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INFORMAȚII PROBĂ

Nume:
CNP:
Data nașterii:
Sex:
Adresă:
Proba #1: TESUT INCLUS IN PARAFINA
Cod probă #1

Raport nr:
Medic trimițător:
Data inregistrarii :
Data rezultat:
Tip tumoră: CANCER BRONHOPULMONAR

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

Rezumatul raportului

27	Gene (**7** fuziuni) analizate	**1**	Alterări genomice detectate în tumoră
12	Terapii aprobate asociate biomarkerilor în funcție de indicație	**6**	Terapii cu potențiale beneficii asociate biomarkerilor
0	Terapii cu potențială rezistență asociate biomarkerilor	**29**	Studii clinice asociate biomarkerilor

Rezultate și interpretare*

Biomarker	Rezultat	Terapii aprobate în funcție de indicație	Terapii cu beneficiu potențial	Terapii cu potențială rezistență/toxicitate	Studii clinice
KRAS	Exon 2 c.34G>T (p.G12C)	Sotorasib (1A.1) Adagrasib (1A.1) -	- Cobimetinib (2C.1) Binimetinib (2C.1) Trametinib (2C.1) Avutometinib+Defactinib (2C.1) Adagrasib+Cetuximab (2C.1) Sotorasib+Panitumumab (2C.1)	- -	da
Expresia PD-L1 (22C3)	TPS 90% Pozitiv	Pembrolizumab Nivolumab Durvalumab Cemiplimab Nivolumab+Ipilimumab		-	-
Expresia PD-L1 (SP263)	TC 90% Pozitiv	Pembrolizumab Nivolumab Durvalumab Cemiplimab Nivolumab+Ipilimumab		-	-

*Nota: Nivelul de dovezi al variantelor (de exemplu, 1A.1, 2C.1, 1B etc.) se bazează pe recomandarea consensului comun AMP, ACMG, ASCO și CAP pentru raportarea variantelor genetice în cancer. Pentru o descriere detaliată a recomandării, vă rugăm să consultați Fig. 1

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SAMPLE INFORMATION

Name:
Medical ID:
Date Of Birth:
Sex:
Location:
Material #1: PARAFFIN EMBEDDED
Sample #1 ID: TISSUE 199378

Report No :
Req. Physician:
Registration Date :
Date of Report:
Tumor type: Lung Cancer

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Report Summary

27	Unique Genes (**7** Fusions) analyzed	**1**	Genomic alterations identified in tumor
12	Biomarker related approved therapies for indication	**6**	Biomarker related therapies with potential benefit
0	Biomarker related therapies with potential resistance	**29**	Biomarker related Clinical Trials

Results and Interpretation*

Biomarker	Result	Approved therapies for indication	Therapies with potential benefit	Therapies with potential resistance/toxicity	Clinical Trials
KRAS	Exon 2 c.34G>T (p.G12C)	Sotorasib (1A.1) Adagrasib (1A.1) -	- Cobimetinib (2C.1) Binimetinib (2C.1) Trametinib (2C.1) Avutometinib+Defactinib (2C.1) Adagrasib+Cetuximab (2C.1) Sotorasib+Panitumumab (2C.1)	- -	yes
PD-L1 expression (22C3)	TPS 90% Positive	Pembrolizumab Nivolumab Durvalumab Cemiplimab Nivolumab+Ipilimumab		-	-
PD-L1 expression (SP263)	TC 90% Positive	Pembrolizumab Nivolumab Durvalumab Cemiplimab Nivolumab+Ipilimumab		-	-

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*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

***KRAS:* c.34G>T (p.G12C)**	**VAF*:71%**	**OncoKB**	**CIViC**	**PMKB**

Treatment Information

The KRAS (p.G12C) mutation detected in this patient represents about 13% of mutations in non-small cell lung cancers and can be targeted by the following drugs:

