Marsden360
Developed in partnership with Guardant Health

The ROYAL MARSDEN Clinical Genomics

Consulting physician		Patient		Sample	
Report Date	11/06/2024	Name		Accession Number	19235531
		Diagnosis	Lung cancer	Collection site	Not provided

Panel Analysis: Somatic cancer

Marsden360 sequences 74 cancer-associated genes to identify somatic alterations. Cell-free circulating DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using Illumina platforms and hg19 as the reference genome.

Overall comment

An activating mutation in exon 19 of the EGFR gene has been detected. Clinical evidence would suggest this patient may benefit from EGFR TKi targeted therapy.

Pathogenic variants in the TP53 and RB1 genes were also detected. TP53 variants are observed in 50% of patients with lung cancer and are associated with poorer responses to chemotherapy and radiotherapy. Furthermore, pathogenic variants in RB1 are associated with poorer prognosis in lung cancer .

MSI High NOT DETECTED.

If there is uncertainty around these results, please refer to GTAB.

Analysis results: Clinically relevant variants detected

1 Variant of strong clinical significance, Tier 1	Approved treatments	Trials and Supplementary Information
EGFR, p.E746_A750del, VAF 1.2%, Pathogenic	EGFR tyrosine kinase inhibitor Afatinib Bevacizumab/erlotinib Dacomitinib Erlotinib Erlotinib/ramucirumab Gefitinib Osimertinib	NCCN Recommended: afatinib /cetuximab Trials: 2 Phase 3 6 Phase 2 3 Phase 1/Phase 2 3 Phase 1

1 Variant of potential clinical significance, Tier 2	Approved treatments	Trials and Supplementary Information
TP53, p.R248G, VAF 1.47%, Pathogenic	-	-

1 Variant of biological significance, Tier 3
RB1, c.1332+1G>A, VAF 0.34%, Pathogenic

Interactions

None

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 9.

Report content

TREATMENT OPTIONS

Therapies with potential clinical benefit (8)

EGFR TYROSINE KINASE INHIBITOR

FDA-approved EGFR tyrosine kinase inhibitors include erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib.

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

AFATINIB

Afatinib, a kinase inhibitor, is FDA-approved for treating 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, as first-line treatment; metastatic, squamous NSCLC progressing after platinum-based chemotherapy; afatinib is EMA-approved for treating adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) who are EGFR TKI-naïve; and locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum based chemotherapy.

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

BEVACIZUMAB/ERLOTINIB

Bevacizumab, a VEGF-specific angiogenesis inhibitor, in combination with erlotinib, a kinase inhibitor, is EMA-approved for the first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

DACOMITINIB

Dacomitinib, a kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

ERLOTINIB

Erlotinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen; and for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine; erlotinib is EMA-approved for treating patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations for the first-line treatment; locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease for switch maintenance treatment after first-line chemotherapy; locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (in patients with tumours without EGFR activating mutations, erlotinib is indicated when other treatment options are not considered suitable); and metastatic pancreatic cancer, in combination with gemcitabine.

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

ERLOTINIB/RAMUCIRUMAB

Ramucirumab, a VEGFR2 antagonist, in combination with erlotinib, a kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of patients with metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

GEFITINIB

Therapies with potential clinical benefit (8)

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

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

OSIMERTINIB

Osimertinib, a kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test; osimertinib is FDA-approved for treating adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, as adjuvant therapy after tumor resection; and metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy; osimertinib is EMA-approved for treating adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as adjuvant treatment after complete tumour resection; and locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Sensitive

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

AVAILABLE CLINICAL TRIALS

Phase 3 clinical trials (2)

OSIMERTINIB

A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab With Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Patients With Unresected Stage I/II, Lymph-node Negative Non-small Cell Lung Cancer (PACIFIC-4/RTOG-3515)
NCT03833154

Qualifying variant			Contact
Gene	Variant	Classification	AstraZeneca Clinical Study Information Center; information.
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic	center@astrazeneca.com; 1-877-240-9479;

OSIMERTINIB

A Phase III, Double-blind, Randomised, Placebo-Controlled, International Study to Assess the Efficacy and Safety of Adjuvant Osimertinib Versus Placebo in Participants With EGFR Mutation-positive Stage IA2-IA3 Non-small Cell Lung Cancer, Following Complete Tumour Resection
NCT05120349

