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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:**	COLORECTAL CANCER

Com.Pl.i.t. Dx (27 genes, 7 fusions) | Comprehensive Panel for Individualized Treatment

Report Summary

27	Unique Genes (**7** Fusions) analyzed	**2**	Genomic alterations identified in tumor
2	Biomarker related approved therapies for indication	**0**	Biomarker related therapies with potential benefit
0	Biomarker related therapies with potential resistance	**9**	Biomarker related Clinical Trials

Results and Interpretation*

Biomarker	Result	Approved therapies for indication	Therapies with potential benefit	Therapies with potential resistance/toxicity	Clinical Trials
ERBB2 (HER2) amplification by FISH	Negative Ratio of HER2 copy number to CEP17=1.07 Average HER2 copy number=3.55	-	-	-	-
FBXW7	Exon 10 c.1513C>T (p.R505C)	-	-	-	yes
TP53	Exon 6 c.641A>G (p.H214R)	-	-	-	yes
KRAS/NRAS	wildtype	Panitumumab (1A.1) Cetuximab (1A.1)	-	-	yes
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-

*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

***FBXW7:* c.1513C>T (p.R505C)** **VAF*:50%** OncoKB CIViC PMKB

Gene information

The FBXW7 gene encodes an F-box protein subunit involved in substrate recognition by an SCF (Skp1-Cul1-F-box protein)-type ubiquitin ligase complex. Substrates of FBXW7 include the proteins c-MYC, mTOR (PMID: 18787170), NOTCH1, cyclin-E, and JUN, which are instrumental in the regulation of cell division, differentiation and growth, and which are often inappropriately activated in cancer. As most FBXW7 substrates are proto-oncogenes that are processed for degradation by the SCF complex, FBXW7 functions as a tumor suppressor. Inactivation of FBXW7 by mutation or copy number loss results in aberrant accumulation of oncoproteins, which subsequently contributes to malignant transformation (PMID: 27399335). Most mutations in FBXW7 are point mutations that disrupt substrate binding, while (PMID: 17909001). FBXW7-mediated protein degradation, and loss of function of FBXW7 increases the levels of total and activated mTOR. Preclinical data have suggested that inactivating mutations of FBXW7 could predict sensitivity to the mTOR inhibitor rapamycin; however, their clinical utility remains unknown. In colon cancer patients, the incidence of FBXW7 mutations is 11.74% (mycancergenome.org).

Variant information

FBXW7 p.R505C lies within WD repeat 4 of the Fbxw7 protein (UniProt.org). R505C confers a loss of FBXW7-substrate interaction and impairs substrate degradation by FBXW7, resulting in sustained Notch intracellular domain and Myc expression (PMID: 17646409). It also demonstrates aberrant subnuclear localization (PMID: 30510140), and has impaired degradation of Klf5 (PMID: 28963353). For these reasons, R505C is characterized as Likely Pathogenic.

***TP53:* c.641A>G (p.H214R)** **VAF*:63%** OncoKB CIViC PMKB

Gene information

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% to 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). It has been reported in a number of studies that TP53 gene mutation is a poor prognostic factor for patients with NSCLC (PMID: 28838393, 29217530), while targeted therapy for TP53 gene mutation is still under study, and no promising therapies have yet been developed (PMID: 23263379, 30631578).

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Variant information

The p.H214R variant (also known as c.641A>G), located in coding exon 6 of the TP53 gene, results from an A to G substitution at nucleotide position 641. This amino acid position is highly conserved through mammals on sequence alignment. In addition, this alteration is predicted to be deleterious by in silico analysis.

KRAS/NRAS WILD TYPE

The absence of mutation in KRAS/NRAS in stage IV colorectal cancer influences patient response to the anti-EGFR antibody therapies, cetuximab and panitumumab. These drugs are FDA-approved for the treatment of KRAS/NRAS wildtype colorectal tumors, either alongside chemotherapy or as single agents following progression on standard chemotherapy (NCCN Guidelines Version 3.2022).

