Canexia Health

Follow It® Report

Patient Name: | Date of Birth: | Patient ID:

Report ID: | Surgical ID: | Panel: Full

PATIENT INFORMATION

Patient Name:
Date of Birth: Sex: Female
Care Card #: Province of issue: Diagnosis:
Non-Small Cell Lung Cancer
Reason for Referral: Therapeutic Target Identification
Previous Molecular Tests:
Test Requested: Follow It
Date of Receipt:
Date of Report:

HEALTHCARE PROVIDER INFORMATION

Referring Physician
Institution:
Address:

Postal Code:
Phone: Fax:
cc: Fax:

SPECIMEN INFORMATION

Specimen Collection Date:
Sample:

Specimen Source: Blood
Primary Site of Tumour: Lung
Histologic Type: NSCLC

This test is an amplicon based hotspot next-generation sequencing assay (NGS) that interrogates clinically actionable gene alteration in circulating tumour DNA extracted from plasma. The test results, interpretations and clinical trials included in this report are provided in the context of a primary cancer type as reported by the referring physician. In the absence of detectable mutation in ctDNA, it is recommended that a tissue based (biopsy/resection) test be performed.

RECOMMENDATIONS

- Indication for treatment with first and second generation EGFR TKI, erlotinib, gefitinib, afatinib or dacomitinib.
- Indication for treatment with third generation EGFR TKI, osimertinib.
- Absence of resistance mutations to EGFR tyrosine kinase inhibitor (T790M).

SUMMARY OF TEST RESULTS

Key Mutations Present*							
Gene	**cDNA change**	**Amino Acid Change**	**Exon**	**Allelic Ratio (%)**	**Therapeutic Implication**	**Level of Evidence**	**Clinical Trials Available**
EGFR	c.2573T> G (NM_005228.3)	L858R	21	2.0	Indication for treatment with third generation EGFR TKI, osimertinib.	Tier: I.A · Clinical trials · FDA · HealthCanada	1
					Indication for treatment with first and second generation EGFR TKI, erlotinib, gefitinib, afatinib or dacomitinib.	Tier: I.A · FDA · Clinical trials · Health Canada	

TABLE 1: Mutations Present

Key Mutations Absent*			
Gene	Therapeutic Implication	Level of Evidence	Clinical Trials Available
EGFR	No resistance to EGFR TKI identified (T790M)	· FDA · NCCN	0

TABLE 2: Mutations Absent

*All hotspot mutations detected in this sample are shown in Table 1, above. All hotspot mutations tested are listed in the "Hotspot Panel" table (below, after Methodology). Mutations listed in the "Hotspot Panel" but not presented in Table1 were tested, but were not detected in this sample.

INTERPRETATION

PRESENCE of an EGFR activating mutation

An activating EGFR mutation, as described in the table above, was found in the sample from this patient. The presence of an EGFR activating mutation is associated with response to treatment with first and second generation EGFR tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib and afatinib (Rosell R, 2009), (Fukuoka M, 2011), (Sequist LV, 2013). Treatment of patients with activating EGFR mutations (L858R and exon 19 deletion) with EGFR TKI have consistently shown superior efficacy over first line platinum-based chemotherapy and currently represent standard of care in these patients (NCCN: NSCLC). First and second generation EGFR TKIs, including erlotinib, gefitinib and afatinib, are approved by the FDA and Health Canada as monotherapy for first-line treatment of patients with locally advanced or metastatic NSCLC with activating EGFR mutations L858R or EGFR exon 19 deletions.

Osimertinib, a third generation irreversible EGFR inhibitor, represent an additional targeted treatment option. In a recent phase III trial, osimertinib demonstrated a 54% reduction in the risk of progression and fewer severe adverse events compared to gefitinib or erlotinib in first line setting of EGFR mutation positive NSCLC (exon 19 deletion, L858R or T790M) (Soria JC, 2018). In an earlier phase I/II trial, the emergence of the resistance mutation T790M was not observed in TKI naïve NSCLC treated with osimertinib (Ramalingam SS, 2018); however, 2 of 60 patients developed the secondary EGFR S797C resistance mutation (Ramalingam SS, 2018). Osimertinib is approved by the FDA and Health Canada for the treatment of advanced NSCLC with the T790M resistance mutation who progressed on prior EGFR TKI and for first line treatment of EGFR mutation positive NSCLC (L858R and exon 19 deletions).

