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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:**	METASTATIC LUNG CANCER

Com.Pl.i.t. Dx (24 genes, 6 fusions) | Comprehensive Panel for Individualized Treatment

Report Summary

27	Unique Genes (7 Fusions) analyzed	**3**	Genomic alterations identified in tumor
7	Biomarker related approved therapies for indication	**0**	Biomarker related therapies with potential benefit
4	Biomarker related therapies with potential resistance	**26**	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.2235_2249del (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.2369C>T (p.T790M)	Osimertinib (1A.1)	-	Afatinib (1B) Erlotinib (1A.1) Gefitinib (1A.1)	yes
EGFR	Exon 20 c.2389T>A (p.C797S)	-	-	Osimertinib (1B)	yes
PD-L1 expression (Table S2)	Negative TPS<1%	-	-	-	-

*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.2235_2249del (p.E746_A750del)**	**VAF*:30%**	**OncoKB**	**CIViC**	**PMKB**

Treatment information

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).

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Gene information

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 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.

Variant information

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). Patients with in-frame deletions in Exon 19 of EGFR are sensitive to EGFR targeted therapies (PMID: 29075127).

EGFR: **c.2369C>T (p.T790M)**	**VAF*:25%**	**OncoKB**	**CIViC**	**PMKB**

Treatment information

T790M is the most common secondary EGFR mutation that causes resistance to EGFR tyrosine kinase inhibitors (TKIs). Multiple reports have documented that T790M mediates resistance to gefitinib, erlotinib, afatinib, or cetuximab (PMID: 18227510; 27811988; 29141884). Osimertinib, is an FDA approved, third-generation EGFR TKI which is associated with clinical benefit in patients harbouring EGFR T790M mutation. It was developed to specifically bind to and induce degradation of EGFR proteins harboring the T790M variant (PMID: 29141884). In vitro high-throughput study demonstrated that T790M is sensitive to afatinib and osimertinib when co-ocurring with EGFR G719A (PMID: 29141884). Lazertinib is an oral, third-generation, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), under clinical development, for the treatment of non-small cell lung cancer (NSCLC). It is a brain-penetrant, irreversible EGFR-TKI that targets the T790M mutation and activating EGFR mutations Ex19del and L858R, while sparing wild type-EGFR. Lazertinib in combination with amivantamab demonstrated promising clinical activity in the open-label, phase 1 dose-escalation (part 1) and dose-expansion (part 2) CHRYSALIS study (NCT02609776) that is evaluating the efficacy and safety of amivantamab with and without lazertinib in patients with advanced NSCLC harbouring EGFR Exon 19del or L858R activating mutations. Antitumour activity of lazertinib plus amivantamab combination therapy was seen in the ongoing part 2 expansion cohort involving patients with measurable disease who were osimertinib-resistant, chemotherapy-naive or treatment naive. At a median follow-up of 4 months, the ORR in the osimertinib-resistant cohort was 36% and the clinical benefit rate was 60% (https://doi.org/10.1016/j.annonc.2020.08.1572). Finally, in a randomized, double-blind, multinational phase III study for the efficacy and safety of lazertinib versus gefitinib assessment as a first-line treatment of patients with EGFRm advanced NSCLC

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(LASER301; NCT04248829), Lazertinib demonstrated significant improvement in efficacy compared to gefitinib in the front-line treatment of EGFRm advanced NSCLC, with a comparable safety profile (ESMO Asia Congress, S1560-S1597, 2022).

Variant information

This alteration has been reported as activating. T790M occurs in the ATP binding site (amino acids 790-791, UniProt) of the EGFR kinase domain (amino acids 712-979, UniProt) that is essential for EGFR function. Missense mutations in the kinase domain of EGFR are spread along the kinase coding regions (Exons 18-21) and most of these mutations stimulate kinase activity. A genomic alteration resulting in this amino acid change is recorded within dbSNP (rs121434569) (Jan, 2021). The clinical significance of this alteration in ClinVar is drug response (Jan, 2021).

***EGFR:* c.2389T>A (p.C797S)**	**VAF*:24%**	OncoKB	CIViC	PMKB

Treatment information

The EGFR C797S is a known resistance mutation. It has been reported in EGFR-mutant lung cancer patients who have developed acquired resistance to Osimertinib (PMID: 25939061, 26181354). Cells expressing C797S alone or with exon19del were still sensitive to the gefitinib, erlotinib and cetuximab compared with the wildtype (PMID: 28287083, 29922072, 29141884, 25964297). C797S increases hydrophilicity around residue 797 which made it less preferable for drug binding compared with T790M alone (PMID: 28456628) and preclinical studies showed that cells with EGFRexon19del-T790M-C797S triple mutations are resistant to T790M-specific third-generation inhibitor osimertinib, compared to EGFR exon19del-T790M double mutation in addition to resistance to gefitinib, erlotinib and afatinib (PMID: 28287083, 25964297). Among possible osimertinib-resistant mutations, EGFR-C797S was identified as the most common, which accounts for more than 15% but less than 30% of all resistant cases (PMID:31467113).