- Recently, the Food and Drug Administration (FDA) granted accelerated approval to the oral small molecular inhibitor adagrasib, for adult patients with KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Approval was based on KRYSTAL-1, a multicenter, single-arm, open-label clinical trial (NCT03785249) which included patients with locally advanced or metastatic NSCLC with KRAS G12C mutations (PMID: 35658005). Efficacy was evaluated in 112 patients whose disease has progressed on or after platinum-based chemotherapy and an immune checkpoint inhibitor, given either concurrently or sequentially. The ORR was 43% (95% CI: 34%, 53%) and median DOR was 8.5 months (95% CI: 6.2, 13.8). Adagrasib is optimized to sustain target inhibition, an attribute that could be important to treat KRAS G12C mutated cancers, as the KRASG12C protein regenerates every 24-48 hours. Studies of adagrasib have shown that the drug has a long half-life, extensive tissue distribution and is well tolerated. Adagrasib has also shown single-agent responses in colorectal cancer, pancreatic cancer, and other solid tumors with KRASG12C mutations (PMID: 35167329).
- FDA granted accelerated approval to sotorasib for adult patients with KRAS G12C mutated locally advanced or metastatic NSCLC, as determined by an FDA approved test, who have received at least one prior systemic therapy. Approval was based on CodeBreaK 100, a multicenter, single-arm, open label clinical trial (NCT03600883) which included patients with locally advanced or metastatic NSCLC with KRAS G12C mutations. Efficacy was evaluated in 124 patients whose disease had progressed on or after at least one prior systemic therapy. Patients received sotorasib 960 mg orally daily until disease progression or unacceptable toxicity. The main efficacy outcome measures were objective response rate (ORR) according to RECIST 1.1, as evaluated by blinded independent central review and response duration. The ORR was 36% (95% CI: 28%, 45%) with a median response duration of 10 months (range 1.3+, 11.1). A trial evaluating sotorasib as monotherapy or in combination with various agents in patients with NSCLC or other solid tumors is under way (ClinicalTrials.gov NCT04185883) (PMID: 32955176). In the clinic, conventional chemotherapy is widely used to treat patients with KRAS-mutant NSCLC. However, in a meta-analysis of nine clinical trials including 5633 participants with NSCLC, immune checkpoint inhibitors vs. chemotherapy showed improved OS (HR, 0.65; 95% CI) and PFS (HR, 0.49; 95% CI) in NSCLC patients harboring KRAS mutation, with KRAS G12C patients showing a much better PFS with ICIs than with chemotherapy) (PMID: 36061356).

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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 (PMID: 33402199).

The most common MEK inhibitors used in clinical practice are cobimetinib, binimetinib and trametinib. Cobimetinib is a kinase inhibitor, approved by the FDA, for use in combination with vemurafenib for the treatment of advanced melanoma with a BRAF V600E or V600K mutation (IMspire150, NCT02908672). An initial phase Ib study (NCT01988896) was conducted to investigate the safety and efficacy of cobimetinib plus atezolizumab for patients with solid tumors, 28 NSCLC patients included. Atezolizumab plus cobimetinib had manageable safety and clinical activity irrespective of KRAS/BRAF status (PMID: 30918950). Binimetinib is a potent and selective oral mitogen-activated protein kinase 1/2 (MEK 1/2) inhibitor, which is approved by the FDA in combination with encorafenib for patients with unresectable or metastatic melanoma with the BRAF V600E or V600K mutations (COLUMBUS; NCT01909453).

The MEK inhibitor binimetinib has been examined in a number of clinical trials for patients with KRAS-mutated lung cancer, including studies looking at the agent in combination with chemotherapy (NCT02185690 PMID: 34052705, NCT02964689-completed/results non posted) and with palbociclib (NCT03170206-ongoing). Trametinib is a kinase inhibitor, approved by the FDA, for the treatment of melanoma, non-small cell lung cancer, thyroid cancer, and solid tumors with BRAF V600 mutations (METRIC study). The efficacy of MEK inhibitor trametinib, alone or in combination with docetaxel, has been evaluated in KRAS-mutant NSCLC. Trametinib plus docetaxel had encouraging results. Trametinib is being examined with the PD-1 inhibitor pembrolizumab in the phase Ib/II IM-BATTLE-2 trial (NCT03225664). Avutometinib is an inhibitor of Ras-Raf-MEK-ERK signaling being developed as a potential treatment for cancer. Defactinib is a small-molecule, oral focal adhesion kinase (FAK) inhibitor. It works by blocking FAK, a tyrosine kinase involved in cell adhesion and signaling pathways, including RAS/MEK/ERK and PI3K/Akt. Defactinib has been studied in various clinical trials for its potential anti-tumor and anti-angiogenic activities. In 2025 FDA approved defactinib in combination with avutometinib for the treatment of adult patients with recurrent low-grade serous ovarian cancer.

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. Approximately 15-25% of patients with lung adenocarcinoma have tumor associated KRAS mutations. The role of KRAS as either a prognostic or predictive factor in NSCLC is unknown at this time.

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Variant Information

KRAS p. Gly12Cys (G12C) is located at the most frequently occurring hotspot codon in KRAS, within the GTP binding region (amino acids 10-18, UniProt), and has primarily been detected as a somatic alteration. G12C has been shown to be activating (PMID: 26037647) and therefore it is known to be pathogenic. The KRAS G12C-targeted inhibitors sotorasib and adagrasib are FDA-approved for the treatment of adult patients with KRAS G12C mutant non-small cell lung cancer.

*VAF: Variant Allele Frequency

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Associated Treatments Information

Sotorasib

DrugBank

Sotorasib, also known as AMG-510, is an acrylamide derived KRAS inhibitor developed by Amgen. It is indicated in the treatment of adult patients with KRAS G12C mutant non small cell lung cancer. This mutation makes up >50% of all KRAS mutations. Mutant KRAS discovered in 1982 but was not considered a druggable target until the mid-2010s. It is the first experimental KRAS inhibitor. Sotorasib was granted FDA approval on 28 May 2021.