Qualifying variant			Contact
Gene	Variant	Classification	AstraZeneca Clinical Study Information Center; information.
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic	center@astrazeneca.com; 1-877-240-9479;

Phase 2 clinical trials (6)

ZIMBERELIMAB, DOCETAXEL, ETRUMADENANT, SACITUZUMAB GOVITECAN

A Phase 2 Platform Study Evaluating the Safety and Efficacy of Novel Treatment Combinations in Patients With Lung Cancer (VELOCITY-Lung)
NCT05633667

Qualifying variant			Contact
Gene	Variant	Classification	Gilead Clinical Study Information Center; GileadClinicalTrials@gilead.com;
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic	1-833-445-3230;

LAZERTINIB, BEVACIZUMAB, AMIVANTAMAB

A Multicentre Single-arm Phase II Trial of Amivantamab, Lazertinib Plus Bevacizumab in Patients With EGFR-mutant Advanced NSCLC With Progression on Previous Third-generation EGFR-TKI
NCT05601973

Qualifying variant			Contact
Gene	Variant	Classification	Heidi Roschitzki, PhD; heidi.roschitzki@etop.ibcsg.org; +41 31 511 94 00;

Phase 2 clinical trials (6)

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

OSIMERTINIB

An Open-label, Single-arm, Phase II, Multinational, Multicentre Study to Assess the Efficacy and Safety of 5 Years of Osimertinib in Participants With EGFRm-positive Stage II-IIIB NSCLC, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy
NCT05526755

Qualifying variant

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

Contact
AstraZeneca Clinical Study Information Center; information.center@astrazeneca.com; 1-877-240-9479;

CARBOPLATIN, LOW MOLECULAR WEIGHT HEPARIN, PEMETREXED, LAZERTINIB, AMIVANTAMAB

A Phase 2, Open-Label, Parallel Cohort Study of Subcutaneous Amivantamab in Multiple Regimens in Patients With Advanced or Metastatic Solid Tumors Including EGFR-mutated Non-Small Cell Lung Cancer
NCT05498428

Qualifying variant

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

Contact
Study Contact; Participate-In-This-Study@its.jnj.com; 844-434-4210;

PEMBROLIZUMAB, LN-145

A Phase 2, Multicenter Study of Autologous Tumor Infiltrating Lymphocytes (LN 144/LN-145/LN-145-S1) in Patients With Solid Tumors
NCT03645928

Qualifying variant

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

Contact
Iovance Biotherapeutics Study Team; Clinical.Inquiries@iovance.com; 1-844-845-4682;

PEMBROLIZUMAB

A Phase 2, Multicenter, Randomized, Open-Label Trial of GEN1046 as Monotherapy and in Combination Pembrolizumab Therapy in Subjects With Relapsed /Refractory Metastatic Non-Small Cell Lung Cancer After Treatment With Standard of Care Therapy With an Immune Checkpoint Inhibitor
NCT05117242

Qualifying variant

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

Contact
Genmab A/S Trial Information; clinicaltrials@genmab.com; +45 70202728;

Phase 1/Phase 2 clinical trials (3)

PETOSEMTAMAB

Phase 1/2 Dose Escalation and Cohort Expansion Study Evaluating Single-agent MCLA-158 in Metastatic Colorectal Cancer and Other Advanced Solid Tumors
NCT03526835

Qualifying variant

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

Contact
Eduardo Pennella, MD; USenquiries@merus.nl; +1 617 401 4499;

PEMBROLIZUMAB, MRNA-4359

Phase 1/2 Study of mRNA-4359 Administered Alone and in Combination With Immune Checkpoint Blockade in Participants With Advanced Solid Tumors
NCT05533697

Qualifying variant

Gene	Variant	Classification
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic

Contact
Moderna Clinical Trials Support Center; clinicaltrials@modernatx.com; 1-877-777-7187;

FARLETUZUMAB ECTERIBULIN

Phase 1/Phase 2 clinical trials (3)

A Multicenter, Open-Label Phase 1/2 Trial Evaluating the Safety, Tolerability, and Efficacy of MORAb-202, a Folate Receptor Alpha (FRα)-Targeting Antibody-drug Conjugate (ADC) in Subjects With Selected Tumor Types
NCT04300556

