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PRECISION INDIVIDUALIZED MEDICINE

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Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name:	-	**Date Sp. Extracted:**	-
Medical ID:	-	**Req. Physician:**	-
Date Of Birth:	-	**Report No:**	-
Material #1:	PARAFFIN EMBEDDED TISSUE-BLOCK	**Date Received:**	-
Material #2:	-	**Date Of Report:**	-
Sample #1 ID:	-	**Tumor type:**	GLIOBLASTOMA

primeDX - 1021 Unique Genes (38 Fusions) analyzed

1. Report Summary

0	Biomarker related approved therapies for indication	**4**	Biomarker related therapies with potential benefit
0	Biomarker related therapies with potential resistance	**11**	Biomarker related Clinical Trials

2. Clinically Significant Biomarkers*

Biomarker	Result	Approved therapies for indication	Therapies with potential clinical significance or approved in another type of cancer	Therapies with potential resistance	Clinical Trials
PTEN	Exon 6 c.493G>A (p.G165R)	-	Capivasertib+Fulvestrant (2C.1) Everolimus (2C.1) Temsirolimus (2C.1) Sirolimus (2C.1)	-	yes
TP53	Exon 5 c.524G>A (p.R175H)	-	-	-	yes
TERT	c.-146C>T (C250T)	-	-	-	yes
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-
Tumor Mutational Burden (TMB)	1.65 Muts/MB	-	-	-	-
Immunohistochemistry Biomarkers					
PD-L1 expression (Table S2)	TC=40% , IC<1%	Pembrolizumab, Atezolizumab, Nivolumab Durvalumab, Cemiplimab Nivolumab+Ipilimumab		-	-

*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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3. Important biomarkers findings

Gene	Detected Range	Finding (VAF/Copy Number/Germline Mutation)
EGFR	Exon 18	Not detected
	Exon 19	Not detected
	Exon 20(including T790M)	Not detected
	Exon 21	Not detected
ERBB2(HER2)	Copy number gain	Not detected
	Mutation	Not detected
ESR1	Mutation	Not detected
ALK	Rearrangement	Not detected
ROS1	Rearrangement	Not detected
MET	Copy number gain	Not detected
	Exon 14 skipping	Not detected
RET	Rearrangement	Not detected
BRAF	Codon 600 mutation	Not detected
KIT	Exon 9	Not detected
	Exon 11	Not detected
	Exon 13	Not detected
	Exon 17	Not detected
PDGFRA	Exon 12	Not detected
	Exon 18	Not detected
BRCA1	Mutation	Not detected
BRCA2	Mutation	Not detected
KRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
NRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
PIK3CA	Mutation	Not detected
FGFR2	Rearrangement	Not detected
	Mutation	Not detected
FGFR3	Rearrangement	Not detected
	Mutation	Not detected
NTRK1	Rearrangement	Not detected
NTRK2	Rearrangement	Not detected
NTRK3	Rearrangement	Not detected
IDH1	Mutation	Not detected

Note:

1. 'Not detected/-' indicates the corresponding variations were not detected in this tested individual.
2. The genetic variations listed above are covered, but not limited to this list.
3. For a detailed information about listed variants, please refer to the Report Summary and the respective Interpretations sections.

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4. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant		Result	Clinical Interpretation
Biomarkers for predicting efficacy			
Tumor mutation burden (TMB)		TMB-L 1.65	-
Microsatellite instability (MSI)		Stable (MSS)	-
Affect the treatment effect - positive correlation			
PD-L1 amplification		Not detected	-
PBRM1 inactivating mutation Renal clear cell carcinoma)		Not detected	-
MLH1 suspected germline deleterious mutation		Not detected	-
MSH2 suspected germline deleterious mutation		Not detected	-
MSH6 suspected germline deleterious mutation		Not detected	-
PMS2 suspected germline deleterious mutation		Not detected	-
POLE mutation (driver)		Not detected	-
POLD1 mutation (driver)		Not detected	-
Other DNA damage repair (DDR) pathway genes	*ATM* mutation	Not detected	-
	ATR mutation	Not detected	-
	BAP1 mutation	Not detected	-
	BLM mutation	Not detected	-
	BRCA1 mutation	Not detected	-
	BRCA2 mutation	Not detected	-
	BRIP1 mutation	Not detected	-
	CHEK1 mutation	Not detected	-
	CHEK2 mutation	Not detected	-
	ERCC3 mutation	Not detected	-
	ERCC4 mutation	Not detected	-
	ERCC5 mutation	Not detected	-
	FANCA mutation	Not detected	-
	FANCC mutation	Not detected	-
	MRE11A mutation	Not detected	-
	NBN mutation	Not detected	-
	RAD50 mutation	Not detected	-
	RAD51 mutation	Not detected	-
	RAD51B mutation	Not detected	-
	RAD51D mutation	Not detected	-
	RAD54L mutation	Not detected	-
TP53 mutation		Detected	May increase the benefit rate of PD-1/PD-L1 inhibitors
KRAS mutation		Not detected	-
Biomarker/Variant		**Result**	**Clinical Interpretation**

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Affect the treatment effect - negative correlation		
PTEN inactivating mutation	Detected	Increased of resistance risk when treated with PD-1/PD-L1 inhibitors
JAK1 inactivating mutation	Not detected	-
JAK2 inactivating mutation	Not detected	-
B2M inactivating mutation	Not detected	-
EGFR mutation （L858R/EX19del）	Not detected	-
ALK rearrangement	Not detected	-
STK11 inactivating mutation	Not detected	-
KEAP1 inactivating mutation	Not detected	-
11q13 amplification	Not detected	-
MDM2 amplification	Not detected	-
MDM4 amplification	Not detected	-
DNMT3A inactivating mutation	Not detected	-
Indicator affecting prognosis of immune checkpoint inhibitor therapy		
HLA-I Zygosity (At least one of type A, B, C is homozygous)	Not detected	-

Note:

1. Not detected/- indicates the corresponding variation were not detected in this tested individual.
2. The interpretation of the detection results of *PBRM1* inactivating mutations is only applicable to renal clear cell carcinoma.
3. The indicators/gene clinical interpretations listed above are for reference only, and the specific decisions need to refer to professional physician instructions.
4. For a detailed interpretation, showed in Interpretation for biomarker of checkpoint inhibitor.
5. *POLE* and *POLD1* mutations are restricted to currently reported mutations that may lead to hypermutation in tumor, resulting in tumor mutation burden increase.
6. HLA-I results analyzed by the phenotypes of HLA-A, HLA-B and HLA-C loci detected from tumor samples. Due to the lack of control samples, HLA-I typing cannot be accurately analyzed and it is possible that show homozygosity because of the occurrence of HLA-LOH in the tumor tissue.

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5. Interpretations for targeted therapies

Genetic Variation:	*NM_000314.4(PTEN):c.493G>A(p.G165R)* VAF: 61.5%	OncoKB	CIViC	COSMIC
Therapies:	Capivasertib+Fulvestrant,Everolimus,Temsirolimus,Sirolimus (2C.1),			

Gene Description

PTEN (phosphatase and tensin homolog deleted on chromosome ten) is a lipid/protein phosphatase that plays a role in multiple cell processes, including growth, proliferation, survival, and maintenance of genomic integrity. Cancer-associated alterations in PTEN often result in PTEN inactivation and thus increased activity of the PI3K-AKT pathway. Cancer-associated alterations in PTEN often result in PTEN inactivation and thus increased activity of the PI3K-AKT pathway. Germline loss-of-function PTEN mutations occur in approximately 80% of patients with the cancer predisposition syndrome Cowden disease, which is associated with high-penetrance breast and thyroid cancer (PMID: 21430697). Somatic mutations of PTEN occur in multiple malignancies, including gliomas, melanoma, prostate, endometrial, breast, ovarian, renal, and lung cancers. PTEN inactivation is induced by mutations that lead to a loss of expression and is induced to a lesser extent by a loss of heterozygosity. While the most critical duty of PTEN is the negative regulation of the PI3K/mTOR/Akt oncogenic pathway, thus inhibiting uncontrolled cell survival, growth and migration, further crucial antioncogenic functions have been attributed to PTEN. Mutations in PTEN have often been detected in metastases of prostate cancer; however, lower rates of mutations have been found in localized tumors (0 to 20% in different studies) (PMID: 26000489,26000489,17701929).

Variant Description

PTEN G165R lies within the phosphatase tensin-type domain of the Pten protein (UniProt.org). G165R results in suppression of Akt signaling similar to wild-type Pten in cell culture (PMID: 32704382), but results in a loss of phosphatase activity in an in vitro assay and a yeast assay (PMID: 10866302, 29706350), and therefore, is predicted to result in a loss of Pten protein function. Based on the available evidence to date, this variant is likely to be pathogenic.

Targeted Drug Interpretation

Food and Drug Administration approved capivasertib with fulvestrant for adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test. The mTOR inhibitor Everolimus is FDA approved, in combination with the aromatase inhibitor exemestane, to treat postmenopausal women with hormonereceptor- positive, HER2-negative advanced breast cancer. Temsirolimus is an mTOR inhibitor that is FDA approved to treat advanced renal cell carcinoma. These therapies and other mTOR inhibitors are in clinical trials in breast cancer and other solid tumor types. Inhibitors of PI3K and AKT, alone or in combination with other therapies are also in clinical trials in solid tumors. A preclinical study indicates that PIK3CA mutation predicts sensitivity to the PI3K-alpha-specific inhibitor alpelisib, which may have a bigger therapeutic window than pan-PI3K inhibitors The use of everolimus and sirolimus in patients with PTEN-mutant glioblastoma has been examined in clinical trials.

Capivasertib DrugBank

Capivasertib is a serine/threonine kinase inhibitor used to treat hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. On November 17th, 2023, capivasertib, under the brand name TRUQAP, was approved by the FDA for the treatment of adult patients HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more alterations in PIK3CA/AKT1/PTEN gene(s) in combination with fulvestrant.

Fulvestrant DrugBank

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Fulvestrant is a drug treatment of hormone receptor (HR)-positive metastatic breast cancer in post-menopausal women with disease progression following anti-estrogen therapy. It is an estrogen receptor antagonist with no agonist effects, which works both by down-regulating and by degrading the estrogen receptor. While it is used as monotherapy for the treatment of breast cancers, it is also used in combination with for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer For the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy, as monotherapy or in combination with other antineoplastic agents.

Everolimus DrugBank

Everolimus is a derivative of Rapamycin (sirolimus), and works similarly to Rapamycin as an mTOR (mammalian target of rapamycin) inhibitor. It is currently used as an immunosuppressant to prevent rejection of organ transplants. In a similar fashion to other mTOR inhibitors Everolimus' effect is solely on the mTORC1 protein and not on the mTORC2 protein. Everolimus is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole; indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease; indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib; indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery; indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Temsirolimus DrugBank

Temsirolimus is a derivative of sirolimus used in the treatment of renal cell carcinoma (RCC). It was developed by Wyeth Pharmaceuticals under the trade name Torisel. Temsirolimus was approved by the FDA in late May 2007 as well as the European Medicines Agency (EMEA) on November 2007. For the treatment of renal cell carcinoma (RCC). Also investigated for use/treatment in breast cancer, lymphoma (unspecified), rheumatoid arthritis, and multiple myeloma.