Sotorasib is indicated in the treatment of adults with KRAS G12C mutant non small cell lung cancer.

Adagrasib

DrugBank

Adagrasib (MRTX849) is an oral, small-molecule KRAS inhibitor developed by Mirati Therapeutics.. Adagrasib targets KRASG12C, one of the most common KRAS mutations, at the cysteine 12 residue and inhibits KRAS-dependent signalling. Adagrasib is a covalent inhibitor of KRASG12C that irreversibly and selectively binds and locks KRASG12C in its inactive, guanosine diphosphate bound state. On December 12, 2022, the Food and Drug Administration (FDA) granted accelerated approval to the oral small molecular inhibitor adagrasib, for adult patients with KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Approval was based on KRYSTAL-1, a multicenter, single-arm, open-label clinical trial (NCT03785249) which included patients with locally advanced or metastatic NSCLC with KRAS G12C mutations (PMID: 35658005). The ORR was 43% (95% CI: 34%, 53%) and median DOR was 8.5 months (95% CI: 6.2, 13.8).

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.

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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.

Avutometinib

DrugBank

Avutometinib is an inhibitor of Ras-Raf-MEK-ERK signaling being developed as a potential treatment for cancer. In 2025 FDA approved avutometinib in combination with defactinib for the treatment of adult patients with recurrent low-grade serous ovarian cancer.

Defactinib

DrugBank

Defactinib is a small-molecule, oral focal adhesion kinase (FAK) inhibitor. It works by blocking FAK, a tyrosine kinase involved in cell adhesion and signaling pathways, including RAS/MEK/ERK and PI3K/Akt. Defactinib has been studied in various clinical trials for its potential anti-tumor and anti-angiogenic activities. In 2025 FDA approved defactinib in combination with avutometinib for the treatment of adult patients with recurrent low-grade serous ovarian cancer.

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

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agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

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.

Pembrolizumab

DrugBank

Pembrolizumab is a highly selective IgG4-kappa humanized monoclonal antibody against PD-1 receptor. It was generated by grafting the variable sequences of a very high-affinity mouse antihuman PD-1 antibody onto a human IgG4-kappa isotype with the containing a stabilizing S228P Fc mutation. It contains 32 cysteine residues and the complete folded molecule includes 4 disulfide linkages as interchain bonds and 23 interchain bonds. It was firstly approved by the FDA on September 4, 2014, for the treatment of metastatic malignant melanoma. This is the first approved therapy against PD-1. Its approval in melanoma was extended to several countries such as Australia, Israel, Korea, Macau, the European Union and the United Arab Emirates. On June 12, 2018, Pembrolizumab was approved for the treatment of cervical cancer under the status of accelerated approval.

Pembrolizumab is indicated for the treatment patients with unresectable or metastatic melanoma; as a single therapy, pembrolizumab is indicated for first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have high PD-L1 expression as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; as a single therapy, pembrolizumab is indicated for first-line treatment of patients with metastatic non-small cell lung cancer whose tumors express PD-L1 (TPS≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to treatment. The following indications present the status of accelerated approval based on tumor response rate and durability of the response and thus, the approval of this indications are contingent upon verification and description of clinical benefit in confirmatory trials; patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS > 1) as determined by an FDA-approved test; in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer ;patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy ;treatment of adults and pediatric patients with refractory classical Hodgkin lymphoma or who have relapsed after 3 or more prior lines of therapy ;treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma or who have

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relapsed after 2 or more prior lines of therapy ;treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy ;patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy ;treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient with solid tumors that have progressed following previous treatment and colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan ;patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS >1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

Nivolumab

DrugBank

Nivolumab is a fully human IgG4 antibody targeting the immune checkpoint programmed death receptor-1 (PD-1). This molecule was produced entirely on mice and grafted onto human kappa and IgG4 Fc region with the mutation S228P for additional stability and reduced variability. It was originally FDA approved on December 22, 2014. Since this approval, nivolumab has been approved for a variety of other uses related to cancer therapy. On 2017, was notably approved for the treatment of hepatocellular carcinoma and on July 11, 2018, the FDA approved this agent in combination with low doses of for the treatment of MSI-H/dMMR metastatic colorectal cancer.

Nivolumab is indicated to treat unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic non-small cell lung cancer, small cell lung cancer, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, and hepatocellular carcinoma.