Qualifying variant			Contact
Gene	Variant	Classification	Eisai Medical Information; esi_oncmedinfo@eisai.com;
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic	1-888-274-2378;

Phase 1 clinical trials (3)

DOSTARLIMAB

A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients With Advanced Solid Tumors
NCT02715284

Qualifying variant			Contact
Gene	Variant	Classification	US GSK Clinical Trials Call Center; GSKClinicalSupportHD@gsk.com;
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic	877-379-3718;

AMIVANTAMAB/RECOMBINANT HUMAN HYALURONIDASE, LAZERTINIB, AMIVANTAMAB

An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Amivantamab, a Human Bispecific EGFR and cMet Antibody for the Treatment of Advanced Solid Malignancies
NCT04606381

Qualifying variant			Contact
Gene	Variant	Classification	Study Contact; Participate-In-This-Study@its.jnj.com;
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic	844-434-4210;

ALFLUTINIB

A Phase 1b Dose Escalation and Dose Expansion Study Evaluating the Safety, Pharmacokinetics, and Antitumor Activity of Furmonertinib in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) With Activating Epidermal Growth Factor Receptor (EGFR) or Human Epidermal Growth Factor Receptor 2 (HER2) Mutations
NCT05364073

Qualifying variant			Contact
Gene	Variant	Classification	Nichole Baio; FURMO002CT@arrivent.com;
EGFR	p.E746_A750del c.2236_2250del	Tier 1A Pathogenic	628-277-4836;

VARIANT DETAILS

Variant of strong clinical significance (1)

EGFR E746_A750del

Gene: EGFR
Nucleotide: NM_005228.5: g.55242466_55248 0del c.2236_2250del
Assessment: Pathogenic
Exon: 19
Amino Acid: p.E746_A750del
Allelic Fraction: 1.2%
Classification: Tier 1A

Treatment options
8 Sensitive
14 Trials

Biomarker summary: *EGFR*-E746_A750del (NM_005228) is an activating mutation.

Clinical relevance: *EGFR* activating mutations or amplification may predict sensitivity to Egfr-targeted therapies, including inhibitors of multiple ErbB family members, and several have received agency approval in some tumor types [93, 121, 144]. The Egfr TKIs erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib have been approved by the EMA for the treatment of non-small cell lung cancer (NSCLC) with activating *EGFR* mutations; osimertinib has additionally been approved for the treatment of NSCLC with *EGFR* T790M [136, 157, 92, 130, 120, 129, 15, 93]. Amivantamab has been approved by the EMA for NSCLC patients with *EGFR* exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy [118].

Disease summary: *EGFR* mutations in non-small cell lung carcinoma (NSCLC) have been found to be more common in women, never-smokers, those of East Asian ethnicity, and in patients with adenocarcinoma histology [132, 77, 6, 104, 65, 169, 69, 67, 154]. Studies have reported non-squamous NSCLC patients with metastatic disease and tumors harboring an *EGFR* exon 19 deletion or L858R mutation to be sensitive to osimertinib, erlotinib, afatinib, gefitinib, dacomitinib, and the combination of erlotinib plus ramucirumab [161, 120, 157, 93, 15, 136, 96]. Less common activating *EGFR* mutations have variable sensitivity to *EGFR* tyrosine kinase inhibitors [98]. Some patients with *EGFR*-mutant NSCLC exhibit resistance to Egfr inhibition; resistance has been associated with insertions in *EGFR* exon 20, the T790M mutation in *EGFR*, and amplification of the gene *MET* [19, 27, 63]. Several studies have reported that resistance to Egfr TKIs in non-small cell lung cancer (NSCLC) is mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features; these transformed SCLC cases have been shown to be responsive to standard SCLC therapy regimens involving platinum and etoposide–based chemotherapy [10, 128, 40, 66].

Molecular function: E746_A750del, also described as K745_A750delinsK, is located in the kinase domain of Egfr; this mutation and other exon 19 deletions have been shown to activate the tyrosine kinase activity of Egfr and confer sensitivity to Egfr tyrosine kinase inhibitors such as erlotinib and gefitinib [77, 104, 105].