Sirolimus DrugBank

A macrolide compound obtained from Streptomyces hygroscopicus that acts by selectively blocking the transcriptional activation of cytokines thereby inhibiting cytokine production. It is bioactive only when bound to immunophilins. Sirolimus is a potent immunosuppressant and possesses both antifungal and antineoplastic properties. For the prophylaxis of organ rejection in patients receiving renal transplants.

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Genetic Variation:	*NM_000546.5(TP53):c.524G>A(p.R175H)*	VAF: 60.9%	OncoKB	CIViC	COSMIC
Therapies:	Under investigation in clinical trials				

Gene Description

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 lung, ovarian, esophageal, colorectal, head and neck and larynx 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).

Variant Description

TP53 p.Arg175His is present in population databases (rs28934578, ExAC 0.001%) and has been observed in individuals and families affected with Li-Fraumeni syndrome, osteosarcoma, breast cancer and ovarian carcinoma (PMID: 8825920, 8164043, 21761402, 22006311, 16401470). ClinVar contains an entry for this variant (Variation ID: 12374). This is a well-studied variant, located in a known mutation hotspot within the central DNA-binding domain of TP53 (PMID: 23263379, 20516128, 24573247, 12007217). It causes not only loss of the tumor suppressor function of the TP53 protein, but also oncogenic gain-of-function (PMID: 23792586, 23263379).

Genetic Variation:	*NM_198253.2(TERT): c.-146C>T (C250T)*	VAF: 32.4%	OncoKB	CIViC	COSMIC
Therapies:	Under investigation in clinical trials				

Gene Description

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity. TERT expression is low or absent in somatic cells; however, telomerase activity is upregulated in a vast majority of tumors and likely contributes to cancer cell immortality (PMID: 9282118). Sequencing of the TERT promoter identified activating mutations in a number of cancer types including melanoma, hepatocellular carcinoma, urothelial carcinoma, medulloblastoma and glioma (PMID: 23530248). Tumors with highly recurrent TERT promoter mutations tend to originate from tissues with lower rates of self-renewal (PMID: 23530248). In addition to promoter mutations, TERT, located on chromosome 5p, is amplified across many cancer types (PMID: 20164920). A comprehensive analysis of a TCGA data set found that among 6835 cancers, 73% expressed TERT. The TERT-expressing cancers were associated with TERTp mutations and with other point mutations, genomic rearrangements, DNA amplifications, or transcript fusions, and these alterations could predict telomerase activity (PMID: 28135248). Regarding glioblastoma, mutations commonly occur at two hotspots, referred to as C228T and C250T, which are mutually exclusive and occur in 80â€“90% of glioblastoma patients (PMID: 23530248, 26061753, 26143636, 26765760, 25681309). Such tumors most frequently have a frontal (PMID: 29650441) or temporal location (PMID: 27230769) and occur more frequently in older patients compared to IDH-mutated (IDH-mut) glioblastoma. Recently, two other TERTp gain-of-function alterations were described: TERTp c.1-100_1-79dup and TERTp c.1-110_1-89. These newly-described alterations occur in less than 1% of glioblastoma IDH-wild type (IDH-wt). The prognostic role of TERTp mutations has not been clearly established since there are numerous confusing factors both clinical such as age, initial surgical procedure, and molecular such as IDH mutations, MGMT methylation status, or EGFR amplification.

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A better understanding of the molecular mechanisms underlying TERTp-mutated glioblastoma could lead to the development of TERT-targeted therapies. Preclinical and clinical trials are ongoing, but no such therapy has yet demonstrated clinical efficiency in glioblastoma patient care.

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6. Interpretation for polymorphism variants related with chemotherapy drugs

Biomarkers associated with treatment response

Drug Classes	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level
5-Fluorouracil (5-Fu), Fluoropyrimidines	5-Fu + Oxaliplatin	*GSTP1*	rs1695	GG	Associated with better response to treatment	2A
Anthracyclines	Epirubicin	*GSTP1*	rs1695	GG	Associated with poorer response to treatment	2A
Aromatase inhibitors	Letrozole, Anastrozole	*CYP19A1*	rs4646	CC	Associated with poorer response to treatment	3
	Anastrozole	*ABCB1*	rs2032582	CC	Associated with poorer response to treatment	3
Cyclophosphamide	Cyclophosphamide	*XRCC1*	rs25487	CC	Associated with better response to treatment	3
	Cyclophosphamide	*SOD2*	rs4880	AG	Associated with moderate response to treatment	2B
	Cyclophosphamide + Epirubicin	*GSTP1*	rs1695	GG	Associated with poorer response to treatment	2A
Methotrexate	Methotrexate	*ATIC*	rs4673993	CC	Associated with better response to treatment	2B
Pemetrexed	Pemetrexed	*MTHFR*	rs1801133	GG	Associated with better response to treatment	3
Platinum-Based Chemotherapy	Carboplatin	*MTHFR*	rs1801133	GG	Associated with poorer response to treatment	2A
	Platinum compounds	*XRCC1*	rs1799782	GG	Associated with poorer response to treatment	NA
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AG	Associated with poorer response to treatment	2B
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*XRCC1*	rs25487	CC	Associated with better response to treatment	2B
Taxanes	Paclitaxel + Cisplatin	*TP53*	rs1042522	CC	Associated with better response to treatment	2B
	Paclitaxel	*ABCB1*	rs2032582	CC	Associated with poorer response to treatment	3
Vinca alkaloids	Vincristine	*ABCB1*	rs1045642	GG	Associated with better response to treatment	3

Biomarkers associated with drug toxicity

Drug Classes	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level
5-Fluorouracil (5-Fu), Fluoropyrimidines	5-Fu or Capecitabine	*DPYD*	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
	5-Fu or Capecitabine	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
	5-Fu + Leucovorin or Tegafur + Leucovorin	*UMPS*	rs1801019	GG	Associated with decreased risk of drug toxicity	2B
	Fluoropyrimidine-based therapy	*DPYD*	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
	Fluoropyrimidine-based therapy	*DPYD*	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
	Fluoropyrimidine-based therapy	*DPYD*	rs3918290	CC	Associated with decreased risk of drug toxicity	1A

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Anthracyclines	Anthracyclines	*CBR3*	rs1056892	AG	Associated with increased risk of drug toxicity	2B
	Epirubicin	*GSTP1*	rs1695	GG	Associated with increased risk of drug toxicity	2A
Capecitabine	Capecitabine-Based Chemotherapy	*MTHFR*	rs1801131	TT	Associated with decreased risk of drug toxicity	2A
	Capecitabine-Based Chemotherapy	*DPYD*	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
	5-Fu or Capecitabine	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
	Capecitabine	*DPYD*	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
	Capecitabine	*DPYD*	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
	Capecitabine	*DPYD*	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Cyclophosphamide	Cyclophosphamide	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
	Cyclophosphamide + Epirubicin	*GSTP1*	rs1695	GG	Associated with increased risk of drug toxicity	2A
Gemcitabine	Gemcitabine	*CDA*	rs2072671	AC	Associated with increased risk of neutropenia and hematologic toxicity	2B
Irinotecan	Irinotecan	*UGT1A1*	rs8175347	6TA/6TA	Associated with decreased risk of drug toxicity	2A
	Irinotecan	*UGT1A1*	rs4148323	GG	Associated with decreased risk of drug toxicity	2A
	Irinotecan	*C8orf34*	rs1517114	GG	Associated with decreased risk of drug toxicity	2B
Methotrexate	Methotrexate	*MTRR*	rs1801394	AG	Associated with increased risk of drug toxicity	2B
	Methotrexate	*ABCB1*	rs1045642	GG	Associated with decreased risk of drug toxicity	2A
Platinum-Based Chemotherapy	Cisplatin	*XPC*	rs2228001	GT	Associated with increased risk of drug toxicity	1B
	Platinum compounds	*GSTP1*	rs1695	GG	Associated with decreased risk of drug toxicity	2A
	Cisplatin, Platinum, Platinum compounds	*ERCC1*	rs3212986	AC	Associated with increased risk of drug toxicity	2B
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AG	Associated with increased risk of drug toxicity	2B
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*XRCC1*	rs25487	CC	Associated with increased risk of drug toxicity	2B

Note:

1. The level of variant-drug associations evidence is based on PharmGKB website, for more detailed information please see http://www.pharmgkb.org/page/clinAnnLevels.

Level 1A: Annotation for a variant-drug combination in a CPIC- or medical society-endorsed pharmacogenomics guideline, or implemented at a PGRN site, or in another major health system;

Level 1B: Annotation for a variant-drug combination in which the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant P-values, and, preferably with a strong effect size;

Level 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely;

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Level 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small;

Level 3: Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association;

Level 4: Annotation based on a case report, non-significant study, or in vitro, molecular, or functional assay evidence only.

2. The variant-drug correlation relationship derived from multiple independent studies, therefore, the interpretations of the same class of drug for the tested individual may be inconsistent. The final drug instruction needs to combine with the specific clinical situation.

3. The detection results are only based on the analysis of tumor samples and lack of control, the results of some loci may be specific to tumor tissues due to factors such as loss of heterozygosity.

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7. Other Genomic findings*

***Note**: In this section, damaging variants in genes without clinical actionability or without convincing evidence of cancer association are reported.

Genetic Variation:	-
Therapies:	-

8. Variants of Uncertain Significance (VUS)

The clinical significance of the variants listed in the below table is uncertain at this time. Until the uncertainty is resolved, these variants should not be used in clinical management decisions.

Gene	Variant	Interpretation
ERCC1	c.442C>G (p.L148V)	ERCC1 (ERCC Excision Repair 1, Endonuclease Non-Catalytic Subunit) functions in the nucleotide excision repair pathway, and is required for the repair of DNA lesions (PMID: 26074087, 32099408). ERCC1 expression level has been correlated with response to platinum-based therapies in various tumor types, including ovarian, non-small cell lung, and head and neck cancers (PMID: 26804248, 26179868, 26870207). A missense alteration in ERCC1,p.L148V, is identified in this case. This alteration is of uncertain clinical significance. (ACMG & Clingen classification)

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9. Suspected Germline variants

Gene	Transcript	Exon	c.HGVS	p.HGVS	Zygosity	Classification
-	-	-	-	-	-	-

Note:

1. - indicates no relevant variations were detected in this test.
2. When detected, pathogenic or likely pathogenic variants are reported. Variants of uncertain significance or variants that are benign or likely benign are not reported.
3. The somatic or germline origin of the alteration identified cannot be verified due to the absence of control sample analysis (blood or saliva).
4. Variant classification interpretation is based on ACMG (American College of Medical Genetics and Genomics) guidelines for the interpretation of germline sequence variants (PMID:25741868).

10. HLA-I Polymorphism variation

Somatic HLA-I Zygosity

The anti-tumor activity of immune checkpoint inhibitor therapy is related to CD8+ T cells. The recognition of cancer cells by CD8+ T cells is achieved by HLA-I (human leukocyte antigen class I) molecules presenting tumor antigens.

