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ΠΛΗΡΟΦΟΡΙΕΣ

Εξεταζόμενος:		**Ημ. Συλλογής Δείγμ.:**	
ΑΜΚΑ:		**Παραπέμπων:**	
Ημερ. Γέννησης:		**Report No:**	
Τύπος Δείγμ. #1:	ΠΛΑΣΜΑ	**Ημερ. Παρ. Δειγμ.:**	
Τύπος Δείγμ. #2:		**Ημερ. Αποτελ.:**	
Κωδικός Δείγμ. #1		**Τύπος όγκου:**	ΚΑΡΚΙΝΟΣ ΠΑΧΕΟΣ ΕΝΤΕΡΟΥ

Com.Pl.i.t. DX Liquid Biopsy (12 genes and 3 fusions) | Comprehensive Panel for Individualized Treatment

Περίληψη έκθεσης αποτελέσματος

12	Γονίδια (**3** αναδιατάξεις) αναλύθηκαν)	**1**	Γενωμικές αλλοιώσεις που ανιχνεύθηκαν στον όγκο
0	Εγκεκριμένες θεραπείες που σχετίζονται με Βιοδείκτες για την ένδειξη	**3**	Θεραπείες με πιθανό όφελος που σχετίζονται με Βιοδείκτες
2	Θεραπείες με πιθανή αντίσταση που σχετίζονται με Βιοδείκτες	**11**	Κλινικές μελέτες που σχετίζονται με Βιοδείκτες

Αποτελέσματα και ερμηνεία*

Βιοδείκτης	Αποτέλεσμα	Εγκεκριμένες θεραπείες για την ένδειξη	Θεραπείες με πιθανό όφελος	Θεραπείες με πιθανή αντίσταση/τοξικότητα	Κλινικές μελέτες
KRAS	Exon 2 c.38G>A (p.G13D)	-	Cobimetinib (2C.1) Binimetinib (2C.1) Trametinib (2C.1)	Panitumumab (1A.1) Cetuximab (1A.1)	ναι

*Σημείωση: Το επίπεδο σημαντικότητας των παραλλαγών (Level of Evidence, LoE) (π.χ. 1A.1, 2C.1, 1B κλπ) βασίζονται στις οδηγίες για την αναφορά γενετικών παραλλαγών στον καρκίνο που δόθηκαν με κοινή συναίνεση των AMP, ACMG, ASCO και CAP. Για λεπτομερή περιγραφή των οδηγιών αυτών, ανατρέξτε στην Εικόνα 1.

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Genomic Alterations Identified

***KRAS:* c.38G>A (p.G13D)**	**VAF*:1,3%**	**OncoKB**	**CIViC**	**PMKB**

The presence of KRAS mutations is associated with a high likelihood of resistance to therapies targeting EGFR (Panitumumab, Cetuximab) (PMID: 18202412,24024839,18316791). To date, most efforts to treat cancers with RAS mutations have focused on targeting downstream effectors of mutant RAS, such as RAF, MEK, or PI3K, each of which is druggable. MEK inhibitors have been the most widely investigated, typically as a combination therapy, despite the presence of multiple inhibitors that are being explored to target different KRAS-activated pathways. In the IMblaze370 trial, which evaluated Atezolizumab alone and in combination with Cobimetinib against monotherapy use of Regorafenib, the combination did not demonstrate improved overall survival (PMID: 31003911). Currently, there are no other clinical trials including cobimetinib for colorectal cancer. The MEK inhibitor binimetinib is being examined in a number of clinical trials for patients with KRAS-mutated colorectal cancer, including studies looking at the agent in combination with mFOLFIRII (NCT02613650) and with palbociclib (NCT03981614). Clinical trials evaluating the efficacy of trametinib, a potent MEK inhibitor clinically approved for BRAF mutant cancers (mainly melanoma), in colorectal cancer have been conducted (NCT03317119, NCT03668431, NCT03714958, NCT04111458). A phase I clinical trial of RMC-6236 in patients with advanced refractory solid cancers harboring specific KRAS mutations (G12A, G12D, G12R, G12S, G12V) is ongoing (NCT05379985). Finally, a phase I/II trial of SX-628 (CXCR1/2 inhibitor) in combination with nivolumab is ongoing in refractory RAS mutant, MSS CRC (NCT04599140). Efforts to induce an immune response against these tumors are under investigation (PMID: 36638742).

Gene information

The KRAS gene encodes the protein KRAS, which is a small GTPase that acts as a molecular switch for various cellular processes by coupling cell membrane growth factor receptors to intracellular signalling pathways and transcription factors. One KRAS mutation is present in up to 25% of all human tumors, and this is one of the most frequently activated oncogenes. They are found in approximately 30% to 50% of metastatic colorectal tumors and are common in other tumor types.

