT	ANGPT1	ANK3	ANKRD11	ANKRD30A	ANKRD30B	APEX1
APOBEC3B	ARAP3	ARFGEF1	ARFGEF2	ARHGAP29	ARHGAP35	ARID4B	ARID5B	ARNT	ASCL4
ASH1L	ASMTL	ASPM	ASTN1	ASXL2	ATIC	ATP11B	ATP12A	ATP1A1	ATP2B3
BAZ2B	BBC3	BBS9	BCAS1	BCL10	BCL11A	BCL11B	BCL2A1	BCL2L11	BCL3
BCL6	BCL9	BCORL1	BCR	BIRC3	BMPR2	BNC2	BPTF	BRD2	BRD3
BRSK1	BRWD1	BTLA	BUB1	C15orf23	C15orf55	C1QA	C1S	C3orf70	C7orf53
C8orf34	CACNA1E	CADM2	CALR	CAMTA1	CASP1	CASQ2	CBLB	CBR1	CBR3
CCDC168	CCNA1	CCNB3	CCT3	CCT5	CCT6B	CD22	CD33	CD5L	CD74
CDA	CDH11	CDH18	CDH23	CDK13	CHD1	CHD1L	CHD4	CHD6	CHD8
CHD9	CHFR	CHI3L1	CHN1	CIITA	CLDN18	CLP1	CLSPN	CLTC	CNOT3
CNOT4	CNTN1	CNTN5	CNTNAP1	CNTNAP5	COL1A1	COL2A1	COL5A1	COL5A2	COL5A3
COPS2	CPS1	CRIPAK	CRLF2	CRNKL1	CRTC1	CSF1	CSF3R	CSMD1	CSMD3
CSNK1A1	CSNK1G3	CTLA4	CTNNA2	CTNND1	CUX1	CXCR4	CYBA	CYP19A1	CYP1A1
CYP1B1	CYP2A13	CYP2C8	CYP2D6	CYP3A4	CYP3A5	DCC	DDX3X	DDX5	DEK
DHX35	DHX9	DIAPH1	DIS3L2	DLC1	DMD	DNAH6	DNAJB1	DNM2	DNMT1
DNMT3B	DOCK2	DOCK7	DPYD	DRGX	DTX1	DUSP22	DYSF	E2F3	EBF1
ECT2L	EED	EEF1A1	EGFL7	EGR3	EIF2AK3	EIF2C3	EIF3A	EIF4A2	EIF4G3
ELAC2	ELF1	ELF3	ELMO1	ELN	EME2	EMID2	EML4	EPC1	EPHA1
EPHA4	EPHA7	EPHB2	EPHB4	EPOR	EPPK1	EPS15	ERBB2IP	ERCC2	ESR2
ETS1	ETV1	ETV5	ETV6	EWSR1	EZR	F8	FAM131B	FAM135B	FAM157B
FAM46C	FAM5C	FAP	FASLG	FAT3	FAT4	FCGR1A	FCGR2A	FCGR2B	FCGR3A
FCRL4	FGF10	FGF12	FGF14	FGF23	FGF6	FLG	FLI1	FLNC	FMN2
FN1	FNDC4	FOXA2	FOXO1	FOXO3	FOXQ1	FRMPD4	FUS	FXR1	FYN