*VAF: Variant Allele Frequency

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Associated Treatments Information

Panitumumab

DrugBank

Panitumumab (ABX-EGF) is a recombinant human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). This drug is an antineoplastic agent.

It is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma that is refractory to fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens.

Cetuximab

DrugBank

Cetuximab is an epidermal growth factor receptor binding FAB. Cetuximab is composed of the Fv (variable; antigen-binding) regions of the 225 murine EGFr monoclonal antibody specific for the N-terminal portion of human EGFr with human IgG1 heavy and kappa light chain constant (framework) regions.

Cetuximab, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Cetuximab administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

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Clinical Trials to consider

TP53 associated clinical trials

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

Press here for a live search of clinical trials for TP53

FBXW7 associated clinical trials

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

Press here for a live search of clinical trials for FBXW7

KRAS associated clinical trials

NCT05797467	Phase 3
Title	Adjuvant Chemotherapy Combined With Targeted Therapy or Not in the T3-4N2 Colorectal Cancer Patients
Treatment	FOLFOX chemotherapy regimens| Bevacizumab
Location	China

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NCT04745130	Phase 2
Title	Efficacy and Safety of Sintilimab Combined With Regorafenib and Cetuximab / Sintilimab Combined With Regorafenib in Posterior Line Therapy of Advanced Colorectal Cancer (Regosinti)
Treatment	Sintilimabï¼Œregofinibï¼Œcetuximab| KRAS BRAF mutant Sintilimab + regafinil
Location	China

NCT04189055	Phase 2
Title	Cetuximab as Salvage Therapy in Patients With Neo Wild-type RAS/RAF Metastatic Colorectal Cancer With Liver Metastases.
Treatment	Cetuximab| Irinotecan
Location	France

NCT04117945	Phase 2
Title	Regorafenib, With Cetuximab or Panitumumab, for the Treatment of Unresectable, Locally Advanced, or Metastatic Colorectal Cancer
Treatment	Cetuximab| Irinotecan| Panitumumab| Regorafenib
Location	United States

NCT05775900	Phase 1|Phase 2
Title	Efficacy and Safety of Triweekly Cetuximab in Combination With Capecitabine as First-line Maintenance Treatment for KRAS/BRAF Wild-type Metastatic Colorectal Cancer
Treatment	Cetuximab| Capecitabine
Location	China

NCT04256707	Phase 1|Phase 2
Title	Relative Bioavailability/Bioequivalence of Different Formulations of Selinexor, the Impact of Hepatic Impairment on Selinexor Pharmacokinetics, Tolerability and Antitumor Activity of Selinexor Combination Treatment
Treatment	Selinexor 100 mg| Docetaxel| Pembrolizumab| FOLFIRI| Selinexor 40 mg| Selinexor 80 mg| Selinexor 60 mg
Location	Israel

Press here for a live search of clinical trials for KRAS

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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.

Microsatellite instability

Cancer-associated instabilities at microsatellite locations throughout the genome have been shown to be predictive of response to immunotherapy treatment. A Microsatellite Instability High (MSI-H) status can result when the DNA Mismatch Repair (MMR) system fails to work appropriately. Genomic DNA was extracted from the tumor tissue after microscopic observation and macro-dissection. A nextgeneration sequencing based assay using 76 markers was used to assess Microsatellite Instability (MSI) status in tumor-only and tumor-normal samples utilizing Ion Ampliseq technology. Sequencing was carried out using the Next Generation Sequencing platform Ion Gene Studio S5 Prime System (Thermo Fisher Scientific). The test provides results for individual microsatellites and generates an MSI score. A sample is considered positive if the MSI score is >30.