HLA alleles have the characteristics of polymorphism and codominance. HLA-I loci subdivided into HLA-A, HLA-B and HLA-C. When a patient's HLA-I is homozygous at least one locus, this patient is expected to present less and less diverse tumor neoantigens to T cells compared to patients who are heterozygous at all three loci. In two cohorts, patients with heterozygous HLA-I showed longer OS than those with homozygous alleles, cohort1: HR=1.4 (1.02-1.9), P-value=0.036; cohort2: HR=1.31 (1.03- 1.7), P-value=0.028; among 32 patients with heterozygous HLA-I but at least one locus with LOH (loss of heterozygosity), patients with HLA-I LOH have a higher survival risk (P = 0.05, HR = 1.60, 95% CI 1.03-2.43), and these patients mainly with low mutation burden (P = 0.0006, HR = 3.68, 95% CI 1.64-8.23) (PMID:29217585).

Gene	Test Content	Result
HLA-A	Zygosity	Heterozygosity
HLA-B	Zygosity	Heterozygosity
HLA-C	Zygosity	Heterozygosity

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11. Clinical Trials to consider

PTEN associated clinical trials

NCT05554380	Phase 2
Title	Study of Chemotherapy Plus Ipatasertib for People With Solid Tumors With PTEN/AKT Mutations, A ComboMATCH Treatment Trial
Treatment	Biopsy| Biospecimen Collection| Computed Tomography| Ipatasertib| Magnetic Resonance Imaging| Paclitaxel
Location	United States, Puerto Rico

NCT02029001	Phase 2
Title	Adapting Treatment to the Tumor Molecular Alterations for Patients With Advanced Solid Tumors: MyOwnSpecificTreatment
Treatment	Nilotinib (400 mg BID)| Everolimus (10 mg QD)| Sorafenib (400 mg BID)| Lapatinib (1500 mg QD)| Pazopanib (800 mg QD)| Olaparib (300 mg BID)| Durvalumab + Tremelimumab
Location	France

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

NCT05432518	EARLY_Phase 1
Title	Pilot Trial for Treatment of Recurrent Glioblastoma
Treatment	Afatinib| Dasatinib| Palbociclib| Everolimus| Olaparib
Location	Canada

NCT04997993	Phase 1
Title	Leflunomide in Patients With PTEN-Altered Advanced Solid Malignancies
Treatment	Leflunomide
Location	United States

Press here for a live search of clinical trials for PTEN

TERT associated clinical trials

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NCT06622434	Phase 1|Phase 2
Title	New Adjuvant Vaccine in Glioblastoma, a Phase 1/2a Study
Treatment	immunization
Location	France

NCT04309552	Phase 1
Title	Tumor Hypoxia and Proliferation in Patients With High-Grade Glioma
Treatment	18F-FMISO PET| 18F-FLT PET
Location	United States

Press here for a live search of clinical trials for TERT

TP53 associated clinical trials

NCT05631886	Phase 1
Title	Combination of CAR-DC Vaccine and ICIs in Malignant Tumors
Treatment	TP53-EphA-2-CAR-DC| Abraxane| Cyclophosphamide| anti-PD-1 antibody| Anti-CTLA4 Monoclonal Antibody
Location	China

NCT05432518	EARLY_Phase 1
Title	Pilot Trial for Treatment of Recurrent Glioblastoma
Treatment	Afatinib| Dasatinib| Palbociclib| Everolimus| Olaparib
Location	Canada

NCT05877599	Phase 1
Title	A Study of NT-175 in Adult Subjects with Unresectable, Advanced, And/or Metastatic Solid Tumors That Are Positive for HLA-A*02:01 and the TP53 R175H Mutation
Treatment	Autologous, engineered T Cells targeting TP53 R175H
Location	United States

NCT06329206	Phase 1
Title	A Phase Ia/Ib Study of GH2616 Tablet in Subjects With Advanced Solid Tumors
Treatment	GH2616 Tablets

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Location	China

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12. Appendix

12.a. Immune checkpoint inhibitors predictive biomarkers

Tumor Mutation Burden (TMB)

Tumor mutation burden (TMB) refers to the number of somatic mutations in the coding region, usually indicated as the total number of somatic mutations within each MB tumor genome region. The clinical utility of TMB as a predictive biomarker for anti-PD1 immunotherapy has been established in the KEYNOTE-158 trial which led to the site-agnostic FDA-approval of pembrolizumab for metastatic/untreatable solid tumors with tissue TMB value≥10muts/MB (PMID: 32919526). The results of TMB are divided into three types: TMB-H, which means high tumor mutation burden; TMB-L, which means low tumor mutation burden; TMB-U, means that the sample does not meet the TMB assessment conditions (the tissue or pleural and ascites sample may fail to pass the TMB indicator calculation quality index due to low DNA quality and/or low tumor cell content).

Table S1. TMB interpretation and cut-offs.

Tumour Type	Immunotherapy agent	Study/Trial	TMB high cut-off	Type of benefit
TMB assessed through a multi-gene assay				
NSCLC (1L or 2L)	Anti PD-L1	FIR/BIRCH [1]	**13.5 Muts/Mb (1L)** **17.1 Muts/Mb (2L)**	ORR, OS, PFS
NSCLC (2L)	Anti PD-L1	POPLAR [1]	**15.8 Muts/Mb**	ORR, OS, PFS
NSCLC (2L)	Anti PD-L1	POPLAR/OAK [2-3]	**16 Muts/Mb (blood)**	OS, PFS
NSCLC (1L)	Anti PD-L1	BFAST and B-F1RST [4-6]	**16 Muts/Mb (blood)**	DOR, ORR, PFS, OS
NSCLC	Anti PD-L1	Rizvi *et al*, 2018 [7]	**7.4 Muts/Mb**	DCB, ORR, PFS
NSCLC	Anti PD-1	Singal *et al,* 2017 [8]	**20 Muts/Mb**	OS
NSCLC (1L)	Anti PD-1/Anti-CTL4	CheckMate 227 [9]	**10 Muts/Mb**	ORR, PFS
NSCLC (1L)	Anti PD-1/Anti-CTL4	CheckMate 568 [10]	**10 Muts/Mb**	ORR, PFS
NSCLC	various immunotherapies	Rozenblum *et al*, 2017 [11]	**9.6 Muts/Mb**	ORR
Melanoma	various immunotherapies	Johnson *et al*, 2016 [12]	**23.1 Muts/Mb**	ORR, OS, PFS
Bladder (1L or 2L)	Anti PD-L1	IMvigor 210 [13-14]	**16 Muts/Mb**	ORR, OS
Bladder (2L)	Anti PD-L1	IMvigor 211 [15]	**9.65 Muts/Mb**	OS
Multiple solid tumours	various immunotherapies	Goodman *et al*, 2017 [16]	**20 Muts/Mb**	ORR, OS, PFS
Multiple solid tumours (2L)	various immunotherapies	Bonta *et al*, 2017 [17]	**8 Muts/Mb**	ORR
Multiple solid tumours	anti-CTLA-4 or anti-PD-1	Samstein *et al*, 2019 [18]	**varies across cancer types**	OS
mTNBC	Anti PD-1	KEYNOTE-119 [19]	**10 Muts/Mb**	ORR, OS
All solid tumours	Anti PD-1	KEYNOTE-158 [20]	**10 Muts/Mb**	ORR

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Microsatellite Instability (MSI)

MSI (microsatellite instability, MSI) refers to the phenomenon that the sequence of microsatellites increases or decreases. Microsatellite (MS), also called Short Tandem Repeats (STRs) or Simple Sequence Repeat (SSRs), consists of repeated sequences of 1-6 nucleotides. This report uses NGS panel detection and is based on the 1021 Panel platform. The results of MSI are divided into three types: MSI-H, which means microsatellites are highly unstable; MSS, which means microsatellites are stable; MSI-U, which means that the sample does not meet the MSI evaluation conditions (tissues or pleural fluid samples may not have passed the MSI indicator calculation quality control due to the low DNA and/or content of tumor cells).

FDA approved pembrolizumab for solid tumors with MSI-H or dMMR (highly unstable microsatellites or MMR defects) and approved for MSI-H or dMMR colorectal cancer as the first-line treatment (PMID: 35680043, 33264544). FDA approved nivolumab for the treatment of children or adults who have progressed after 5-FU/oxaliplatin/irinotecan treatment with MSI-H or dMMR metastatic colorectal cancer. The NCCN clinical practice guidelines for colorectal cancer indicate that pembrolizumab/nivolumab can be used for the treatment of patients with dMMR/MSI-H colorectal cancer (PMID: 28734759).

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PD-L1 expression

Table S2. PD-L1 interpretation and cut-offs.

Cancer type	Therapy	PD-L1	Cut-off	We report
Non-Small Cell Lung Cancer (NSCLC)	Anti-PD-1 [1-4]	VENTANA (SP263)	1L TPS ≥ 50% 2L TPS ≥ 1%	%TPS
	Anti-PD-L1 [5-7]	VENTANA (SP263)	2L TPS ≥ 1%	%TPS
		VENTANA (SP263)	1L TPS ≥ 50%	%TPS
		VENTANA (SP142)	1L TC ≥ 50% or IC ≥ 10%	%TC/%IC
	Anti-PD-1 + Anti-CTLA-4 [8]	VENTANA (SP263)	1L TPS ≥ 1%	%TPS
Urothelial Cancer (UC)	Anti-PD-1 [9]	Dako 22C3	1L CPS ≥ 10	CPS
	Anti-PD-1 [19]	VENTANA (SP263)	1L TC≥ 1%	%TC
	Anti-PD-L1 [10]	VENTANA (SP142)	2L IC ≥ 5%	%IC
Triple Negative Breast Cancer (TNBC)	Anti-PD-L1 [11]	VENTANA (SP142)	1L IC ≥ 1%	%IC
	Anti-PD-1 [12] + chemotherapy	Dako 22C3	1L CPS ≥ 10	CPS
Cervical cancer	Anti-PD-1 [16]	Dako 22C3	2L CPS ≥ 1	CPS
Head and Neck Squamous Cell Carcinoma (HNSCC)	Anti-PD-1 [14,15]	Dako 22C3	1L CPS ≥ 1 2L TPS ≥ 50%	CPS and %TPS
Gastric cancer (adenocarcinoma) (HER-2 Positive)	Anti-PD-1 [13,20]	Dako 22C3	1L CPS ≥ 1	CPS
Gastric cancer (adenocarcinoma) (HER-2 Negative)	Anti-PD-1 [18, 20]	Dako 22C3	1L CPS ≥5	CPS
Oesophageal (Adenocarcinoma and squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 10	CPS
Oesophageal (squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L TC ≥ 1%	%TC
Oesophageal (Adenocarcinoma) (HER-2 Negative)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 5	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Negative)	Anti-PD-1 [17,20] *Depending on PD-L1 inhibitor	Dako 22C3	1L CPS ≥ 5 or* 1L CPS ≥ 10	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Positive)		Dako 22C3	1L CPS ≥ 1	

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TPS: Tumor Proportion Score = $\frac{\#\text{PD-L1 positive tumor cells}}{Total\ \#PD\text{-}L1\ positive + PD\text{-}L1\ negative\ tumor\ cells} \times 100$

TC: tumor cell

CPS: Combined Positive Score = $\frac{\#\text{PD-L1 staining cells (tumor cells,lymphocytes,macrophages)}}{Total\ \#\ of\ viable\ tumor\ cells} \times 100$

IC: immune cell

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

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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 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.