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FZD1	G3BP1	G3BP2	GAB2	GABRA6	GATA1	GATA2	GFRAL	GIGYF1	GKN2
GLB1L3	GLI1	GLI2	GLI3	GMPS	GNA13	GNG2	GPC3	GPR124	GPS2
GPX1	GRB7	GSK3B	GSTM5	GSTP1	GUSB	H3F3A	H3F3B	H3F3C	HCLS1
HCN1	HDAC4	HDAC9	HECW1	HEY1	HIST1H1C	HIST1H1D	HIST1H1E	HIST1H2AC	HIST1H2AG
HIST1H2AL	HIST1H2AM	HIST1H2BC	HIST1H2BD	HIST1H2BJ	HIST1H2BK	HIST1H2BO	HIST1H3B	HIST1H3C	HIST1H3D
HIST1H3F	HIST1H3G	HIST1H3H	HIST1H3I	HIST1H4I	HIST3H3	HLA-A	HLA-B	HLA-C	HLF
HMCN1	HNF1B	HNRPDL	HOXA11	HOXA13	HOXA3	HOXA9	HOXC13	HOXD11	HOXD13
HSD3B1	HSP90AA1	HSP90AB1	HSPA8	HSPD1	HSPH1	ICK	ICOSLG	ID3	IFITM3
IGF1	IGF2	IGF2R	IGLL5	IKZF2	IKZF3	IL10	IL1RAPL1	IL21R	IL6
IL6ST	IMPG1	ING1	INHBA	INPP4A	INPPL1	INSR	IRF4	IRF6	IRS1
ITGB3	ITK	ITSN1	JARID2	KALRN	KAT6A	KAT6B	KCNJ5	KCNQ2	KDM2B
KEL	KIF5B	KLF4	KLHL6	KLK1	KRTAP5-5	L3MBTL1	LAMA2	LATS1	LATS2
LCP1	LEF1	LGALS8	LIFR	LPHN2	LPP	LRP2	LRP4	LRP5	LRP6
LRRC7	LRRK2	LYN	LZTS1	MACF1	MAD1L1	MAGI2	MAML2	MAML3	MAP3K13
MAPK3	MCC	MCM3	MDC1	MECOM	MEF2C	MGA	MIB1	MIOS	MKL1
MLL4	MLLT3	MMP11	MMP2	MN1	MNDA	MNX1	MSH4	MSN	MSR1
MTHFR	MTRR	MUC5B	MYH11	MYH14	MYH9	MYO3A	MYOD1	NAP1L1	NAV3
NCAM2	NCF2	NCF4	NCK1	NCOA3	NCOA4	NCOR2	NCSTN	NDUFA13	NFATC4
NFE2L3	NKX3-1	NLRC3	NOD1	NOS3	NOTCH4	NQO1	NR1I2	NR2F2	NR4A2
NRG1	NRP2	NRXN1	NTM	NUMA1	NUP107	NUP210	NUP93	NUP98	OBSCN
OGDH	OMD	OPCML	OR11G2	OR2T4	OR4A15	OR4C6	OR5L2	OR6F1	P2RY8
P4HB	PABPC1	PABPC3	PAG1	PAK1	PAK3	PASK	PAX3	PAX7	PC
PCDH18	PCSK6	PCSK7	PDCD11	PDE4DIP	PDGFB	PDILT	PER1	PGR	PHF1
PHF6	PIK3C2A	PIK3C2B	PIK3C2G	PIK3C3	PIM1	PKD1L2	PKHD1	PLAG1	PLCB1
PLCG1	PLCG2	PLK1	PLXNA1	PLXNB2	PNRC1	POLQ	POM121	POM121L12	POU2AF1
PPM1D	PPP1R17	PPP6C	PRDM16	PREX2	PRF1	PRKAA1	PRKCB	PRKCI	PRKDC
PRRX1	PRX	PSG2	PSIP1	PSMB1	PSMB5	PTGS1	PTGS2	PTPN13	PTPN2
PTPRB	PTPRK	PTPRO	PTPRS	PTPRT	PTPRU	RAB35	RAC2	RAD21	RAD54B
RANBP2	RASA1	RASGRP1	RBL1	REL	RELN	RFC1	RGS3	RHEB	RHOH
RHOT1	RIT1	RNASEL	ROBO1	ROBO2	ROBO3	ROCK1	RPGR	RPS6KB1	RPS6KB2
RSPO2	RSPO3	RUNX1T1	RUNX2	RXRA	RYR1	RYR2	SBDS	SCUBE2	SDC4
SEC31A	SEMA3A	SEMA3E	SEMA6A	SERPINA7	SETBP1	SETDB1	SF1	SF3A1	SFPQ
SGCZ	SGK1	SH2B3	SH2D1A	SH3PXD2A	SHH	SI	SIN3A	SLC16A1	SLC1A2
SLC22A16	SLC22A18	SLC22A2	SLC22A3	SLC34A2	SLCO1B3	SLIT1	SLIT2	SMARCD1	SMARCE1