Durvalumab

DrugBank

Durvalumab is a human monoclonal antibody that blocks programmed death ligand 1 (PD-L1), or CD 274. In May, 2017 it received FDA approval for previously treated patients with locally advanced or metastatic cancer in the urinary system (as Imfinzi). It is shown to be effective in patients with continued disease progression after the platinum-based chemotherapy. This drug has a relatively tolerable safety profile and its structural modification advantageously prevents the induction of antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

Durvalumab is indicated for patients with urothelial carcinoma, such as urinary bladder, urethra or ureter cancer. Patients with prolonged disease progression due to failed platinum-based chemotherapy such as cisplatin and carboplatin are most likely to benefit from durvalumab treatment. Its clinical effectiveness is especially enhanced in PD-L1-positive patient groups.

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Cemiplimab

DrugBank

Cemiplimab is a fully human monoclonal antibody that works against programmed death receptor-1 (PD-1), which is a negative regulator of T cell function. By blocking PD-1, cemiplimab works to enhance T cell-mediated antitumour responses. Cemiplimab was first approved by the FDA on September 28, 2018, as the first FDA-approved treatment for advanced cutaneous squamous cell carcinoma (CSCC). It was later approved to be used in basal cell carcinoma and non-small non-small cell lung cancer. Cemiplimab was also approved by the European Commission on June 28, 2019. In October 2022, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended cemiplimab be granted marketing authorization for the treatment of cervical cancer. Cemiplimab is indicated to treat:
- Locally advanced or metastatic cutaneous squamous cell carcinoma (mCSCC) in patients who are not candidates for curative surgery or curative radiation.
- Locally advanced basal cell carcinoma (laBCC) in previously treated patients with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
- Metastatic basal cell carcinoma (mBCC) in patients who were previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. This indication is approved under accelerated approval based on tumour response rate and durability of response. Continued approval for mBCC may be contingent upon verification and description of clinical benefit.
- Locally advanced non-small cell lung cancer (NSCLC) in combination with platinum-based chemotherapy for the firstâ€ line treatment of adults with no EGFR, ALK or ROS1 aberrations, who are not candidates for surgical resection or definitive chemoradiation. It is also indicated to treat metastatic NSCLC in combination with platinum-based chemotherapy as first-line treatment in adults.
- Locally advanced or metastatic NSCLC as monotherapy for the first-line treatment of adults whose tumours have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations. Patients with locally advanced NSCLC must not be candidates for surgical resection or definitive chemoradiation.
- Recurrent or metastatic cervical cancer in adults with disease progression on or after platinum-based chemotherapy.

Ipilimumab

DrugBank

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody used to treat metastatic or unresectable melanoma. On April 8, 2025, the Food and Drug Administration approved nivolumab with ipilimumab for adult and pediatric patients 12 years of age and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). The FDA also converted the accelerated approval to regular

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approval for single agent nivolumab for adult and pediatric patients 12 years of age and older with MSI-H or dMMR metastatic CRC, that has progressed following fluoropyrimidine, oxaliplatin, and irinotecan. Efficacy of nivolumab with ipilimumab was evaluated in CHECKMATE-8HW (NCT04008030), a randomized, three-arm, open-label trial in immunotherapy-naÃ¯ve patients with unresectable or metastatic CRC with known MSI-H or dMMR status. Median PFS was NR in the nivolumab + ipilimumab arm and 39.3 months in the nivolumab arm. ORR was 71% in the nivolumab + ipilimumab arm and 58% in the nivolumab arm.

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Clinical Trials to consider

KRAS associated clinical trials

NCT06416410	Phase 3
Title	JAB-21822 Combined With JAB-3312 Compared SOC in the First Line for Treatment of Advanced Non-small Cell Lung Cancer With KRAS p.G12C Mutation
Treatment	JAB-21822| Tislelizumab| JAB-3312| Pemetrexed| Carboplatin
Location	China

NCT06008093	Phase 3
Title	A Study to Investigate the Efficacy of Durvalumab Plus Tremelimumab in Combination With Chemotherapy Compared With Pembrolizumab in Combination With Chemotherapy in Metastatic NSCLC Patients With Non-squamous Histology Who Have Mutations and/or Co-mutations in STK11, KEAP1, or KRAS
Treatment	Durvalumab| Tremelimumab| Pemetrexed| Pembrolizumab| Carboplatin| Cisplatin
Location	United States

NCT06881784	Phase 3
Title	Study of Daraxonrasib (RMC-6236) in Patients With RAS Mutated NSCLC (RASolve 301)
Treatment	daraxonrasib| docetaxel
Location	United States, Australia, Belgium, France, Germany, Hong Kong, Ireland, Italy, Japan, Netherlands, Poland, Puerto Rico, Singapore, South Korea, Spain, Switzerland, Taiwan