KRAS G13D is the third most common KRAS mutation in colon cancer (PMID: 12727799, 19679400). Colon cancer cell lines expressing this mutant form of KRAS showed malignant morphological features and KRAS-mediated tumorigenesis in mice, anchorage-independent growth, and increased expression of growth-promoting genes (PMID: 8465203). Therefore, this mutation is characterized as Pathogenic.

*VAF: Variant Allele Frequency

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Associated Treatments Information

Cobimetinib

DrugBank

Cobimetinib is an orally active, potent and highly selective small molecule inhibiting mitogen-activated protein kinase kinase 1 (MAP2K1 or MEK1), and central components of the RAS/RAF/MEK/ERK signal transduction pathway.

It has been approved in Switzerland and the US, in combination with vemurafenib, a BRAF inhibitor, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.

Binimetinib

DrugBank

Binimetinib, is a potent and selective oral mitogen-activated protein kinase 1/2 (MEK 1/2) inhibitor which is combined with Encorafenib.

On June 27, 2018, the Food and Drug Administration approved the combination of Encorafenib and Binimetinib for patients with unresectable or metastatic melanoma with the BRAF V600E or V600K mutations.

Trametinib

DrugBank

Trametinib dimethyl sulfoxide is a kinase inhibitor. Trametinib is indicated for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test

In May 2018, the U.S. Food and Drug Administration approved dabrafenib and trametinib, administered together, for the treatment of anaplastic thyroid cancer (ATC) that cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive). Thyroid cancer is a disease in which cancer cells form in the tissues of the thyroid. Anaplastic thyroid cancer is a rare, aggressive type of thyroid cancer. The National Institutes of Health (NIH) estimates there will be 53,990 new cases of thyroid cancer and an estimated 2,060 deaths from the disease in the United States in 2018. Anaplastic thyroid cancer accounts for approximately 1 to 2 percent of all thyroid cancers.

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.

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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

KRAS associated clinical trials

NCT05223673	Phase 3
Title	Phase 3 Study of Futuximab/Modotuximab in Combination With Trifluridine/Tipiracil Versus Trifluridine/Tipiracil Single Agent in Participants With Previously Treated Metastatic Colorectal Cancer
Treatment	Futuximab/modotuximab| Trifluridine/Tipiracil| Trifluridine/Tipiracil
Location	United States, Belgium, Denmark, Finland, Japan

NCT05593328	Phase 2
Title	Study of Onvansertib in Combination With FOLFIRI and Bevacizumab Versus FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer in Participants With a Kirsten Rat Sarcoma Virus Gene (KRAS) or Neuroblastoma-RAS (NRAS) Mutation
Treatment	Onvansertib| FOLFIRI| Bevacizumab
Location	United States

NCT03874026	Phase 2
Title	Study of Folfiri/Cetuximab in FcGammaRIIIa V/V Stage IV Colorectal Cancer Patients
Treatment	Folfiri/Cetuximab
Location	Italy

NCT04775862	Phase 2
Title	A Prospective Study Utilizing Circulating Cell Free DNA (cfDNA) Use in the Detection of RAS Mutations in Patients With Advanced Colorectal Cancer.
Treatment	investigator choice re-challenge with anti EGFR Rx
Location	Saudi Arabia

NCT05726864	Phase 1|Phase 2
Title	A Study of ELI-002 7P in Subjects With KRAS/NRAS Mutated Solid Tumors
Treatment	ELI-002 7P
Location	United States

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NCT05200442	Phase 1|Phase 2
Title	A Study of VS-6766 and Cetuximab in Patients With Advanced Colorectal Cancer
Treatment	VS-6766| Cetuximab| Pill Diary
Location	United States

NCT04720976	Phase 1|Phase 2
Title	JAB-3312 Based Combination Therapy in Adult Patients With Advanced Solid Tumors
Treatment	JAB-3312| Binimetinib| Pembrolizumab| Sotorasib| Osimertinib
Location	United States

NCT04965818	Phase 1|Phase 2
Title	Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer
Treatment	Futibatinib and Binimetinib
Location	United States

NCT05585320	Phase 1|Phase 2
Title	A Phase 1/2a Study of IMM-1-104 in Participants With Previously Treated, RAS-Mutant, Advanced or Metastatic Solid Tumors
Treatment	IMM-1-104
Location	United States

NCT05789082	Phase 1|Phase 2
Title	A Study Evaluating the Safety, Activity, and Pharmacokinetics of GDC-6036 in Combination With Other Anti-Cancer Therapies in Participants With Previously Untreated Advanced or Metastatic Non-Small Cell Lung Cancer With a KRAS G12C Mutation
Treatment	GDC-6036| Pembrolizumab
Location	Korea, Republic of

NCT05039177	Phase 1|Phase 2
Title	A Study of ERAS-007 in Patients With Advanced Gastrointestinal Malignancies
Treatment	ERAS-007| Encorafenib| Cetuximab| Palbociclib

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Location	United States

Press here for a live search of clinical trials for KRAS

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Methodology

NGS analysis

DNA and RNA were extracted from the sample under investigation using the QIAamp Circulating Nucleic Acid Kit (Qiagen). Mutation hotspot regions of 12 genes were amplified using Oncomine Lung cell free total nucleic acid assay (Thermo Fisher Scientific). Copy number variations, SNPs, and indels were analyzed. Additionally, ALK, ROS1, RET fusions & expression were tested. Sequencing was carried out using the Next Generation Sequencing platform Ion GeneStudio S5 Prime System (ThermoFisher). The variant detection limit of the assay is 0.1%, with 90% sensitivity and >98% specificity for SNV hotspots and indels.