Dacomitinib, a second generation EGFR inhibitor, was also recently approved by the FDA and Health Canada for first line treatment of metastatic NSCLC positive for a L858R or exon 19 deletion. The approval is based on the Archer 1050 phase III study which showed a median PFS median PFS was 14.7 months with dacomitinib compared with 9.2 months with gefitinib (Mok TS, 2018).

ABSENCE of a resistance EGFR mutation

The tumour sample submitted for analysis tested negative for the EGFR gene mutations associated with EGFR TKI resistance, mainly the T790M mutation (Tan CS, 2015).

OTHER COMMENTS

Additional targeted treatment options, if available, are listed in the clinical trial section. It is the responsibility of the oncology team to select the most suitable clinical trial for the patient. Additional tumour testing may be needed to determine patient's eligibility for a particular trial.

The therapeutic implication of these results should be considered in conjunction with other clinical information and/or tests. A list of benign changes, if identified in the tumour DNA of this patient, is available upon request. The ability to detect a particular variant in a given specimen will depend upon the allele proportion of the variant in the extracted DNA combined with the lower limit of detection of the assay.

CLINICAL TRIALS

Study	Genes	Phase	Countries	Title
NCT02155621			Canada	Personalized Oncogenomics (POG) Program of British Columbia: Utilization of Genomic Analysis to Better Understand Tumour Heterogeneity and Evolution
NCT02498613		Phase 2	Canada	A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors
NCT03829332		Phase 3	Canada	A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) With or Without Lenvatinib (E7080/MK-7902) in Participants With Treatment-naïve, Metastatic Non-small Cell Lung Cancer (NSCLC) Whose Tumors Have a Tumor Proportion Score (TPS) Greater Than or Equal to 1% (LEAP-007)
NCT03745989		Phase 1	Canada	Phase 1b Open-label Study of MK-8353 in Combination With Selumetinib (MK-5618) in Participants With Advanced/Metastatic Solid Tumors
NCT03769103	EGFR	Phase 2	Canada	Open Label, Multicenter, Phase II Study of Patients With Treatment Naïve Metastatic Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) With Brain Metastases Randomized to Stereotactic Radiosurgery (SRS) and Osimertinib or Osimertinib Alone

TABLE 3: We select trials based on tumour histotype and mutation status, with a specific focus on trials of targeted therapy. The inclusion of a trial in our report does not necessarily mean that the patient would be eligible. Patients' eligibility for a trial, and the benefit that they may derive from it, will depend on additional factors that must be assessed by the oncologist. Conversely, the list of potentially relevant trials in our report may not be complete. We may have overlooked relevant trials on these websites, or there may be relevant trials listed elsewhere. Please let us know if you identify a trial of targeted therapy that could have been included in a patient's report.

METHODOLOGY

This test includes targeted sequence analysis of hotspot mutations/coding exons of the requested genes and transcripts (listed below). Genomic DNA is extracted and targets of interest amplified using a highly multiplexed in-house designed PCR assay. The targeted regions are sequenced using Illumina technology with 151bp paired-end reads. Sequence reads that pass defined quality threshold metrics are aligned to the reference sequence (Genome Build hg19) and variants are identified and annotated using a validated, custom-built bioinformatics pipeline. Standard acceptance criteria for reporting of analytical runs are a minimum read depth of ≥500, a base quality score of ≥30, a mapping quality score of >30, a variant allele fraction of ≥1% for single nucleotide changes and >5% for insertion/deletion events and a probability score of ≥0.70 for single nucleotide changes or a quality score of ≥400 for insertion/deletion events. The probability score is the likelihood that a detected mutation is a true positive. The variant allele fraction (VAF) is defined as the proportion of alleles with a mutation to the total number of alleles present in a sample, expressed as a percentage.

Hotspot variants are categorised into clinical significance tiers as per Li et al, J Mol Diagn 2017, 19(1):4-23. Variants of strong or potential clinical significance (tier I or II) will be reported. VUS and likely benign variants (tier III and IV) will not be reported. Please contact the laboratory if tier III or IV variants are required.