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SMC1A	SMC1B	SNCAIP	SNTG1	SNX29	SOD2	SOS1	SOX10	SOX17	SPEN
SPRR3	SPSB4	SPTA1	SRD5A2	SRGAP1	SRGAP3	SRSF2	SRSF7	STAG1	STAT1
SUCLG1	SUCLG2	SULT1A1	SUZ12	SVEP1	SYNCRIP	SYNE1	TAF1	TAF15	TAF1L
TAL1	TBL1XR1	TBX15	TBX22	TCEB1	TCF12	TCF3	TCF4	TCL1A	TEC
TENM3	TERT	TET1	TFDP1	TFDP2	TFE3	TGFBR1	THBS2	TJP1	TLE1
TLL2	TLR4	TLX3	TMEM132D	TNFSF11	TNN	TP53BP1	TP63	TP73	TPM3
TPR	TRAF2	TRAF7	TRIM24	TRIM58	TRIO	TRPC5	TRRAP	TSHZ2	TSHZ3
TTF1	TUBA3C	TUBB3	TUSC3	TXNIP	TYMS	TYR	UBE2D2	UBR5	UGT1A1
UMPS	UPF3B	USH2A	USP6	USP8	VEZF1	VIM	VTCN1	WASF3	WDR90
WDTC1	WHSC1	WHSC1L1	WIPF1	WNK1	WNT5A	WSCD2	WWOX	WWP1	WWP2
XIAP	XPC	XRCC1	XRCC3	YAP1	YY1AP1	ZBTB16	ZC3H11A	ZFHX3	ZFP36L1
ZFP36L2	ZFPM2	ZIC3	ZNF217	ZNF384	ZNF521	ZNF638	ZNF750	ZNF804B	