NCT06119581	Phase 3
Title	A Study of First-Line Olomorasib (LY3537982) and Pembrolizumab With or Without Chemotherapy in Patients With Advanced KRAS G12C-Mutant Non-small Cell Lung Cancer
Treatment	LY3537982| Pembrolizumab| Placebo| Cisplatin| Carboplatin| Pemetrexed
Location	United States, Australia, Austria, Belgium, Brazil, Canada, China, Czechia, Denmark, France, Germany, Greece, Hungary, India, Italy, Japan, Mexico, Netherlands, Norway, Poland, Portugal, Romania, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey (TÃ¼rkiye), United Kingdom

NCT03486873	Phase 3
Title	Long-term Safety and Efficacy Extension Study for Participants With Advanced Tumors Who Are Currently on Treatment or in Follow-up in a Pembrolizumab (MK-3475) Study (MK-3475-587/KEYNOTE-587)

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Treatment	Pembrolizumab| Standard of Care (SOC)| Lenvatinib| Olaparib| MK-4280| MK-4280A
Location	United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Costa Rica, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Portugal, Puerto Rico, Romania, Russia, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey (TÃ¼rkiye), Ukraine, United Kingdom, Vietnam

NCT07291037	**Phase 3**
Title	Phase III Study of Datopotamab Deruxtecan Versus Docetaxel in Previously Treated TROP2-positive Advanced or Metastatic Non-squamous NSCLC Without Actionable Genomic Alterations
Treatment	Datopotamab deruxtecan (Dato-DXd)| Docetaxel
Location	United States, Australia, Austria, Belgium, Brazil, Canada, China, Germany, Hungary, India, Italy, Japan, Poland, South Korea, Taiwan, Thailand, Turkey (TÃ¼rkiye), United Kingdom, Vietnam

NCT06300177	**Phase 3**
Title	D-1553 Tablet Versus Docetaxel Injection for KRAS G12C Mutation-positive Locally Advanced or Metastatic Non-small Cell Lung Cancer After Prior Standard Therapy Failure
Treatment	D-1553 Tablet| Docetaxel injection
Location	China

NCT06875310	**Phase 3**
Title	A Study of Adagrasib Plus Pembrolizumab Plus Chemotherapy vs. Placebo Plus Pembrolizumab Plus Chemotherapy in Participants With Previously Untreated Non-squamous Non-small Cell Lung Cancer With KRAS G12C Mutation (KRYSTAL-4)
Treatment	Adagrasib| Pembrolizumab| Carboplatin| Pemetrexed| Placebo| Cisplatin
Location	United States, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Poland, Portugal, Romania, Saudi Arabia, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey (TÃ¼rkiye), United Kingdom

NCT06345729	**Phase 3**
Title	A Study of MK-1084 Plus Pembrolizumab (MK-3475) in Participants With KRAS G12C Mutant Non-small Cell Lung Cancer (NSCLC) With Programmed Cell Death Ligand 1 (PD-L1) Tumor Proportion Score (TPS) â‰¥50% (MK-1084-004/KANDLELIT-004)
Treatment	MK-1084| Placebo| Pembrolizumab

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Location	United States, Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Chile, China, France, Georgia, Germany, Greece, India, Italy, Japan, Mexico, Netherlands, New Zealand, Philippines, Poland, Romania, South Korea, Spain, Turkey (TÃ¼rkiye), Ukraine, United Kingdom

NCT07174908	**Phase 3**
Title	A Phase 3 Study of IN10018 in Combination With D-1553 Versus Standard Therapy for First Line Non-squamous Non-small Cell Lung Cancer With KRAS G12C Mutation
Treatment	IN10018 in combination with D-1553| anti-PD-1 monoclonal antibody in combination with platinum and pemetrexed
Location	China

NCT06793215	**Phase 3**
Title	A Study Evaluating the Efficacy and Safety of Divarasib and Pembrolizumab Versus Pembrolizumab and Pemetrexed and Carboplatin or Cisplatin in Participants With Previously Untreated, KRAS G12C-Mutated, Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer
Treatment	Divarasib| Pembrolizumab| Pemetrexed| Carboplatin| Cisplatin
Location	United States, Argentina, Australia, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Netherlands, New Zealand, Poland, Portugal, Singapore, South Korea, Spain, Switzerland, Taiwan, United Kingdom

NCT06890598	**Phase 3**
Title	Study of Olomorasib (LY3537982) in Combination With Standard of Care in Participants With Resected or Unresectable KRAS G12C-mutant Non-Small Cell Lung Cancer
Treatment	Olomorasib| Pembrolizumab| Durvalumab| Placebo
Location	United States, Australia, Austria, Belgium, Brazil, Chile, China, Czechia, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey (TÃ¼rkiye), United Kingdom

NCT05920356	**Phase 3**
Title	A Study Evaluating Sotorasib Platinum Doublet Combination Versus Pembrolizumab Platinum Doublet Combination as a Front-Line Therapy in Participants With Stage IV or Advanced Stage IIIB/C Nonsquamous Non-Small Cell Lung Cancers (CodeBreaK 202)
Treatment	Sotorasib| Pembrolizumab
Location	United States, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czechia, Denmark, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey (TÃ¼rkiye), United Kingdom