Genes Analyzed

12 gene alterations									
ALK	BRAF	EGFR	ERBB2	KRAS	MAP2K1	MET	NRAS	PIK3CA	RET
ROS1	TP53								

3 fusion transcripts						
ALK	ROS1	RET				

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Appendix

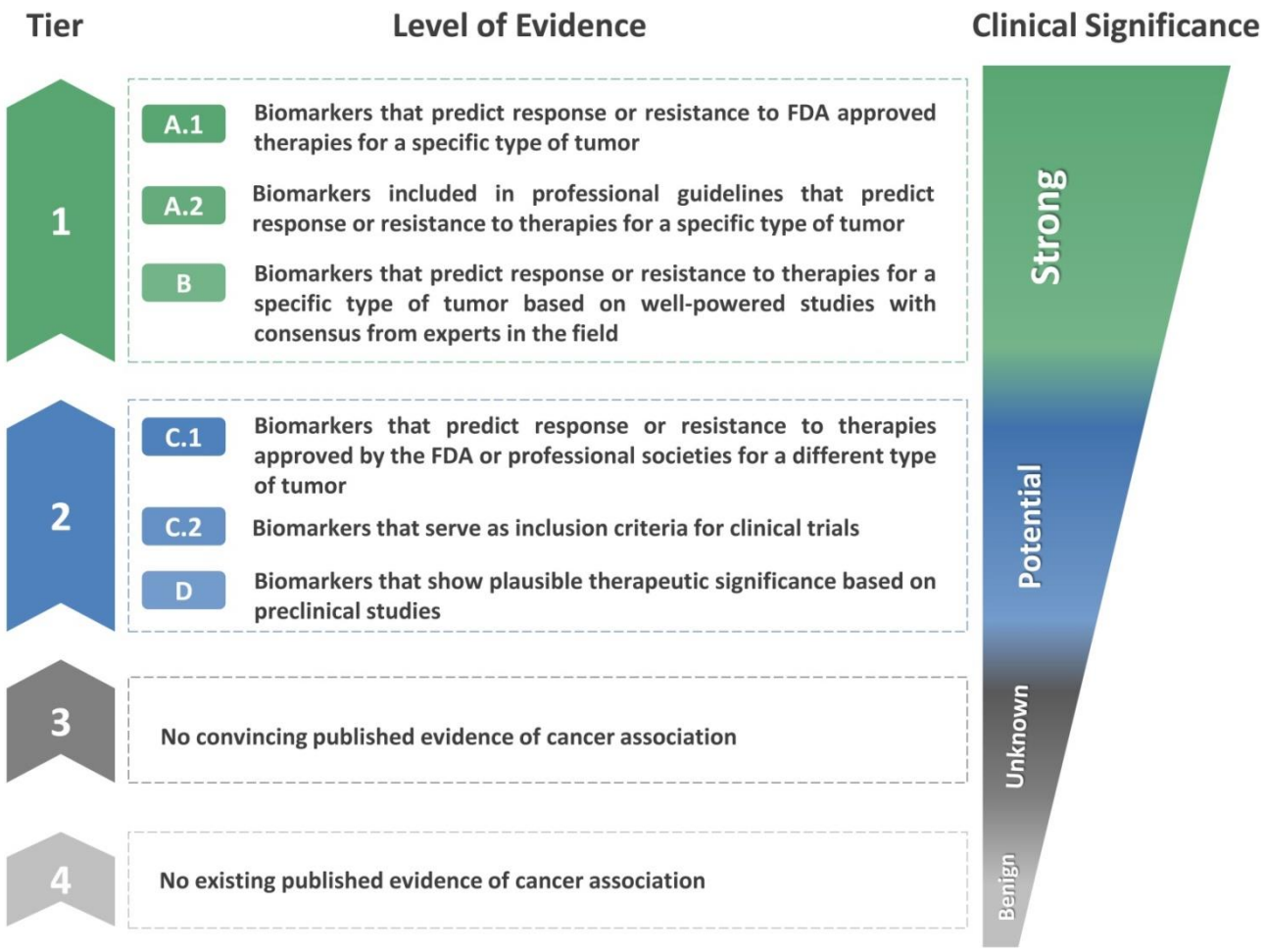

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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