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Appendix

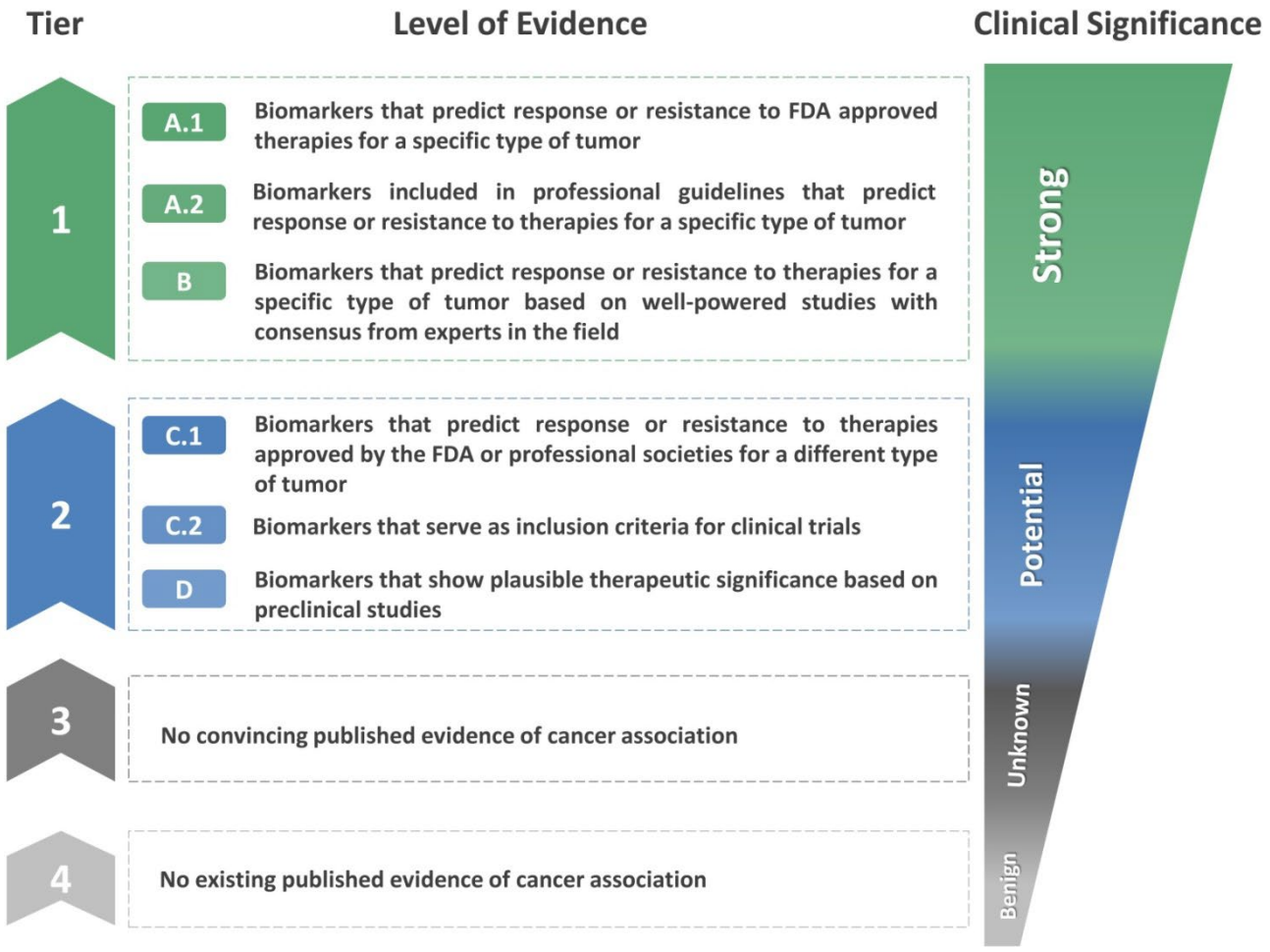

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

1. Leichsenring J, Horak P, Kreutzfeldt S, et al. Int J Cancer. 2019 Dec 1;145(11):2996-3010.
2. Li MM, Datto M, Duncavage EJ, et al. J Mol Diagn. 2017 Jan;19(1):4-23.

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Loss of Heterozygosity (LOH)

Loss of heterozygosity (LOH) events accumulate as genomic 'scars' due to faulty DNA double-strand break repair when the homologous recombination pathway is defective (HRD). This is reflected in the loss of heterozygosity (LOH) score, which is a profile of the percentage of the tumor genome that is under focal loss of one allele.

Clinical evidence suggests that patients with ovarian cancer who have higher levels of genomic LOH may respond better to PARP inhibitors medicines. Rucaparib induced substantially longer median PFS and ORR for patients with LOH score 16% in platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube cancer. Patients who were LOH-high achieved a 12-month progression-free survival (PFS) of 28% versus 10% for the LOH-low group. Moreover. patients with a platinum sensitivity and BRCA1/2 wild type had a better progression-free survival (PFS) with rucaparib versus placebo in the maintenance setting, with median PFS of 9.7 months versus 5.4 months (HR=0.44) and 6.7 months versus 5.4 months (HR=0.58), respectively, for the LOH score 16% and LOH score 16% cohorts, respectively (PMID: 33941784, 28916367, 27908594).

Similar findings have been reported for maintenance therapy with niraparib in ovarian cancer and olaparib when a different measure of HRD that includes genomic LOH is used (PMID: 27717299, 26957554, 31851799, 33004253).

Although high levels of %LOH are more commonly observed in breast and ovarian cancers, they can be found in a variety of tumor types, which may affect their responsiveness to PARP inhibitor therapy (PMID: 33462368, 35740616). The extent of this impact is, however, yet unclear.