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FISH HER2

Analysis is carried out using the kit ZytoLight SPEC ERBB2/CEN17 Dual Color by ZytoVision CE IVD for the detection of the amplified signal of the gene *HER2*. Twenty (20) nuclei from at least three different regions of the section were microscopically analyzed. The analysis of the images was performed,using ISIS FISH Imaging System by Metasystems. ISH ratios of Her2/CEP17 >= 2.0 positive, < 2.0 negative

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

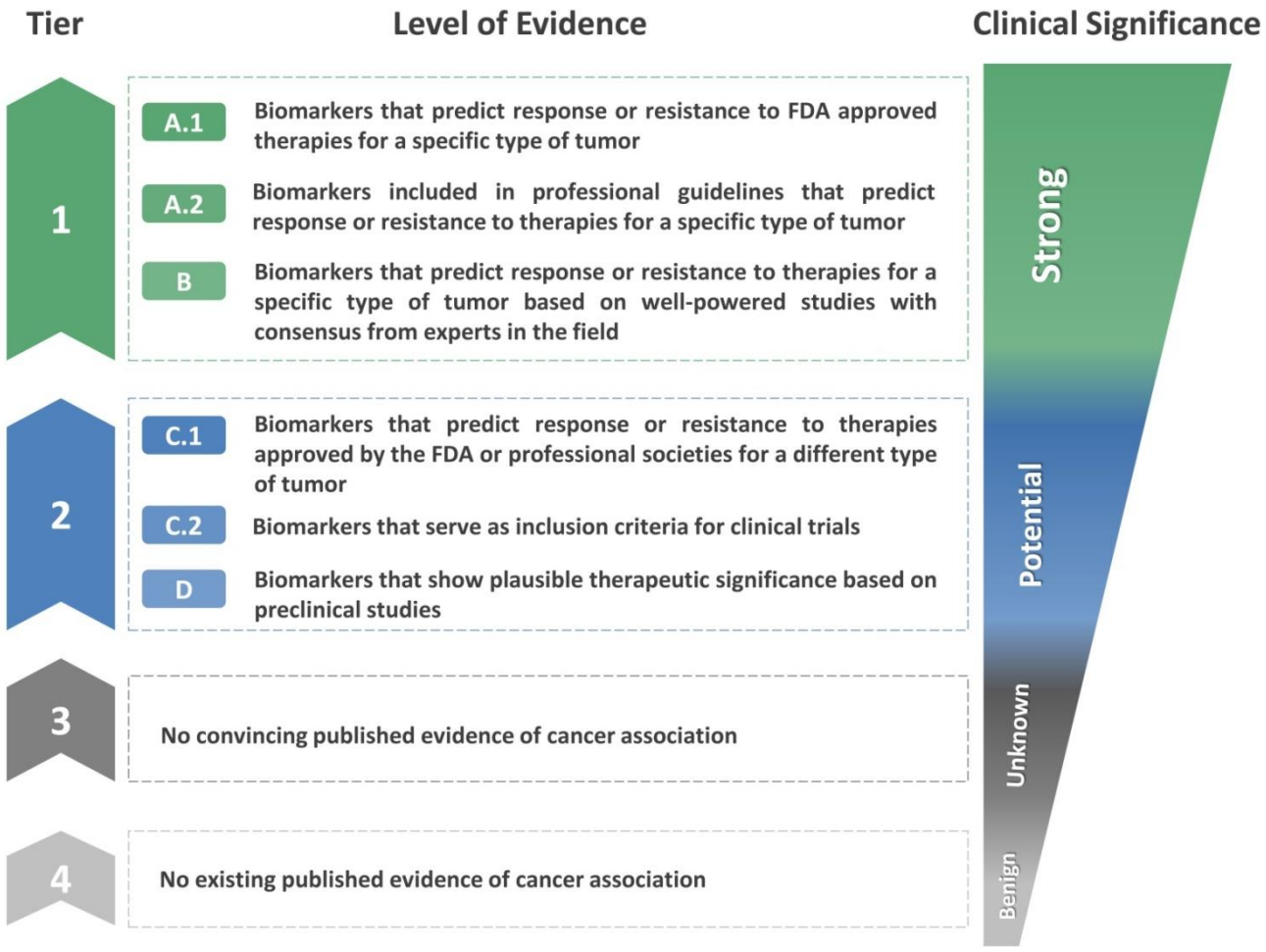

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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