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NCT07190248	Phase 3
Title	A Clinical Study of MK-1084 and Other Treatments for Participants With Non-Small Cell Lung Cancer (MK-1084-007/KANDLELIT-007)
Treatment	MK-1084| Pembrolizumab (+) Berahyaluronidase alfa| Pemetrexed| Cisplatin| Carboplatin
Location	United States, Argentina, Australia, Austria, China, France, Greece, Hungary, Israel, Japan, Poland, Romania, South Korea, Spain, Taiwan, Ukraine

NCT04322890	Phase 2
Title	Treatment Strategies and Survival Outcome for Non-small Cell Lung Cancer With Oncogenic Mutation
Treatment	Osimertinib| Alectinib 150 MG| Crizotinib 250 MG| Savolitinib, Crizotinib.| Chemotherapy
Location	China

NCT04302025	Phase 2
Title	A Study of Multiple Therapies in Biomarker-selected Participants With Resectable Stages IB-III Non-small Cell Lung Cancer (NSCLC)
Treatment	Alectinib| Entrectinib| Vemurafenib| Cobimetinib| Pralsetinib| Atezolizumab| SBRT| Resection| Chemotherapy| Divarasib
Location	United States

NCT06015724	Phase 2
Title	Anti-CD38 Antibody With KRAS Vaccine and Anti-PD-1 Antibody in Subjects With Pancreatic Ductal Adenocarcinoma and Refractory Non-Small Cell Lung Cancer
Treatment	Daratumumab| KRAS vaccine| Nivolumab
Location	United States

NCT04589845	Phase 2
Title	Tumor-agnostic Precision Immuno-oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study
Treatment	Entrectinib| Alectinib| Atezolizumab| Ipatasertib| Trastuzumab emtansine| Inavolisib| Belvarafenib| Pralsetinib| Divarasib| Camonsertib
Location	United States, Australia, Belgium, Brazil, Canada, China, Denmark, France, Germany, Hong Kong, Israel, Italy, Japan, New Zealand, Poland, Portugal, Puerto Rico, Singapore, South Africa, South Korea, Spain, Switzerland, Taiwan, United Kingdom

NCT06582771	Phase 2

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Title	A Study of Sotorasib in People With Non-Small Cell Lung Cancer
Treatment	Sotorasib
Location	United States

NCT07209111	**Phase 2**
Title	A Clinical Study of MK-1084 in People With Advanced Solid Tumors (MK-1084-014)
Treatment	MK-1084| Cetuximab
Location	United States, Denmark, Israel, Italy, Norway, Poland, South Korea, Spain, Sweden

NCT06793813	**Phase 2**
Title	Cadonilimab in Patients (Pts) with Advanced Non-small Cell Lung Cancer (NSCLC)
Treatment	cadonilimabï¼Œbevacizumabï¼Œdocetaxel
Location	China

NCT05398094	**Phase 2**
Title	Clinical Trial of AMG510 in Stage III Unresectable NSCLC KRAS p.G12C Patients and Ineligible for Chemo-radiotherapy
Treatment	Sotorasib
Location	Spain

NCT05118854	**Phase 2**
Title	A Phase II Study of Neoadjuvant Sotorasib in Combination With Cisplatin or Carboplatin and Pemetrexed for Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a KRAS p.G12C Mutation
Treatment	AMG 510| Cisplatin| Carboplatin| Pemetrexed
Location	United States

NCT06563999	**Phase 2**
Title	Neoadjuvant Umbrella Trial for Patients With Unresectable Stage III NSCLC Harboring Rare Mutations.
Treatment	Sunvozertinib| Crizotinib| Pralsetinib| Larotrectinib| Savolitinib| Pyrotinib| Dabrafenib+Trametinib| Glecirasib| Ensartinib

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Location	China

NCT05853575	**Phase 2**
Title	Trial of Two Adagrasib Dosing Regimens in NSCLC With KRAS G12C Mutation (KRYSTAL 21)
Treatment	Adagrasib
Location	United States, Brazil, Croatia, France, Greece, Hungary, Israel, Italy, Japan, Mexico, Netherlands, Peru, Poland, Romania, Serbia, South Korea, Spain, Taiwan, Thailand, Turkey (TÃ¼rkiye)

NCT05327010	**Phase 2**
Title	Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial
Treatment	BET Bromodomain Inhibitor ZEN-3694| Biopsy Procedure| Biospecimen Collection| Diagnostic Imaging Testing| Talazoparib
Location	United States

NCT05609578	**Phase 2**
Title	Combination Therapies With Adagrasib in Patients With Advanced NSCLC With KRAS G12C Mutation
Treatment	Adagrasib oral dose of 400 mg twice daily tablets| Pembrolizumab| Chemotherapy: Pemetrexed| Cisplatin/Carboplatin
Location	United States, Brazil, Chile, France, Georgia, Greece, Hungary, Italy, Malaysia, Poland, Serbia, Spain, Switzerland, Thailand