Incidence: *EGFR* mutations have been reported in 17% (29583/178016) of Solid Tumor samples analyzed in COSMIC (May 2023). *EGFR* mutations have been reported in 27% (26714/99814) of Non-small cell lung carcinoma (NSCLC) samples and in 8.5% (108/1267) of Small cell lung carcinoma (SCLC) samples analyzed in COSMIC (May 2023). *EGFR* mutations have been reported in 6.3-29% of Non-small cell lung carcinoma (NSCLC) samples and in 0-50% of Small cell lung carcinoma (SCLC) samples (cBioPortal for Cancer Genomics, May 2023). *EGFR* mutations have been reported in 11-52% of NSCLC cases and are found more commonly in East Asian patients as compared with other ethnicities [166, 119, 133, 64, 169, 41]. In the scientific literature, *EGFR* mutations have been reported in 2-9% of small cell lung carcinoma (SCLC) samples [76, 141, 122, 7]. In addition, *EGFR* mutation, particularly, *EGFR* exon 19del, has been frequently reported in patients with non-small cell lung cancer that transformed into small cell lung cancer after treatment with Egfr inhibitors [4, 81, 164, 167].

Variant of potential clinical significance (1)

Variant of potential clinical significance (1)

TP53 R248G

Gene: TP53
Nucleotide:
NM_000546.6:
g.7577539G>C
c.742C>G
Assessment: Pathogenic
Exon: 7
Amino Acid: p.R248G
Allelic Fraction: 1.47%
Classification: Tier 2C

Biomarker summary: *TP53*-R248G (NM_000546) is an inactivating mutation.

Clinical relevance: *TP53* is a tumor suppressor that encodes the p53 protein; alterations in *TP53* may result in a loss of p53 function, yet an increase in the expression and stability of the mutant p53 protein in the nucleus, sometimes leading to oncogenic effects, including genomic instability and excessive cell proliferation [68, 152, 59, 50, 36, 102]. At present, there are no approved therapies targeting *TP53* alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for *TP53* and (dendritic cell-based) *TP53* vaccines [127, 147, 123]. Tumors with *TP53* mutations may be sensitive to the Wee1 inhibitor adavosertib (MK-1775), and clinical trials are currently underway for patients with solid tumors and hematologic malignancies [34, 8]. Aurora kinase A inhibitors are another therapeutic approach under investigation for *TP53*-mutated cancers [149, 70, 49, 143, 47].

Disease summary: *TP53* is one of the most commonly mutated genes in lung cancer; scientific studies have reported *TP53* mutations in 27-46% of non-small cell lung carcinoma (NSCLC) cases [95, 44, 140, 78]. In addition, *TP53* mutations have been reported in 61-94% of small cell lung cancer (SCLC) cases [109, 74, 85, 16, 43]. *TP53* alterations, as well as loss of p53 function, have been found to be both critically involved and early events in the development of lung cancer; *TP53* mutation has been found to precede lymph node metastasis in NSCLC, and loss of p53 function has been shown to play a central role in SCLC carcinogenesis [11, 139, 56, 87]. Preclinical studies have reported that disruption of *TP53* and *RB1* in pulmonary neuroendocrine cells can give rise to neuroendocrine lesions and SCLC in mouse models [87, 107, 138]. Also, *TP53* mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples [14, 126, 1, 82, 46]. *TP53* mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients [146].

Molecular function: *TP53* R248G is a missense alteration located within the DNA-binding domain (DBD) of the p53 protein. DBD mutations are thought to result in loss of function via the loss of transactivation of p53-dependent genes [50]. *TP53* R248G has been reported to result in substantially reduced transcriptional activity, as compared with wild-type *TP53*, and to function as a dominant negative in yeast assays (The *TP53* Database) [172, 124, 131].

Incidence: *TP53* mutations have been reported in 34% (44622/130494) of Solid Tumor samples analyzed in COSMIC (May 2023). *TP53* is one of the most commonly mutated genes in lung cancer; scientific studies have reported *TP53* mutations in 27-67% of NSCLC cases [95, 44, 140, 125, 62, 39, 37, 78]. Specifically, *TP53* mutations have been reported in 74% (8887/12079) of *KRAS* wild-type and in 37-55% of *KRAS* mutant NSCLC samples [45]. In the scientific literature, *TP53* mutations have been reported in 54-93% of small cell lung cancer (SCLC) cases [38, 160, 162, 43]. *TP53* mutations have been reported in 63-95% of lung large cell neuroendocrine carcinoma (LCNEC) samples analyzed in scientific studies [48, 80, 116, 151, 85]. Scientific studies have reported *TP53* mutation in 4-14% of lung carcinoid samples, although one study reported no *TP53* exons 5-8 mutation in any of 36 lung carcinoid samples [21, 103, 75, 114].