TABLE 4: Hotspot Panel: CG001v4.0_Hotspot_Manifest_Panel4.0.6_20181106.tsv. Neg=Negative, Pos=Positive

Result	Gene	Hotspot	Transcript	Result	Gene	Hotspot	Transcript
Neg	AKT1	E17	NM_001014432.1	Neg	KRAS	G12, G13, A59, Q61, K117, A146	NM_004985.4
Neg	ALK	T1151, L1152, C1156, F1174, L1196, L1198, G1202, D1203, S1206, G1269, R1275	NM_004304.4	Neg	MAP2K1	Q56, K57, K59, D67, C121, P124, P387	NM_002755.3
Neg	AR	F877, H875, L702H, S741, T878, V716, W742	NM_000044.3	Neg	MAP2K2	F57, Q60, K61, L119	NM_030662.3
Neg	BRAF	Q201, G466, F468, G469, Y472, D594, G596, L597, V600, K601	NM_004333.4	Neg	MET	Y1253, exons: 13, 14+25, 14-50, 14, 18	NM_001127500.2
Neg	CTNNB1	D32, S33, G34, S37, T41, S45	NM_001904.3	Neg	NRAS	G12, G13, A59, Q61, K117, A146	NM_002524.4

TABLE 4: Hotspot Panel: CG001v4.0_Hotspot_Manifest_Panel4.0.6_20181106.tsv. Neg=Negative, Pos=Positive

Result	Gene	Hotspot	Transcript	Result	Gene	Hotspot	Transcript
Neg	DDR2	L239, I638, S768	NM_001014796.1	Neg	PDGFRA	D842, L839_Y849, N659, R560_E571	NM_006206.4
Pos	EGFR	S492, exons: 18, 19, 20, 21	NM_005228.3	Neg	PIK3CA	R88, E542, E545, Q546, D549, M1043, N1044, A1046, H1047, G1049	NM_006218.3
Neg	ERBB2	G309, S310, L755, exons: 20	NM_004448.3	Neg	POLE	Exons: 9, 10, 11, 12, 13, 14	NM_006231.3
Neg	ESR1	K303, S463, V534, P535, L536, Y537, D538	NM_001122742.1	Neg	PTCH1	W844, G1093	NM_000264.3
Neg	GNA11	Q209	NM_002067.4	Neg	PTEN	R130	NM_000314.4
Neg	GNAQ	Q209	NM_002072.4	Neg	RET	C634, V804, M918	NM_020975.4
Neg	GNAS	R201	NM_000516.5	Neg	ROS1	L2026, G2032	NM_002944.2
Neg	HRAS	G12, G13, Q61	NM_005343.3	Neg	SMO	D473, S533, W535	NM_005631.4
Neg	IDH1	R132	NM_005896.3	Neg	TP53	Exons: 4, 5, 6, 7, 8, 9	NM_000546.5
Neg	IDH2	R140, R172	NM_002168.3				
Neg	KIT	T670, D816, D820, N822, Y823, A829, exons: 9, 11, 13	NM_000222.2				

QUALITY METRICS

The figure below displays the correlation between the expected variant allelic fraction (VAF) and the observed VAF for the quality control sample.

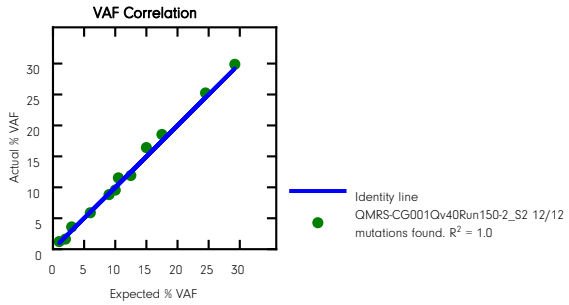

Figure 1: Correlation between the expected and observed variant allelic fraction (VAF) for the quality control sample for this run.

The table below summarises the average amplicon coverage for this patient.

Status	Coverage depth
All 113 amplicons	≥ 1000

TABLE 5: Amplicon Coverage

SIGNATURES

Eric Gagne, Ph.D, DABMGG, FACMG
Molecular Geneticist/Cytogeneticist

Copies sent to:

REFERENCES

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