NCT07172919	**Phase 2**
Title	A Rollover Study Evaluating Sotorasib With or Without Panitumumab in Participants With KRAS p.G12C Mutation
Treatment	Sotorasib| Panitumumab
Location	United States

NCT07252739	**Phase 2**
Title	KEYMAKER-U01 Substudy 01J: A Study of Pembrolizumab Plus MK-1084 in Participants With Non-Small Cell Lung Cancer (NSCLC) With Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) G12C Mutations (MK-3475-01J/KEYMAKER-U01J)
Treatment	MK-1084| Pembrolizumab| Cetuximab| Carboplatin| Pemetrexed
Location	United States, Ukraine

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Methodology

DNA is extracted from the sample under investigation using the Qiamp DNA FFPE Kit (Qiagen). RNA was extracted using the RNeasy FFPE Kit (Qiagen). Mutation hotspot regions of 27 genes are amplified using a custom DNA panel (Thermo Fisher Scientific). Copy number variations, SNPs, and indels are analysed. Additionally, ALK, ROS1, RET, NTRK1, NTRK2, NTRK3 fusions and expression and MET exon 14 skipping were tested using a custom Fusion Panel (Thermo Fisher Scientific). Amplification was performed using the KAPA HyperPrep Kit (Roche). All fusions detected are confirmed with an alternative method (Real-Time PCR). Sequencing was carried out using the Next Generation Sequencing platform Aviti (Element Biosciences). The detection limit of the method is 2-5% of mutant allelic content, depending on the genomic region. DNA variations detected at frequencies of less than 5% are confirmed using NGS or an alternative method (Real-Time PCR).

***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.*

Notes

1. Tissue macro-dissection was performed prior to genetic material extraction.
2. The average effective sequencing depth exceeds 1000X.
3. Over 90% of bases have a quality score of ≥ Q30, indicating a base recognition accuracy rate of >99.9%, which reflects high sequencing fidelity
4. This test is designed to assist in clinical decision-making but does not independently constitute a definitive clinical decision.
5. As scientific knowledge on variants and associated therapies evolves, previous classifications may be revised. Variant interpretations are based on the most current evidence available at the time of analysis.The Fraction of base quality ≥ Q30 is over 90%. The proportion of base quality in sequencing data that reaches or exceeds Q30, indicating that the probability of base recognition accuracy rate exceeds 99.9%.
6. Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follows guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), Database and references used: Reference genome (GRCh37), dbSNP Build 156, ExAC r1.0 GNOMAD r2.1.1, ClinVar 2024_08_26. Primary and secondary analysis of the NGS raw data, is performed using the CE-IVD commercial computational algorithm SeqPilot Version 5.4.3 V01 (JSI Medical Systems).
7. The limit of detection (LOD) of the NGS method used for SNVs is 2-5% of mutant allelic content, depending on the genomic region analyzed (Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%). The LOD for indels is at VAF ≥5%. The LoD is based on as low as 10 ng of gDNA input for library preparation. Gene fusions are detected frequencies as low as 1% or lower in a background of wild-type RNA. Sensitivity and Specificity >99%.

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Limitations

1. Limited tissue sampling may not fully capture the entire spectrum of DNA variations within a lesion, potentially leading to incomplete representation of tumor heterogeneity.
2. Not all patients have genomic variations linked to targeted therapies, limiting treatment options and resistance analysis.
3. The occurrence of insufficient amplification of an allele (allelic dropout) can affect the analysis result.
4. Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples

PD-L1 expression by IHC

1.PD-L1 Antibody Clone SP263 (Automated Testing): Automated IHC PD-L1 testing performed on the Ventana BenchMark platform using Ventana anti-PD-L1 clone (SP263) (US FDA Approved).

Controls:

Cell line control / Reference control / Negative patient control: Validated.

Tumor-Associated Immune Cells (TAIC): Present.

Interpretation Criterion: Binary (positive/negative).

Comments:

TPS/TC (Tumor Proportion Score / Tumor Cells): The percentage of viable tumor cells showing partial or complete membrane staining (≥1+) relative to all viable tumor cells in the sample.

Interpretation:

Positive: TC/TPS ≥ 1%.

Negative: TC/TPS < 1%.

Phenotypic expression of PD-L1 positivity identifies patients with locally advanced NSCLC (non-small cell lung cancer) who are eligible for immunotherapy.

2. PD-L1 Antibody Clone 22C3 (Automated Testing): Automated IHC anti-PD-L1 testing performed on the DAKO platform using the DAKO anti-PD-L1 antibody (clone 22C3) pharmaDx. (US FDA Approved).