Moreover, increased LOH has also been linked to enhanced susceptibility to platinum-containing chemotherapy regimens in ovarian and breast cancer patients as well as other tumor types. (PMID: 30613349, 26957554, 22912389, 25847929, 25847936).

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Table S1. TMB interpretation and cut-offs.

Tumour Type	Immunotherapy agent	Study/Trial	TMB high cut-off	Type of benefit
TMB assessed through a multi-gene assay				
NSCLC (1L or 2L)	Anti PD-L1	FIR/BIRCH [1]	**13.5 Muts/Mb (1L)** **17.1 Muts/Mb (2L)**	ORR, OS, PFS
NSCLC (2L)	Anti PD-L1	POPLAR [1]	**15.8 Muts/Mb**	ORR, OS, PFS
NSCLC (2L)	Anti PD-L1	POPLAR/OAK [2-3]	**16 Muts/Mb (blood)**	OS, PFS
NSCLC (1L)	Anti PD-L1	BFAST and B-F1RST [4-6]	**16 Muts/Mb (blood)**	DOR, ORR, PFS, OS
NSCLC	Anti PD-L1	Rizvi *et al*, 2018 [7]	**7.4 Muts/Mb**	DCB, ORR, PFS
NSCLC	Anti PD-1	Singal *et al,* 2017 [8]	**20 Muts/Mb**	OS
NSCLC (1L)	Anti PD-1/Anti-CTL4	CheckMate 227 [9]	**10 Muts/Mb**	ORR, PFS
NSCLC (1L)	Anti PD-1/Anti-CTL4	CheckMate 568 [10]	**10 Muts/Mb**	ORR, PFS
NSCLC	various immunotherapies	Rozenblum *et al*, 2017 [11]	**9.6 Muts/Mb**	ORR
Melanoma	various immunotherapies	Johnson *et al*, 2016 [12]	**23.1 Muts/Mb**	ORR, OS, PFS
Bladder (1L or 2L)	Anti PD-L1	IMvigor 210 [13-14]	**16 Muts/Mb**	ORR, OS
Bladder (2L)	Anti PD-L1	IMvigor 211 [15]	**9.65 Muts/Mb**	OS
Multiple solid tumours	various immunotherapies	Goodman *et al*, 2017 [16]	**20 Muts/Mb**	ORR, OS, PFS
Multiple solid tumours (2L)	various immunotherapies	Bonta *et al*, 2017 [17]	**8 Muts/Mb**	ORR
Multiple solid tumours	anti-CTLA-4 or anti-PD-1	Samstein *et al*, 2019 [18]	**varies across cancer types**	OS
mTNBC	Anti PD-1	KEYNOTE-119 [19]	**10 Muts/Mb**	ORR, OS
All solid tumours	Anti PD-1	KEYNOTE-158 [20]	**10 Muts/Mb**	ORR

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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
Gastric cancer	Anti-PD-1 [13]	Dako 22C3	2L CPS ≥ 1	CPS
Gastric cancer HER-2 NEGATIVE (Advanced or metastatic gastric or gastro-oesophageal junction)	Anti-PD-1 [18]	Dako 22C3	1L CPS ≥5	CPS
Head and neck squamous cell carcinoma (HNSCC)	Anti-PD-1 [14,15]	Dako 22C3	1L CPS ≥ 1 2L TPS ≥ 50%	CPS and %TPS
Cervical cancer	Anti-PD-1 [16]	Dako 22C3	2L CPS ≥ 1	CPS
Esophageal Adenocarcinoma (HER-2 negative)	Anti-PD-1 [17]	Dako 22C3	2L CPS ≥ 10	CPS
	Anti-PD-1 [18]	Dako 22C3	1L CPS ≥5	CPS
metastatic oesophageal SQUAMOUS cell carcinoma	Anti-PD-1 [17]	Dako 22C3	2L CPS ≥ 10	CPS
	Anti-PD-1 [18]	Dako 22C3	1L TC≥ 1%	TC

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

TC: tumor cell

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

IC: immune cell

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