Atezolizumab

DrugBank

Atezolizumab is a humanized monoclonal antibody used to prevent the interaction of PD-L1 and PD-1, removing inhibition of immune responses seen in some cancers. This medication is reserved for patients whose tumors express PD-L1, cannot receive platinum based chemotherapy, or whose tumors do not respond to platinum based chemotherapy. Atezolizumab was granted FDA approval on 18 October 2016. Atezolizumab is indicated to treat locally or advanced metastatic urothelial carcinoma in patients ineligible for cicplatin-containing chemotherapy with tumors expressing PD-L1, in patients ineligible for cisplatin-containing chemotherapy irrespective of PD-L1, have disease progression following platinum containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant chemotherapy. Atezolizumab is also indicated first line for non small cell lung cancer in combination with bevacizumab, paclitaxel, and carboplatin with no EGFR or ALK genomic abnormalities. It can be used in patients with disease progression during or after platinum containing chemotherapy even if they have EGFR and ALK abnormalities. Atezolizumab is indicated in combination with paclitaxel protein-bound to treat locally advanced or metastatic triple negative breast cancer expressing PD-L1. Finally, atezolizumab is indicated in combination with carboplatin and etoposide as first line treatment for extensive stage small cell lung cancer.

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

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(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.

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) â‰¥ 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.

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.

Ipilimumab

DrugBank

Ipilimumab is a fully humanized IgG1 monoclonal antibody that blocks cytotoxic T lymphocyte antigen-4 (CTLA-4). Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is an inhibitory molecule that competes with the stimulatory CD28 for binding to B7 on antigen presenting cells.

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CTLA-4 and CD28 are both presented on the surface of T-cells3 Blocking CTLA-4 removes an inhibitory signal from reducing the activity of T lymphocytes. Ipilimumab was granted FDA approval on 25 March 2011. Ipilimumab is indicated to treat unresectable or metastatic melanoma, as an adjuvant in the treatment of cutaneous melanoma, to treat microsatellite-high or mismatch repair deficient metastatic colorectal cancer, or to treat hepatocellular carcinoma. Ipilimumab with nivolumab is indicated to treat advanced renal cell carcinoma. Additionally, FDA has approved the use of nivolumab plus ipilimumab given with 2 cycles of platinum-doublet chemotherapy as a first-line treatment for adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.

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12.c. Methodology

DNA was extracted from the sample under investigation using the MagMax Total Nucleic Acid Isolation Kit (ThermoFisher). A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology Multi-Gene Variant Assay (GenePlus) which is a qualitative in vitro diagnostic test that detects variants in 1021 tumor-related genes and gene rearrangements / fusions in 38 genes. Sequencing was carried out on an MGI sequencing platform (DNBSEQ-G400). The analysis includes the entire exon regions of 312 genes, introns/promoters/fusion breakpoint regions of 38 genes and partial coding exons of 709 genes. The test also reports 30+ immune response biomarkers, including Tumor Mutational Burden (TMB) score and Microsatellite Instability (MSI) status.

Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system.

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 100%. Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 100%.

Limit of Detection (LoD): The limit of detection (LoD) of this assay is listed in the table below. The LoD is based on as low as 50 ng of gDNA input for library preparation. The assay can also be used to test the microsatellite instability (MSI) with a tumor cell content as low as 10%.

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Insertions/deletions (Indel)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Fusion (or rearrangement)	VAF ≥2%

PD-L1 expression by IHC

The level of expression of the PD-L1 protein is defined as A. the percentage of viable tumor cells (TC) showing partial or complete membrane staining at any intensity and B. as the percentage of Tumor Infiltrating Immune Cells (IC) showing staining at any intensity.

VENTANA SP263 (CE IVD) by IHC is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone SP263, intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissue, on a VENTANA BenchMark Series automated staining instrument. The specimen submitted for testing should contain at least 100 viable TC to be considered adequate for evaluation.

Disclaimer

1. This test is mainly used to assist clinical decision-making and the result does not represent clinical decision.
2. The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
3. The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: https://clinicaltrials.gov/.

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4. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
5. 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), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).
6. Translocations detected at the DNA level are confirmed by an RNA-based NGS method.
7. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

Limitations

1. Limited tissue detection may not represent the whole DNA variations of lesions because of tumor heterogeneity.
2. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
3. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
4. The detection could not distinguish between somatic mutations and germline mutations effectively without control sample analysis.
5. Fraction of base quality ≥ Q30: 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. 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.

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12.d. Quality Control Results

Quality Control Index		Result	Criterion
Sequencing Quality Assessment	Average effective sequencing depth[1]	1011	≥ 500
	Fraction of target covered with ≥ 50x[2]	100%	≥99%
	Fraction of base quality ≥ Q30[3]	94%	≥80%
Tumor cell content [4]		85%	>20%
Overall Assessment[5]		PASS	

Note :

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. Fraction of target covered with ≥ 50x: The proportion of bases that sequencing depth reach or above 50x on target, this index reflecting the coverage uniformity of sequencing.
3. Fraction of base quality ≥ Q30: The proportion of base quality in sequencing data that reach or above Q30, that is the probability of base recognition accuracy rate exceeds 99.9%.
4. Overall A tumor cell content percentage of ≥ 20% is recommended for the efficient detection of somatic alterations in the sample analyzed.
5. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.

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12.e. Genes Analyzed

312 genes including all exon regions and available for detecting SNV / Indel / CNV									
ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	APC	AR	ARAF	ARID1A
ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2
AXL	B2M	BAP1	BARD1	BCL2	BCL2L1	BCOR	BLM	BMPR1A	BRAF
BRCA1	BRCA2	BRD4	BRIP1	BTK	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD274	CDC73	CDH1	CDK12	CDK4	CDK6	CDK8
CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP
CRKL	CSF1R	CTCF	CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDR1	DDR2
DICER1	DNMT3A	DOT1L	EGFR	EIF1AX	EMSY	EP300	EPAS1	EPCAM	EPHA2
EPHA3	EPHA5	EPHB1	EPHB6	ERBB2	ERBB3	ERBB4	ERCC1	ERCC3	ERCC4
ERCC5	ERG	ERRFI1	ESR1	EXT1	EXT2	EZH2	FAM123B	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FANCM	FAS	FAT1	FAT2
FBXW7	FGF19	FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN
FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXP1	FUBP1	GALNT12	GATA3	GNA11
GNAQ	GNAS	GRIN2A	GRM3	HDAC1	HGF	HNF1A	HOXB13	HRAS	IDH1
IDH2	IFNG	IFNGR1	IGF1R	IKBKE	IKZF1	IL7R	INPP4B	IRF2	IRS2
JAK1	JAK2	JAK3	JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT
KRAS	LRP1B	MAF	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAPK1	MAX	MCL1
MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLH3	MLL
MLL2	MLL3	MPL	MRE11A	MS4A1	MSH2	MSH3	MSH6	MST1R	MTOR
MUTYH	MYC	MYCL1	MYCN	MYD88	NBN	NCOR1	NF1	NF2	NFE2L2
NFKB1A	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NSD1	NTHL1	NTRK1
NTRK2	NTRK3	PALB2	PARK2	PARP1	PAX5	PBRM1	PCK1	PDCD1	PDCD1LG2
PDGFRA	PDGFRB	PDK1	PIK3CA	PIK3CB	PIK3CG	PIK3R1	PIK3R2	PMS1	PMS2
POLD1	POLE	POT1	PPP2R1A	PRDM1	PRKAR1A	PTCH1	PTCH2	PTEN	PTPN11
PTPRD	RAC1	RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1
RARA	RB1	RBM10	RECQL	RECQL4	RET	RHOA	RICTOR	RINT1	RNF43
ROS1	RPTOR	RUNX1	SDHA	SDHAF2	SDHB	SDHC	SDHD	SERPINB3	SERPINB4
SETD2	SF3B1	SLX4	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1
SOX2	SOX9	SPOP	SRC	STAG2	STAT3	STK11	SUFU	SYK	TBX3
TCF7L2	TERC	TET2	TGFBR2	TMEM127	TMPRSS2	TNFAIP3	TNFRSF14	TOP1	TOP2A
TP53	TSC1	TSC2	TSHR	U2AF1	VEGFA	VHL	WRN	WT1	XPO1
XRCC2	ZMAT3								

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38 genes including specific intron, promoter and fusion breakpoint regions and available for detecting gene rearrangement or fusion									
ALK	BCL2L11	BRAF	BRCA1	BRD4	CD74	EGFR	EML4	ERG	ETV6
EZR	FGFR1	FGFR2	FGFR3	KIF5B	KIT	MAML2	MET	MSH2	MYC
MYCL1	NCOA4	NOTCH2	NTRK1	NTRK2	NTRK3	PDGFRA	RAF1	RET	ROS1
RSPO2	SDC4	SLC34A2	TERT	TFE3	TMPRSS2	TPM3	PMS2		
709 genes including partial exon regions and available for detecting SNV / Indel									
ABCA13	ABCB1	ABCC1	ABCC11	ABCC2	ABCG2	ABL2	ACACA	ACIN1	ACTB
ACTG1	ACTG2	ACVR2A	ACVRL1	ADAM29	ADAMTS5	ADCY1	AFF1	AFF2	AFF3
AHNAK	AKAP9	ALB	AMOT	ANGPT1	ANK3	ANKRD11	ANKRD30A	ANKRD30B	APEX1
APOBEC3B	ARAP3	ARFGEF1	ARFGEF2	ARHGAP29	ARHGAP35	ARID4B	ARID5B	ARNT	ASCL4
ASH1L	ASMTL	ASPM	ASTN1	ASXL2	ATIC	ATP11B	ATP12A	ATP1A1	ATP2B3
BAZ2B	BBC3	BBS9	BCAS1	BCL10	BCL11A	BCL11B	BCL2A1	BCL2L11	BCL3
BCL6	BCL9	BCORL1	BCR	BIRC3	BMPR2	BNC2	BPTF	BRD2	BRD3
BRSK1	BRWD1	BTLA	BUB1	C15orf23	C15orf55	C1QA	C1S	C3orf70	C7orf53
C8orf34	CACNA1E	CADM2	CALR	CAMTA1	CASP1	CASQ2	CBLB	CBR1	CBR3
CCDC168	CCNA1	CCNB3	CCT3	CCT5	CCT6B	CD22	CD33	CD5L	CD74
CDA	CDH11	CDH18	CDH23	CDK13	CHD1	CHD1L	CHD4	CHD6	CHD8
CHD9	CHFR	CHI3L1	CHN1	CIITA	CLDN18	CLP1	CLSPN	CLTC	CNOT3
CNOT4	CNTN1	CNTN5	CNTNAP1	CNTNAP5	COL1A1	COL2A1	COL5A1	COL5A2	COL5A3
COPS2	CPS1	CRIPAK	CRLF2	CRNKL1	CRTC1	CSF1	CSF3R	CSMD1	CSMD3
CSNK1A1	CSNK1G3	CTLA4	CTNNA2	CTNND1	CUX1	CXCR4	CYBA	CYP19A1	CYP1A1
CYP1B1	CYP2A13	CYP2C8	CYP2D6	CYP3A4	CYP3A5	DCC	DDX3X	DDX5	DEK
DHX35	DHX9	DIAPH1	DIS3L2	DLC1	DMD	DNAH6	DNAJB1	DNM2	DNMT1
DNMT3B	DOCK2	DOCK7	DPYD	DRGX	DTX1	DUSP22	DYSF	E2F3	EBF1
ECT2L	EED	EEF1A1	EGFL7	EGR3	EIF2AK3	EIF2C3	EIF3A	EIF4A2	EIF4G3
ELAC2	ELF1	ELF3	ELMO1	ELN	EME2	EMID2	EML4	EPC1	EPHA1
EPHA4	EPHA7	EPHB2	EPHB4	EPOR	EPPK1	EPS15	ERBB2IP	ERCC2	ESR2
ETS1	ETV1	ETV5	ETV6	EWSR1	EZR	F8	FAM131B	FAM135B	FAM157B
FAM46C	FAM5C	FAP	FASLG	FAT3	FAT4	FCGR1A	FCGR2A	FCGR2B	FCGR3A
FCRL4	FGF10	FGF12	FGF14	FGF23	FGF6	FLG	FLI1	FLNC	FMN2
FN1	FNDC4	FOXA2	FOXO1	FOXO3	FOXQ1	FRMPD4	FUS	FXR1	FYN
FZD1	G3BP1	G3BP2	GAB2	GABRA6	GATA1	GATA2	GFRAL	GIGYF1	GKN2
GLB1L3	GLI1	GLI2	GLI3	GMPS	GNA13	GNG2	GPC3	GPR124	GPS2
GPX1	GRB7	GSK3B	GSTM5	GSTP1	GUSB	H3F3A	H3F3B	H3F3C	HCLS1
HCN1	HDAC4	HDAC9	HECW1	HEY1	HIST1H1C	HIST1H1D	HIST1H1E	HIST1H2AC	HIST1H2AG
HIST1H2AL	HIST1H2AM	HIST1H2BC	HIST1H2BD	HIST1H2BJ	HIST1H2BK	HIST1H2BO	HIST1H3B	HIST1H3C	HIST1H3D