Controls:

Cell line control / Reference control / Negative patient control: Validated.

Tumor-Associated Immune Cells (TAIC): Present.

Interpretation Criterion: Binary (positive/negative).

Comments:

TPS/TC (Tumor Proportion Score / Tumor Cells): The percentage of viable tumor cells showing partial or complete membrane staining (≥1+) relative to all viable tumor cells in the sample.

Interpretation:

Positive: TC/TPS ≥ 1%.

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Name : Barcode :

Negative: TC/TPS < 1%.

Phenotypic expression of PD-L1 positivity identifies patients with locally advanced NSCLC (non-small cell lung cancer) who are eligible for immunotherapy.

Genes Analyzed

27 gene alterations									
AKT1	ALK	BRAF	CDKN2A	CTNNB1	DDR2	EGFR	ERBB2	FBXW7	FGFR1
FGFR2	FGFR3	HRAS	KEAP1	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

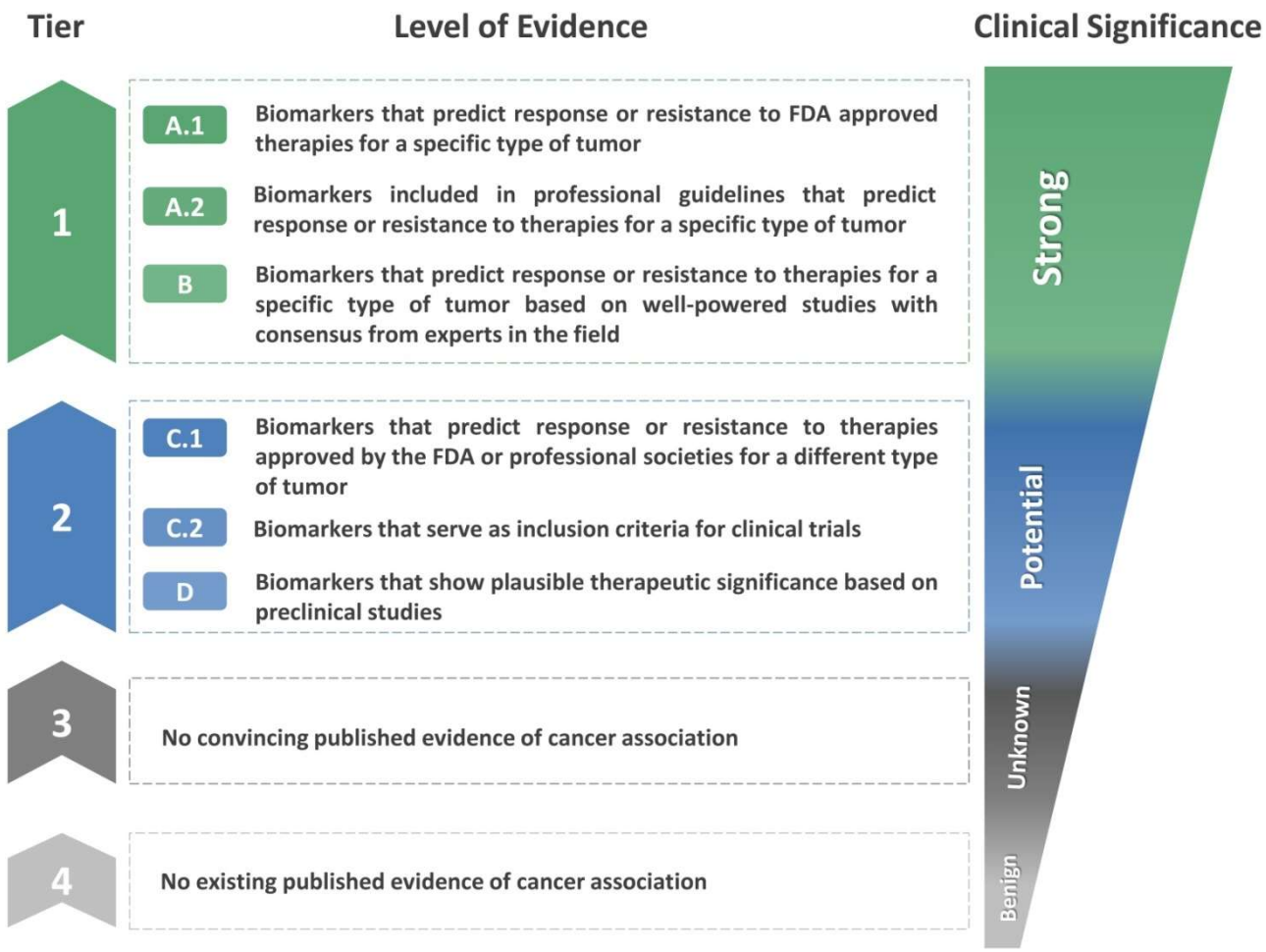

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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