Variant of biological significance (1)

RB1 c.1332+1G>A

Gene: RB1
Nucleotide:
NM_000321.3:
g.48951171G>A
c.1332+1G>A
Assessment: Pathogenic
Exon: 13
Allelic Fraction: 0.34%
Classification: Tier 3

Biomarker summary: *RB1*-splice site 1332+1G>A (NM_000321) is predicted to be an inactivating mutation.

Clinical relevance: *RB1* encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle. Loss of Rb function, which has been identified in many cancer types due to various mechanisms, results in the upregulation of transcription and cell proliferation [9, 57]. Loss of *RB1* has been associated with lack of response to Cdk4/6 inhibitors [22, 88, 99, 155, 142, 163, 33]. At this time, there are no therapeutic options to target the inactivation of Rb. Preclinical studies are actively investigating possible therapies to address Rb inactivation, exploring avenues such as Aurora kinase inhibitors, Bcl-2 family inhibitors, and Notch pathway activation [35, 2, 148, 58].

Disease summary: *RB1* inactivation by various mechanisms, such as mutation and deletion, has been reported as a common event in small cell lung carcinoma (SCLC), with loss of Rb protein expression considered a hallmark molecular event in SCLC [56, 86, 156]. Inactivation of the Rb pathway has also been reported to occur frequently in non-small cell lung carcinoma (NSCLC) and play a role in NSCLC carcinogenesis [165, 60, 26, 171]. *RB1* loss in lung adenocarcinoma tumors harboring an *EGFR* activating mutation has been reported to be associated with transformation to small cell lung carcinoma [113, 100]. Several studies have reported that resistance to Egfr tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) can be mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features [153, 10, 112, 128].

Molecular function: The *RB1* splice site 1332+1G>A alteration occurs at a conserved splice donor site at the splice junction between transcribed exons 13 and 14, corresponding to amino acid 444 out of 928 of the Rb protein (IGV). Splice site mutations may lead to exon skipping or protein truncation. Therefore, a splicing error at this position, which is located within the A domain, may result in the loss of the B domain, the *LIMD1* interaction domain, and the C domain, all of which mediate various protein interactions, as well as a probable nuclear localization signal (UniProt). Splice site alterations in the *RB1* gene have been reported in retinoblastoma and found to lead to exon skipping [168, 108, 73]. Therefore, although this alteration has not been functionally characterized, it may lead to a loss of protein function.

Incidence: *RB1* mutations have been reported in 5.3% (3239/61413) of Solid Tumor samples analyzed in COSMIC (May 2023). One study analyzing 14,483 NSCLC samples reported *RB1* mutations in 11% of samples [119]. Literature studies have reported *RB1* mutations in 40-84% of small cell lung carcinoma (SCLC) samples, 0-3% of lung carcinoid samples, and 26-51% of lung large cell neuroendocrine samples [91, 13, 32, 134, 21, 135, 151, 137, 122, 24, 43, 159].

REPORT INFORMATION

Genes tested

Marsden360 reports single nucleotide variants and splice site mutations in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