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HIST1H3F	HIST1H3G	HIST1H3H	HIST1H3I	HIST1H4I	HIST3H3	HLA-A	HLA-B	HLA-C	HLF
HMCN1	HNF1B	HNRPDL	HOXA11	HOXA13	HOXA3	HOXA9	HOXC13	HOXD11	HOXD13
HSD3B1	HSP90AA1	HSP90AB1	HSPA8	HSPD1	HSPH1	ICK	ICOSLG	ID3	IFITM3
IGF1	IGF2	IGF2R	IGLL5	IKZF2	IKZF3	IL10	IL1RAPL1	IL21R	IL6
IL6ST	IMPG1	ING1	INHBA	INPP4A	INPPL1	INSR	IRF4	IRF6	IRS1
ITGB3	ITK	ITSN1	JARID2	KALRN	KAT6A	KAT6B	KCNJ5	KCNQ2	KDM2B
KEL	KIF5B	KLF4	KLHL6	KLK1	KRTAP5-5	L3MBTL1	LAMA2	LATS1	LATS2
LCP1	LEF1	LGALS8	LIFR	LPHN2	LPP	LRP2	LRP4	LRP5	LRP6
LRRC7	LRRK2	LYN	LZTS1	MACF1	MAD1L1	MAGI2	MAML2	MAML3	MAP3K13
MAPK3	MCC	MCM3	MDC1	MECOM	MEF2C	MGA	MIB1	MIOS	MKL1
MLL4	MLLT3	MMP11	MMP2	MN1	MNDA	MNX1	MSH4	MSN	MSR1
MTHFR	MTRR	MUC5B	MYH11	MYH14	MYH9	MYO3A	MYOD1	NAP1L1	NAV3
NCAM2	NCF2	NCF4	NCK1	NCOA3	NCOA4	NCOR2	NCSTN	NDUFA13	NFATC4
NFE2L3	NKX3-1	NLRC3	NOD1	NOS3	NOTCH4	NQO1	NR1I2	NR2F2	NR4A2
NRG1	NRP2	NRXN1	NTM	NUMA1	NUP107	NUP210	NUP93	NUP98	OBSCN
OGDH	OMD	OPCML	OR11G2	OR2T4	OR4A15	OR4C6	OR5L2	OR6F1	P2RY8
P4HB	PABPC1	PABPC3	PAG1	PAK1	PAK3	PASK	PAX3	PAX7	PC
PCDH18	PCSK6	PCSK7	PDCD11	PDE4DIP	PDGFB	PDILT	PER1	PGR	PHF1
PHF6	PIK3C2A	PIK3C2B	PIK3C2G	PIK3C3	PIM1	PKD1L2	PKHD1	PLAG1	PLCB1
PLCG1	PLCG2	PLK1	PLXNA1	PLXNB2	PNRC1	POLQ	POM121	POM121L12	POU2AF1
PPM1D	PPP1R17	PPP6C	PRDM16	PREX2	PRF1	PRKAA1	PRKCB	PRKCI	PRKDC
PRRX1	PRX	PSG2	PSIP1	PSMB1	PSMB5	PTGS1	PTGS2	PTPN13	PTPN2
PTPRB	PTPRK	PTPRO	PTPRS	PTPRT	PTPRU	RAB35	RAC2	RAD21	RAD54B
RANBP2	RASA1	RASGRP1	RBL1	REL	RELN	RFC1	RGS3	RHEB	RHOH
RHOT1	RIT1	RNASEL	ROBO1	ROBO2	ROBO3	ROCK1	RPGR	RPS6KB1	RPS6KB2
RSPO2	RSPO3	RUNX1T1	RUNX2	RXRA	RYR1	RYR2	SBDS	SCUBE2	SDC4
SEC31A	SEMA3A	SEMA3E	SEMA6A	SERPINA7	SETBP1	SETDB1	SF1	SF3A1	SFPQ
SGCZ	SGK1	SH2B3	SH2D1A	SH3PXD2A	SHH	SI	SIN3A	SLC16A1	SLC1A2
SLC22A16	SLC22A18	SLC22A2	SLC22A3	SLC34A2	SLCO1B3	SLIT1	SLIT2	SMARCD1	SMARCE1
SMC1A	SMC1B	SNCAIP	SNTG1	SNX29	SOD2	SOS1	SOX10	SOX17	SPEN
SPRR3	SPSB4	SPTA1	SRD5A2	SRGAP1	SRGAP3	SRSF2	SRSF7	STAG1	STAT1
SUCLG1	SUCLG2	SULT1A1	SUZ12	SVEP1	SYNCRIP	SYNE1	TAF1	TAF15	TAF1L
TAL1	TBL1XR1	TBX15	TBX22	TCEB1	TCF12	TCF3	TCF4	TCL1A	TEC
TENM3	TERT	TET1	TFDP1	TFDP2	TFE3	TGFBR1	THBS2	TJP1	TLE1
TLL2	TLR4	TLX3	TMEM132D	TNFSF11	TNN	TP53BP1	TP63	TP73	TPM3
TPR	TRAF2	TRAF7	TRIM24	TRIM58	TRIO	TRPC5	TRRAP	TSHZ2	TSHZ3
TTF1	TUBA3C	TUBB3	TUSC3	TXNIP	TYMS	TYR	UBE2D2	UBR5	UGT1A1

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UMPS	UPF3B	USH2A	USP6	USP8	VEZF1	VIM	VTCN1	WASF3	WDR90
WDTC1	WHSC1	WHSC1L1	WIPF1	WNK1	WNT5A	WSCD2	WWOX	WWP1	WWP2
XIAP	XPC	XRCC1	XRCC3	YAP1	YY1AP1	ZBTB16	ZC3H11A	ZFHX3	ZFP36L1
ZFP36L2	ZFPM2	ZIC3	ZNF217	ZNF384	ZNF521	ZNF638	ZNF750	ZNF804B	
36 HRR genes analyzed									
ATM	ATR	ATRX	BAP1	BARD1	BLM	BRCA1	BRCA2	BRIP1	CDK12
CHEK1	CHEK2	C11orf30	ERCC1	FAM175A	FANCA	FANCC	FANCD2	FANCE	FANCF
FANCG	FANCL	FANCM	MRE11	NBN	PALB2	RAD50	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RECQL	RECQL4	WRN				

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12.f. Levels of Evidence for Genomic Biomarkers

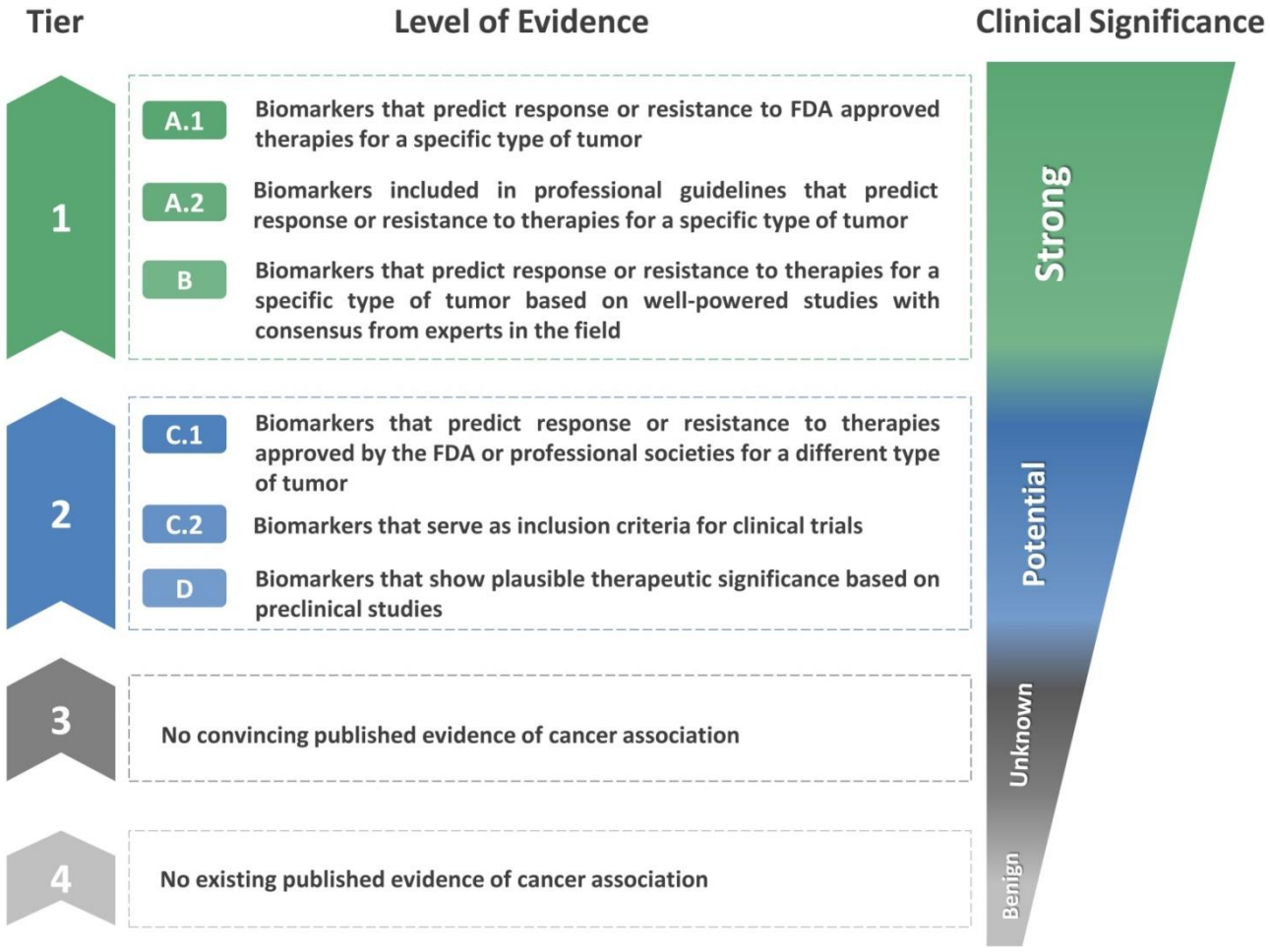

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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SAMPLE INFORMATION