Variant information

The EGFR exon 20 C797S mutation is located in the EGFR tyrosine kinase domain. While this variant has not been functionally characterized per se, it has been reported that C797S mutation confers resistance to osimertinib (PMID: 25939061, 26181354). The clinical significance of this alteration in ClinVar is not provided (Apr, 2021).

*VAF: Variant Allele Frequency

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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

DrugBank

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

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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.

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.

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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

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

NCT03645928	Phase 2
Title	Study of Autologous Tumor Infiltrating Lymphocytes in Patients With Solid Tumors
Treatment	Lifileucel| LN-145| Pembrolizumab| LN-145-S1| Ipilimumab| Nivolumab
Location	United States, Canada, France, Germany, Greece, Spain, Switzerland, United Kingdom

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

NCT05219162	Phase 4
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

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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

NCT05800223	Phase 3
Title	Armatinib Alone or in Combination With SRT for Brain Metastases EGFR-mutated Non-small Cell Lung Cancer
Treatment	Almonertinib| SBRT
Location	China

NCT04951635	Phase 3
Title	A Phase III Study to Assess the Effects of Almonertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer
Treatment	Almonertinib| Placebo Almonertinib

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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
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

NCT02824458	**Phase 3**

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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

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

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

NCT05493501	**Phase 3**
Title	Aumolertinib With Chemotherapy or Alone Compared With Osimertinib in Patients With Epidermal Growth Factor Receptor-Mutant Non-Small Cell Lung Cancer
Treatment	Aumolertinib monotherapy| Osimertinib monotherapy| Pemetrexed| Cisplatin| Carboplatin| Paclitaxel| Nab paclitaxel| Gemcitabine
Location	United States

NCT05382728	**Phase 3**
Title	Phase III Study of TY-9591 in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer (FLETEO)
Treatment	TY-9591| placebo Osimertinib| Osimertinib| placebo TY-9591
Location	China

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

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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

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

NCT04143607	**Phase 3**
Title	ASK120067 Versus Gefitinib as First-line Treatment for EGFRm Locally Advanced or Metastatic NSCLC
Treatment	ASK120067| Placebo Gefitinib 250 mg| Gefitinib| Placebo ASK120067
Location	China

NCT05236946	**Phase 3**
Title	Observation or Upfront Cranial RT in Oncogene Mutated NSCLC With Asymptomatic BM: A Phase III RCT
Treatment	Stereotactic radiosurgery/whole brain radiotherapy| Tyrosine kinase inhibitor
Location	India

Press here for a live search of clinical trials for EGFR

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Methodology

NGS analysis

DNA was extracted from the sample under investigation using the Qiasymphony DSP DNA Mini Kit (Qiagen). RNA was extracted using the RNeasy FFPE Kit (Qiagen).

Mutation hotspot regions of 27 genes were amplified using an Ion AmpliSeq Panel (Thermo Fisher Scientific). Copy number variations, SNPs, and indels were analysed. Additionally, ALK, ROS1, RET, NTKR1, NTKR2 & NTKR3 fusions and expression and MET exon 14 skipping were tested using an Ion AmpliSeq RNA Fusion Panel (Thermo Fisher Scientific). All fusions detected are confirmed with an alternative method (Real-Time PCR).

Sequencing was carried out using the Next Generation Sequencing platform Ion GeneStudio S5 Prime System (Thermo Fisher Scientific). The detection limit of the method is 2-5% of mutant allelic content, depending on the genomic region. Mutant alleles detected in less than 5% are confirmed.

Ion Torrent Oncomine Knowledgebase Reporter was used in sequence analysis and interpretation. The application was internally designed and developed by Thermo Fisher Scientific. Variants are reported according to HGVS nomenclature and were classified following ACMG guidelines. Information on therapeutic agents and clinical trials were obtained from publicly available information. Variants, therapies, and trials listed in this report are not ranked in order of potential clinical significance or predicted efficacy for this patient.

**The following hot spot regions are covered by the assay: AKT1 (NM_001014432) exon 4, ALK (NM_001014432) exons 22, 23,25, BRAF (NM_004333) exons 11, 15, CDKN2A (NM_058197) exons 1, 2, CTNNB1 (NM_001904) exon 3, DDR2 (NM_001014796) exons 6, 13, 14, 15, 16, 18, EGFR (NM_005228) exons 12, 18, 19, 20, 21, ERBB2 (NM_004448) exons 19, 20, 21, FBXW7 (NM_033632) exons 5, 8, 9, 10, 11, FGFR1 (NM_023110) exons 4, 7, FGFR2 (NM_022970) exons 9, 12, FGFR3 (NM_001163213) exons 7, 9, 14, 16, 18 , HRAS (NM_001130442) exons 2, 3 KEAP1 (NM_203500) exons 2-6, KRAS (NM_033360) exons 2, 3, 4, MAP2K1 (NM_002755) exon 2, MET (NM_001127500) exons 2, 11, 14, 16, 19, NOTCH1 (NM_017617) exons 26, 27, NRAS (NM_002524) exons 2, 3, 4, PIK3CA (NM_006218) exon 10 (p.E542K, p.E545K, p.E545Q, p.E545G, p.E545V, p.Q546K), 14, 21, POLE (NM_006231) exons 9-14, PTEN (NM_000314) exons 1, 3, 6, 7, 8, RET (NM_020975) exons 10-18, SMAD4 (NM_005359) exons 3, 5, 6-12, SMARCA4 (NM_001128849) exons 2-36, STK11 (NM_000455) exons 1-9, TP53 (NM_000546) exons 2-11.