AKT1 Ω	ALK #Ω	APC Ω	AR †Ω	ARAF Ω	ARID1A Ω	ATM Ω	BRAF †Ω	BRCA1 Ω
BRCA2 Ω	CCND1 †Ω	CCND2 †Ω	CCNE1 †Ω	CDH1 Ω	CDK12 Ω	CDK4 †Ω	CDK6 †Ω	CDKN2A Ω
CTNNB1 Ω	DDR2 Ω	EGFR †Ω	ERBB2 †Ω	ESR1 Ω	EZH2 Ω	FBXW7 Ω	FGFR1 †Ω	FGFR2 †#Ω
FGFR3 #Ω	GATA3 Ω	GNA11 Ω	GNAQ Ω	GNAS Ω	HNF1A Ω	HRAS Ω	IDH1 Ω	IDH2 Ω
JAK2 Ω	JAK3 Ω	KIT †Ω	KRAS †Ω	MAP2K1 Ω	MAP2K2 Ω	MAPK1 Ω	MAPK3 Ω	MET †Ω
MLH1 Ω	MPL Ω	MTOR Ω	MYC †Ω	NF1 Ω	NFE2L2 Ω	NOTCH1 Ω	NPM1 Ω	NRAS Ω
NTRK1 #Ω	NTRK3 Ω	PDGFRA †Ω	PIK3CA †Ω	PTEN Ω	PTPN11 Ω	RAF1 †Ω	RB1 Ω	RET #Ω
RHEB Ω	RHOA Ω	RIT1 Ω	ROS1 #Ω	SMAD4 Ω	SMO Ω	STK11 Ω	TERT Ω‡	TP53 Ω
TSC1 Ω	VHL Ω							

Ω Marsden360 reports insertion and deletion variants (indels) in this gene.
‡ Marsden360 reports alterations in the promoter region of this gene.
# Marsden360 reports fusion events involving this gene for all known gene partners.
† Marsden360 reports amplifications of this gene.

GUIDELINES

The ESMO Clinical Practice Guideline for oncogene-addicted metastatic NSCLC recommends that all patients with a sensitizing *EGFR* mutation should receive first-line *EGFR* TKIs irrespective of clinical parameters including PS, gender, tobacco exposure and histology [31]. For patients with exon 19 deletion or exon 21 L858R, the Guidelines recommend osimertinib as preferable first-line treatment, especially for patients with CNS metastases. Additional first-line treatment options include erlotinib, gefitinib, afatinib and dacomitinib, gefitinib with carboplatin and paclitaxel, *EGFR* TKIs combined with anti-angiogenic therapies, including erlotinib-bevacizumab and erlotinib-ramucirumab [31].

Methods and limitations

All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Marsden360 include single nucleotide variants, gene amplifications, fusions, short insertions/deletions, and splice site-disrupting events. Marsden360 is not validated for detecting other types of genomic alterations, such as complex rearrangements or gene deletions. Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Marsden360 panel. A “Not Detected” result does not preclude MSI-High status in tissue. Marsden360 cannot discern the source of circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot distinguish germline variants from somatic alterations. Marsden360 is not validated for the detection of germline or de novo variants associated with hereditary cancer risk.
Discrepancies in results between molecular testing on both ctDNA and a tumour biopsy may be observed in 20-30% of patients. In the case of ctDNA, discrepancies may be caused by low circulating tumour DNA, assay limitations in the detection of structural/ copy number variants and non-uniform coverage accross the panel with higher coverage over hotspot regions. In the case of tissue, discrepancies may be caused by low tumour content or extensive necrosis in the biopsy. Tissue testing should be considered when plasma analysis is not informative and if clinically appropriate.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools: QIAGEN Clinical Insight Interpret (9.3.0.20240531), Ingenuity Knowledge Base (N-release), CADD (v1.6), NCBI Gene (2023-08-25), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2023-10-03), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2024-05-04 11:55:52.57), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (N-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), TargetScan (7.2), phyloP hg18 (GRCh37 (hg19) 2019-11, GRCh38 2019-11), phyloP hg19 (GRCh37 (hg19) 2019-11, GRCh38 2019-11), GENCODE (Release 44), CentoMD (5.3), dbVar (2021_04), OMIM (October 23, 2023), gnomAD (GRCh37 (hg19) 2.1.1, GRCh38 (hg38) 3.1.2), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2024-03-31), DGV (2016-05-15), COSMIC (v99), HGMD (2023.4), Matched Annotation from NCBI and EMBL-EBI (MANE) (1.2), OncoTree (oncotree_2021_11_02), dbSNP (GRCh37 (hg19) 155, GRCh38 155), SIFT4G (2016-02-23)

Please note that this assay (Marsden360) has not yet been assessed by UKAS for accreditation; an extension to scope applicaton is in progress.

Clinical significance of variants based on AMP / ASCO / CAP guidelines*

Strong clinical significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential clinical significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain clinical significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

*Adapted from PMID:27993330 jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf

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