Name:	-	**Date Sp. Extracted:**	-
Medical ID:	-	**Req. Physician:**	-
Date Of Birth:	-	**Report No:**	-
Material #1:	PLASMA	**Date Received:**	-
Material #2:	WHOLE PERIPHERAL BLOOD	**Date Of Report:**	-
Sample #1 ID:	-	**Tumor type:**	LUNG CANCER

primeDX - 1021 Unique Genes (38 Fusions) analyzed

1. Report Summary

6	Biomarker related approved therapies for indication	**1**	Biomarker related therapies with potential benefit
0	Biomarker related therapies with potential resistance	**35**	Biomarker related Clinical Trials

2a. Clinically Significant Biomarkers*

Biomarker	Result	Approved therapies for indication	Therapies with potential clinical significance or approved in another type of cancer	Therapies with potential resistance	Clinical Trials
ALK fusion	EML4(13)-ALK(20)	Ensartinib (1A.1) Lorlatinib (1A.1) Brigatinib (1A.1) Ceritinib (1A.1) Alectinib (1A.1) Crizotinib (1A.1)	-	-	yes
FGFR3	Exon 7 c.746C>G (p.S249C)	-	Erdafitinib (2C.1)	-	yes
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-
Tumor Mutational Burden (TMB)	8.64 Muts/MB	-	-	-	-

*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

2b. Germline variants

Gene	Finding	Clinical Significance	Zygosity
No pathogenic/likely pathogenic variant was detected			

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3. Important biomarkers findings

Gene	Detected Range	Finding (VAF/Copy Number/Germline Mutation)
EGFR	Exon 18	Not detected
	Exon 19	Not detected
	Exon 20 (including T790M)	Not detected
	Exon 21	Not detected
ERBB2 (HER2)	Copy number gain	Not detected
	Mutation	Not detected
ESR1	Mutation	Not detected
ALK	Rearrangement	***EML4(13)-ALK(20) (3.8%)***
ROS1	Rearrangement	Not detected
MET	Copy number gain	Not detected
	Exon 14 skipping	Not detected
RET	Rearrangement	Not detected
BRAF	Codon 600 mutation	Not detected
KIT	Exon 9	Not detected
	Exon 11	Not detected
	Exon 13	Not detected
	Exon 17	Not detected
PDGFRA	Exon 12	Not detected
	Exon 18	Not detected
BRCA1	Mutation	Not detected
BRCA2	Mutation	Not detected
KRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
NRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
PIK3CA	Mutation	Not detected
FGFR2	Rearrangement	Not detected
	Mutation	Not detected
FGFR3	Rearrangement	Not detected
	Mutation	***p.S249C (3.5%)***
NTRK1	Rearrangement	Not detected
NTRK2	Rearrangement	Not detected
NTRK3	Rearrangement	Not detected
IDH1	Mutation	Not detected

Note:

1. 'Not detected/-' indicates the corresponding variations were not detected in this tested individual.
2. The genetic variations listed above are covered, but not limited to this list.
3. For a detailed information about listed variants, please refer to the Report Summary and the respective Interpretations sections.

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4. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant		Result	Clinical Interpretation
Biomarkers for predicting efficacy			
Tumor mutation burden (TMB)		TMB-L 8.64	-
Microsatellite instability (MSI)		Stable (MSS)	-
Affect the treatment effect - positive correlation			
PD-L1 amplification		Not detected	-
PBRM1 inactivating mutation Renal clear cell carcinoma)		Not detected	-
MLH1 suspected germline deleterious mutation		Not detected	-
MSH2 suspected germline deleterious mutation		Not detected	-
MSH6 suspected germline deleterious mutation		Not detected	-
PMS2 suspected germline deleterious mutation		Not detected	-
POLE mutation (driver)		Not detected	-
POLD1 mutation (driver)		Not detected	-
Other DNA damage repair (DDR) pathway genes	*ATM* mutation	Not detected	-
	ATR mutation	Not detected	-
	BAP1 mutation	Not detected	-
	BLM mutation	Not detected	-
	BRCA1 mutation	Not detected	-
	BRCA2 mutation	Not detected	-
	BRIP1 mutation	Not detected	-
	CHEK1 mutation	Not detected	-
	CHEK2 mutation	Not detected	-
	ERCC3 mutation	Not detected	-
	ERCC4 mutation	Not detected	-
	ERCC5 mutation	Not detected	-
	FANCA mutation	Not detected	-
	FANCC mutation	Not detected	-
	MRE11A mutation	Not detected	-
	NBN mutation	Not detected	-
	RAD50 mutation	Not detected	-
	RAD51 mutation	Not detected	-
	RAD51B mutation	Not detected	-
	RAD51D mutation	Not detected	-
	RAD54L mutation	Not detected	-
TP53 mutation		Not detected	-
KRAS mutation		Not detected	-
Biomarker/Variant		**Result**	**Clinical Interpretation**

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Affect the treatment effect - negative correlation		
PTEN inactivating mutation	Not detected	-
JAK1 inactivating mutation	Not detected	-
JAK2 inactivating mutation	Not detected	-
B2M inactivating mutation	Not detected	-
EGFR mutation （L858R/EX19del）	Not detected	-
ALK rearrangement	***EML4(13)-ALK(20) (3.8%)***	May decrease the benefit rate of PD-1/PD-L1 inhibitors
STK11 inactivating mutation	Not detected	-
KEAP1 inactivating mutation	Not detected	-
11q13 amplification	Not detected	-
MDM2 amplification	Not detected	-
MDM4 amplification	Not detected	-
DNMT3A inactivating mutation	Not detected	-
Indicator affecting prognosis of immune checkpoint inhibitor therapy		
HLA-I Zygosity (At least one of type A, B, C is homozygous)	Not detected	-

Note:

1. Not detected/- indicates the corresponding variation were not detected in this tested individual.
2. The interpretation of the detection results of *PBRM1* inactivating mutations is only applicable to renal clear cell carcinoma.
3. The indicators/gene clinical interpretations listed above are for reference only, and the specific decisions need to refer to professional physician instructions.
4. For a detailed interpretation, showed in Interpretation for biomarker of checkpoint inhibitor.
5. *POLE* and *POLD1* mutations are restricted to currently reported mutations that may lead to hypermutation in tumor, resulting in tumor mutation burden increase.
6. HLA-I results analyzed by the phenotypes of HLA-A, HLA-B and HLA-C loci detected from tumor samples. Due to the lack of control samples, HLA-I typing cannot be accurately analyzed and it is possible that show homozygosity because of the occurrence of HLA-LOH in the tumor tissue.

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5. Interpretations for targeted therapies

Genetic Variation:	*ALK fusion: EML4(13)-ALK(20)*	VAF: 3.8%	OncoKB	CIViC	COSMIC
Therapies:	Crizotinib, Alectinib, Ceritinib, Brigatinib, Lorlatinib (1A.1)				

Gene Description

The anaplastic lymphoma kinase (ALK) gene has been shown to be involved in chromosomal translocations that produce oncogenic fusions with other genes giving rise to activated, transforming ALK protein (PMID: 25971657). The majority of the ALK fusion variants are comprised of portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene, which generate a transforming tyrosine kinase that plays a role in lung cancer (PMID: 17625570). At least nine different EML4-ALK fusion variants have been identified in NSCLC.

Variant Description

EML4-ALK gene rearrangement is the rearrangement of the EML4 gene and ALK gene. The EML4-ALK fusion variant 1 consisting of ALK kinase domain (exons 20-29) fused to EML4 exons 1-13 is the most common EML4-ALK variant, and was discovered in non-small cell lung cancer. Multiple EML4 breakpoint shave been described with differential sensitivity to inhibitors with variant 1 showing greater sensitivity than 3a in cell lines.

Targeted Drug Interpretation

ALK (anaplastic lymphoma kinase) rearrangements, such as the one detected in this patient, are present in approximately 5% of lung adenocarcinomas and occur predominantly in younger individuals who are never- or light smokers (PMID: 31887093). The presence of EML4-ALK fusions is associated with EGFR tyrosine kinase inhibitor (TKI) resistance (PMID: 19667264, 36387181). Importantly, ALK gene fusions in general represent a unique subset of non-small cell lung cancer (NSCLC) patients for whom ALK/ROS1/c-MET inhibitors have high potential as a very effective therapeutic strategy (PMID: 24623980). The following treatment options have been approved:

- On December 18, 2024, the Food and Drug Administration approved ensartinib for adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received an ALK-inhibitor. Efficacy was evaluated in eXALT3 (NCT02767804), an open-label, randomized, active-controlled, multicenter trial in 290 patients with locally advanced or metastatic ALK-positive NSCLC who had not previously received an ALK-targeted therapy. Patients were randomized 1:1 to receive ensartinib or crizotinib. The median PFS was 25.8 months in the ensartinib arm and 12.7 months in the crizotinib arm. There was no statistically significant difference in OS.
- The Food and Drug Administration granted regular approval to lorlatinib, a third-generation TKI, for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ALK-positive, detected by an FDA-approved test. Approval is based on data from Study B7461006 (NCT03052608), a randomized, multicenter, open-label, active-controlled trial conducted in 296 patients with ALK-positive metastatic NSCLC who had not received prior systemic therapy for metastatic disease, demonstrating an improvement in progression-free survival (PFS). Real-world evidence indicates that lorlatinib offers a significant clinical benefit and high intracerebral antitumour activity in heavily pretreated patients with ALK+ NSCLC (IFCT-1803 LORLATU cohort, NCT03727477) (PMID: 35278825).
- FDA approved brigatinib for adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test. Efficacy was investigated in ALTA 1L (NCT02737501), a randomized (1:1), open-label, multicenter trial in adult patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy, where brigatinib

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demonstrated better objective response rate (ORR) per RECIST v1.1 criteria compared to crizotinib (74% and 62%, respectively) (PMID: 32780660, 30280657).