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.

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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 analyses was carried out using the ISIS FISH Imaging System, Metasystems.

Genes Analyzed

27 gene alterations									
AKT1	ALK	BRAF	CDKN2A	CTNNB1	DDR2	EGFR	ERBB2	FBXW7	FGFR1
FGFR2	FGFR3	HRAS	KEAP	KRAS	MAP2K1	MET *	NOTCH1	NRAS	PIK3CA
POLE	PTEN	RET	SMAD4	SMARCA4	STK11	TP53			

***** *MET* amplification and *MET* exon 14 skipping are also included in the analysis

7 fusion transcripts						
ALK	ROS1	RET	NTRK1	NTRK2	NTRK3	MET

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Appendix

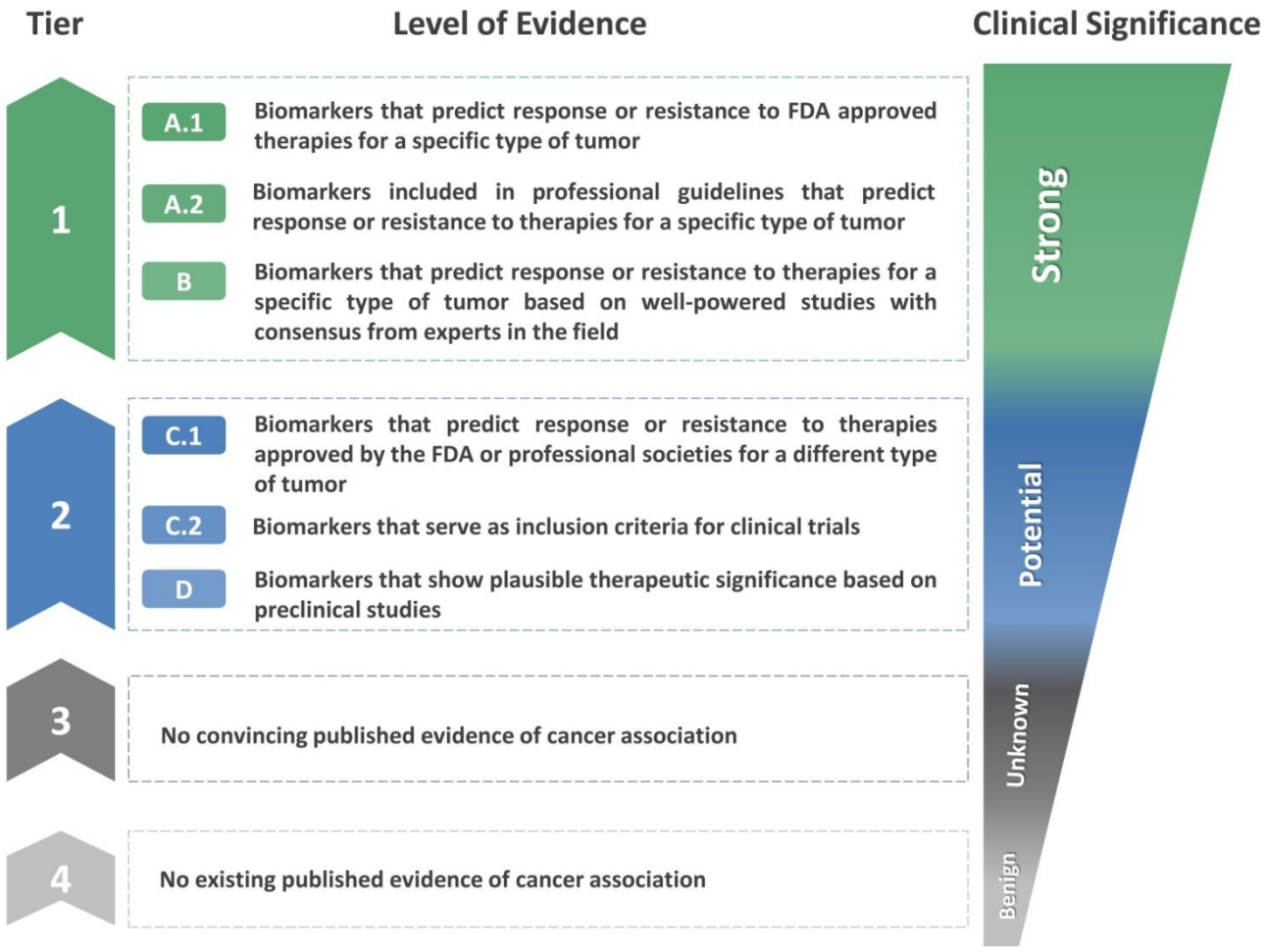

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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Table 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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