- Also, FDA granted regular approval to ceritinib for patients with metastatic ALK-positive NSCLC, based on data from ASCEND-4, a randomized, multicenter, open-label, active-controlled trial conducted in patients with untreated ALK-positive NSCLC, demonstrating an improvement in PFS (NCT01828099) (PMID: 28126333).
- Later, alectinib received accelerated approval for treatment of patients with ALK-positive metastatic NSCLC whose disease progressed on or who were intolerant of crizotinib based on an independent review committee (IRC)-assessed overall response rate (ORR) of 38% and 44% among 87 and 138 patients, respectively, in two single arm trials. Alectinib has better PFS and higher intracranial efficacy compared to crizotinib in ALK-positive NSCLC, and might improve PFS by comparison with ceritinib and brigatinib after crizotinib failure (PMID: 35616090).
- Crizotinib, another TKI, is approved by FDA, EMA, and AIFA for the treatment of patients with ALK or ROS1-positive NSCLC. Crizotinib received accelerated approval for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is ALK-positive (PROFILE 1005, PROFILE 1007) and later, it received regular approval based on confirmation of clinical benefit in study A8081007 (PMID: 25470694, 25170012).

The novel ALK inhibitor NVL-655 demonstrated encouraging activity in heavily pretreated patients with advanced ALK-positive non-small cell lung cancer (NSCLC), including in those who were previously treated with lorlatinib, according to findings from the phase 1 ALKOVE-1 study (NCT05384626) presented at the 2024 ESMO Congress.

Ensartinib DrugBank

Ensartinib (X-396) is a novel, aminopyridazine-based small molecule that potently inhibits ALK. Ensartinib is 10-fold more potent than crizotinib for inhibiting the growth of ALK-positive lung cancer cell lines, and reported activity in a broad spectrum of ALK-mutations.

Crizotinib DrugBank

Crizotinib, an inhibitor of receptor tyrosine kinase for the treatment of non-small cell lung cancer (NSCLC), was approved by FDA in August 26, 2011.Verification of the presence of ALK fusion gene is done by Abbott Molecular's Vysis ALK Break Apart FISH Probe Kit. This verification is used to select for patients suitable for treatment. Crizotinib is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic-lymphoma kinase (ALK)-positive as detected by a FDA-approved test.

Alectinib DrugBank

Alectinib is a second generation oral drug that selectively inhibits the activity of anaplastic lymphoma kinase (ALK) tyrosine kinase. It is specifically used in the treatment of non-small cell lung cancer (NSCLC) expressing the ALK-EML4 (echinoderm microtubule-associated protein-like 4) fusion protein that causes proliferation of NSCLC cells. Inhibition of ALK prevents phosphorylation and subsequent downstream activation of STAT3 and AKT resulting in reduced tumour cell viability. Approved under accelerated approval in 2015, alectinib is indicated for use in patients who have progressed on or were not tolerant of crizotinib, which is associated with the development of resistance. Alectinib is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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Ceritinib DrugBank

Ceritinib is used for the treatment of adults with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) following failure (secondary to resistance or intolerance) of prior crizotinib therapy. About 4% of patients with NSCLC have a chromosomal rearrangement that generates a fusion gene between EML4 (echinoderm microtubule-associated protein-like 4) and ALK (anaplastic lymphoma kinase), which results in constitutive kinase activity that contributes to carcinogenesis and seems to drive the malignant phenotype. Ceritinib exerts its therapeutic effect by inhibiting autophosphorylation of ALK, ALK-mediated phosphorylation of the downstream signaling protein STAT3, and proliferation of ALK-dependent cancer cells. Following treatment with crizotinib (a first-generation ALK inhibitor), most tumours develop drug resistance due to mutations in key "gatekeeper" residues of the enzyme. This occurrence led to development of novel second-generation ALK inhibitors such as ceritinib to overcome crizotinib resistance. The FDA approved ceritinib in April 2014 due to a surprisingly high response rate (56%) towards crizotinib-resistant tumours and has designated it with orphan drug status. Ceritinib is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Brigatinib DrugBank

Brigatinib, originally named AP26113, is a reversible dual inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR). It presents selectivity against the mutant forms of EGFR compared to the wild-type. It also exhibits selectivity against 9 different Crizotinib-resistant mutants of the EML4-ALK fusion gene, which is a pivotal player in the transformation of susceptible lung parenchyma. Brigatinib was developed by Ariad Pharmaceuticals, a subsidiary of Takeda Pharmaceutical Company Limited, and FDA-approved on April 28, 2017. The anaplastic lymphoma kinase positive, metastatic non-small cell lung cancer (ALK+ NSCLC), represents only 3-5% of the NSCLC cancer cases, but the ALK mutation, overexpression and presence in several oncogenic fusion proteins in solid and hematologic tumors have pointed out the importance as well as its potential as a cancer therapy target. The ALK-related cases of NSCLC are associated with the presence of the fusion gene EML4-ALK which fused the ALK protein with the echinoderm microtubule-associated protein like-4 whose original function is the correct formation of microtubules. The presence of the aberrant fusion protein results in abnormal signaling that provokes increased cell growth, proliferation and survival. Crizotinib is indicated for the treatment of such cases but the presence of ALK kinase domain mutations confer resistance to the treatment. Thus, brigatinib is indicated for the treatment of patients with ALK+ NSCLC with intolerance to Crizotinib.

Lorlatinib DrugBank

Lorlatinib has been used in trials studying the basic science and treatment of Non-small Cell Lung Cancer and anaplastic lymphoma kinase (ALK)-positive Non-Small Cell Lung Cancer (NSCLC) and ROS1-positive NSCLC. Despite initial responses from the use of various ALK inhibitors, however, it is virtually almost guaranteed that all patients with the condition in question will develop tumour progression or resistance to the current therapy in use . Considered a third-generation ALK tyrosine kinase inhibitor (TKI) for patients with ALK-positive metastatic NSCLC, lorlatinib's most optimal place in the treatment sequence of this condition has most recently been identified with its latest approval by the US FDA in November of 2018 for the indication of treating those patients' disease which has progressed even after the use of first and second-generation TKIs like crizotinib, alectinib, or ceritinib . Loratinib's ability to move past the blood-brain barrier facilitates its ability to treat progressive or worsening brain metastases as well . Lorlatinib is a third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on a) the prior use of crizotinib and at least one other ALK inhibitor for metastatic disease, or b) the prior use

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of alectinib as the first ALK inhibitor therapy for metastatic disease, or c) the prior use of certinib as the first ALK inhibitor therapy for metastatic disease .

Genetic Variation:	*NM_000142.4 (FGFR3) : c.746C>G (p.S249C)* VAF: 3.5%	OncoKB	CIViC	COSMIC
Therapies:	Erdafitinib (2C.1)			

Gene Description

FGFR3 is a receptor tyrosine kinase that is a member of the fibroblast growth factor receptor (FGFR) family. Binding of FGF ligands to FGFR3 results in the rapid dimerization and activation of downstream signaling pathways including the PI3K/AKT and MAPK pathways (PMID: 28030802). FGFR3 is most highly expressed in neuronal and sensory cell types and FGFR3 signaling contributes to a variety of cellular functions including proliferation, differentiation, cell migration and apoptosis (PMID: 20094046). Alternative splicing events in the FGFR3 gene generate two isoforms, FGFR3b and FGFR3c, which have unique tissue expression patterns and ligand-binding specificity (PMID: 7512569). Somatic activating mutations in FGFR3 have been identified in up to 70% of bladder cancers and in a low percentage of other solid tumor types (PMID: 16338952). FGFR3 alterations can emerge after exposure to ALK inhibitors, driven by selective pressure and clonal evolution.

Variant Description

This sequence change replaces serine with cysteine at codon 249 of the FGFR3 protein (p.Ser249Cys). The serine residue is highly conserved and there is a moderate physicochemical difference between serine and cysteine. This variant is present in population databases (rs121913483, ExAC 0.002%). This variant has been observed in several individuals affected with thanatophoric dysplasia (PMID: 8589699, 11038465, 11879084). ClinVar contains an entry for this variant (Variation ID: 16339). Experimental studies have shown that this missense change results in stable FGFR3 dimerization and constitutive phosphorylation of the receptor at higher levels than wild type protein (PMID: 17384684, 19749790, 25606676). For these reasons, this variant has been classified as Pathogenic.

Targeted Drug Interpretation

Recently, an FGFR kinase inhibitor Erdafitinib, received accelerated FDA approval in urothelial metastatic cancer based on results from a Phase 2 clinical trial (BLC2001, NCT02365597), a multicenter, open-label, single-arm study, of 87 patients with disease that had progressed on or after at least one prior chemotherapy and that had at least one of the following genetic alterations: FGFR3 gene mutations (R248C, S249C, G370C, Y373C) or FGFR gene fusions (FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7), as determined by a clinical trial assay performed at a central laboratory. The results demonstrated a 32.2 percent objective response rate (ORR) as assessed by Blinded Independent Review Committee (BIRC) [95% CI(22.4, 42.0)]. Erdafitinib may potentially be beneficial for lung cacer patients with FGFR3 mutations. Currently, a number of small molecule inhibitors of the FGFR proteins are in use, with the major difference among them being their specificity to FGFR versus other receptor tyrosine kinases (RTKs) (PMID: PMID: 24265351). Anti-FGFR agents (Pazopanib, Ponatinib, Nintedanib) are actively under multiple clinical trials against many types of solid tumor, including lung squamous cell carcinoma, gastric cancer, endometrial cancer, breast cancer and cholangiocarcinoma. Lenvatinib is currently in more than 100 clinical trials (clinicaltrials.com) several of which include patients with diseases associated with FGFR dysfunction.

Erdafitinib DrugBank

In early April of 2019, the US FDA approved Janssen Pharmaceutical Companies' brand name Balversa (erdafitinib) as the first-ever fibroblast growth factor receptor (FGFR) kinase inhibitor indicated for patients with locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy . At the same time, the FDA also

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approved the therascreen FGFR RGQ RT-PCR Kit (Qiagen) for utilization as a companion diagnostic with erdafitinib for selecting patients for the indicated therapy . Erdafitinib's innovation lies in the fact that it is the first personalized treatment targeting susceptible FGFR genetic alterations for patients with metastatic bladder cancer, which demonstrates the design of erdafitinib in developing more personalized and precision medicines with the capacity to target cancer treatment to a patient's specific genetic mutation . Considering urothelial cancer is statistically the fourth most common kind of cancer in the world , the introduction of erdafitinib offers a welcome new option in the ever-expanding therapeutic tool kit to treat such prevalent medical conditions. Nevertheless, although erdafitinib was granted Breakthrough Therapy designation and Accelerated Approval from the FDA so as to allow the agency to focus on and expedite the approval process for a medication indicated for a serious condition that fills an unmet medical need using clinical trial data that is believed to predict a genuine clinical benefit for patients with the given condition, such designations mean further ongoing clinical trials are necessary to confirm the clinical benefit of erdafitinib going forward . Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor that is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has: i) susceptible FGFR3 or FGFR2 genetic alterations and has , ii) progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy . The selection of patients for the treatment of locally advanced or metastatic urothelial carcinoma with erdafitinib should be based on the presence of susceptible FGFR genetic alterations in tumor specimens . This above indication is approved under accelerated approval by the US FDA based on tumor response rate . Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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6. Interpretation for polymorphism variants related with chemotherapy drugs

Biomarkers associated with treatment response

Drug Classes	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level
5-Fluorouracil (5-Fu), Fluoropyrimidines	5-Fu + Oxaliplatin	*GSTP1*	rs1695	AG	Associated with moderate response to treatment	2A
Anthracyclines	Epirubicin	*GSTP1*	rs1695	AG	Associated with better response to treatment	2A
Aromatase inhibitors	Letrozole, Anastrozole	*CYP19A1*	rs4646	AA	Associated with better response to treatment	3
	Anastrozole	*ABCB1*	rs2032582			
Cyclophosphamide	Cyclophosphamide	*XRCC1*	rs25487	CC	Associated with better response to treatment	3
	Cyclophosphamide	*SOD2*	rs4880	AA	Associated with better response to treatment	2B
	Cyclophosphamide + Epirubicin	*GSTP1*	rs1695	AG	Associated with better response to treatment	2A
Methotrexate	Methotrexate	*ATIC*	rs4673993			
Pemetrexed	Pemetrexed	*MTHFR*	rs1801133	GG	Associated with better response to treatment	3
Platinum-Based Chemotherapy	Carboplatin	*MTHFR*	rs1801133	GG	Associated with poorer response to treatment	2A
	Platinum compounds	*XRCC1*	rs1799782	GG	Associated with poorer response to treatment	NA
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AA	Associated with poorer response to treatment	2B
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*XRCC1*	rs25487	CC	Associated with better response to treatment	2B
Taxanes	Paclitaxel + Cisplatin	*TP53*	rs1042522	CC	Associated with better response to treatment	2B
	Paclitaxel	*ABCB1*	rs2032582			
Vinca alkaloids	Vincristine	*ABCB1*	rs1045642	GG	Associated with better response to treatment	3

Biomarkers associated with drug toxicity

Drug Classes	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level
5-Fluorouracil (5-Fu), Fluoropyrimidines	5-Fu or Capecitabine	*DPYD*	rs2297595	CT	Associated with increased risk of drug toxicity	2A
	5-Fu or Capecitabine	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
	5-Fu + Leucovorin or Tegafur + Leucovorin	*UMPS*	rs1801019	GG	Associated with decreased risk of drug toxicity	2B
	Fluoropyrimidine-based therapy	*DPYD*	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
	Fluoropyrimidine-based therapy	*DPYD*	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
	Fluoropyrimidine-based therapy	*DPYD*	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Anthracyclines	Anthracyclines	*CBR3*	rs1056892	GG	Associated with increased risk of drug toxicity	2B

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	Epirubicin	*GSTP1*	rs1695	AG	Associated with decreased risk of drug toxicity	2A
Capecitabine	Capecitabine-Based Chemotherapy	*MTHFR*	rs1801131	GG	Associated with increased risk of drug toxicity	2A
	Capecitabine-Based Chemotherapy	*DPYD*	rs2297595	CT	Associated with increased risk of drug toxicity	2A
	5-Fu or Capecitabine	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
	Capecitabine	*DPYD*	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
	Capecitabine	*DPYD*	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
	Capecitabine	*DPYD*	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Cyclophosphamide	Cyclophosphamide	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
	Cyclophosphamide + Epirubicin	*GSTP1*	rs1695	AG	Associated with decreased risk of drug toxicity	2A
Gemcitabine	Gemcitabine	*CDA*	rs2072671	AC	Associated with increased risk of neutropenia and hematologic toxicity	2B
Irinotecan	Irinotecan	*UGT1A1*	rs8175347	6TA/6TA	Associated with decreased risk of drug toxicity	2A
	Irinotecan	*UGT1A1*	rs4148323	GG	Associated with decreased risk of drug toxicity	2A
	Irinotecan	*C8orf34*	rs1517114			
Methotrexate	Methotrexate	*MTRR*	rs1801394	GG	Associated with increased risk of drug toxicity	2B
	Methotrexate	*ABCB1*	rs1045642	GG	Associated with decreased risk of drug toxicity	2A
Platinum-Based Chemotherapy	Cisplatin	*XPC*	rs2228001	GT	Associated with increased risk of drug toxicity	1B
	Platinum compounds	*GSTP1*	rs1695	AG	Associated with increased risk of drug toxicity	2A
	Cisplatin, Platinum, Platinum compounds	*ERCC1*	rs3212986	CC	Associated with increased risk of drug toxicity	2B
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AA	Associated with increased risk of drug toxicity	2B
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*XRCC1*	rs25487	CC	Associated with increased risk of drug toxicity	2B

Note:

1. The level of variant-drug associations evidence is based on PharmGKB website, for more detailed information please see http://www.pharmgkb.org/page/clinAnnLevels.

Level 1A: Annotation for a variant-drug combination in a CPIC- or medical society-endorsed pharmacogenomics guideline, or implemented at a PGRN site, or in another major health system;

Level 1B: Annotation for a variant-drug combination in which the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant P-values, and, preferably with a strong effect size;

Level 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely;

Level 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small;

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Level 3: Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association;

Level 4: Annotation based on a case report, non-significant study, or in vitro, molecular, or functional assay evidence only.

2. The variant-drug correlation relationship derived from multiple independent studies, therefore, the interpretations of the same class of drug for the tested individual may be inconsistent. The final drug instruction needs to combine with the specific clinical situation.

3. The detection results are only based on the analysis of tumor samples and lack of control, the results of some loci may be specific to tumor tissues due to factors such as loss of heterozygosity.

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7. Other Genomic findings*

***Note**: In this section, damaging variants in genes without clinical actionability or without convincing evidence of cancer association are reported.

Genetic Variation:	-
Therapies:	-

8. Variants of Uncertain Significance (VUS)

The clinical significance of the variants listed in the below table is uncertain at this time. Until the uncertainty is resolved, these variants should not be used in clinical management decisions.

Gene	Variant	Interpretation
-	-	-

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9. Germline variants

Gene	Transcript	Exon	c.HGVS	p.HGVS	Zygosity	Classification
-	-	-	-	-	-	-

Note:

1. - indicates no relevant variations were detected in this test.
2. When detected, pathogenic or likely pathogenic variants are reported. Variants of uncertain significance or variants that are benign or likely benign are not reported.
3. Variant classification interpretation is based on ACMG (American College of Medical Genetics and Genomics) guidelines for the interpretation of germline sequence variants (PMID:25741868).

10. HLA-I Polymorphism variation

Somatic HLA-I Zygosity

The anti-tumor activity of immune checkpoint inhibitor therapy is related to CD8+ T cells. The recognition of cancer cells by CD8+ T cells is achieved by HLA-I (human leukocyte antigen class I) molecules presenting tumor antigens.

HLA alleles have the characteristics of polymorphism and codominance. HLA-I loci subdivided into HLA-A, HLA-B and HLA-C. When a patient's HLA-I is homozygous at least one locus, this patient is expected to present less and less diverse tumor neoantigens to T cells compared to patients who are heterozygous at all three loci. In two cohorts, patients with heterozygous HLA-I showed longer OS than those with homozygous alleles, cohort1: HR=1.4 (1.02-1.9), P-value=0.036; cohort2: HR=1.31 (1.03- 1.7), P-value=0.028; among 32 patients with heterozygous HLA-I but at least one locus with LOH (loss of heterozygosity), patients with HLA-I LOH have a higher survival risk (P = 0.05, HR = 1.60, 95% CI 1.03-2.43), and these patients mainly with low mutation burden (P = 0.0006, HR = 3.68, 95% CI 1.64-8.23) (PMID:29217585).

Gene	Test Content	Result
HLA-A	Zygosity	Heterozygosity
HLA-B	Zygosity	Heterozygosity
HLA-C	Zygosity	Heterozygosity

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11. Clinical Trials to consider

ALK associated clinical trials

NCT06074588	Phase 3
Title	Sacituzumab Tirumotecan (MK-2870) Versus Chemotherapy in Previously Treated Advanced or Metastatic Nonsquamous Non-small Cell Lung Cancer (NSCLC) With EGFR Mutations or Other Genomic Alterations (MK-2870-004)
Treatment	Sacituzumab tirumotecan| Docetaxel| Pemetrexed
Location	United States, Australia, Brazil, Canada, Chile, China, Czechia, France, Germany, Greece, Hong Kong, Israel, Italy, Japan, Korea, Republic of, Malaysia, Mexico, Philippines, Poland, Spain, Taiwan, Thailand, Turkey, United Kingdom, Vietnam

NCT03645928	Phase 2
Title	Study of Autologous Tumor Infiltrating Lymphocytes in Patients With Solid Tumors
Treatment	Lifileucel| LN-145| Pembrolizumab| LN-145-S1| Ipilimumab| Nivolumab
Location	United States, Canada, France, Germany, Greece, Spain, Switzerland, United Kingdom

NCT05525338	Phase 4
Title	Comparison of Standard Dose Alectinib to Alectinib in Adjusted Dose Based on Alectinib Bloodlevels
Treatment	Alectinib
Location	France, Netherlands

NCT04401059	Phase 4
Title	Synergistic Effect of Elemene Plus TKIs Compared With TKIs in EGFR-mutated Advanced NSCLCï¼šProspective Study
Treatment	Elemene plus first or third generation EGFR-TKIs| First or third generation EGFR-TKIs
Location	China

NCT05522660	Phase 3
Title	Immunotherapy or Targeted Therapy with or Without Stereotactic Radiosurgery for Patients with Brain Metastases from Melanoma or Non-small Cell Lung Cancer
Treatment	Stereotactic radiosurgery| Immune checkpoint inhibitor
Location	Italy, Netherlands, Spain, Switzerland, United Kingdom

NCT02201992	Phase 3
Title	Crizotinib in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer That Has Been Removed by Surgery and ALK Fusion Mutations (An ALCHEMIST Treatment Trial)

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Treatment	Clinical Observation| Crizotinib| Laboratory Biomarker Analysis
Location	United States, Guam, Puerto Rico

NCT06082635	**Phase 3**
Title	TGRX-326 Chinese Phase III for Advanced Non-small Cell Lung Cancer (NSCLC)
Treatment	TGRX-326| Crizotinib
Location	China

NCT05236946	**Phase 3**
Title	Observation or Upfront Cranial RT in Oncogene Mutated NSCLC With Asymptomatic BM: A Phase III RCT
Treatment	Stereotactic radiosurgery/whole brain radiotherapy| Tyrosine kinase inhibitor
Location	India

NCT05170204	**Phase 3**
Title	A Study Evaluating the Efficacy and Safety of Multiple Therapies in Cohorts of Participants With Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer (NSCLC)
Treatment	Alectinib| Entrectinib| Durvalumab
Location	United States, Australia, Belgium, Brazil, Canada, Chile, China, Colombia, Costa Rica, France, Germany, Hong Kong, India, Israel, Italy, Japan, Korea, Republic of, Netherlands, New Zealand, Norway, Poland, Serbia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom

NCT06074588	**Phase 3**
Title	Sacituzumab Tirumotecan (MK-2870) Versus Chemotherapy in Previously Treated Advanced or Metastatic Nonsquamous Non-small Cell Lung Cancer (NSCLC) With EGFR Mutations or Other Genomic Alterations (MK-2870-004)
Treatment	Sacituzumab tirumotecan| Docetaxel| Pemetrexed
Location	United States, Australia, Brazil, Canada, Chile, China, Czechia, France, Germany, Greece, Hong Kong, Israel, Italy, Japan, Korea, Republic of, Malaysia, Mexico, Philippines, Poland, Spain, Taiwan, Thailand, Turkey, United Kingdom, Vietnam

NCT03194893	**Phase 3**
Title	A Rollover Study of Alectinib in Patients With Anaplastic Lymphoma Kinase (ALK)-Positive or Rearranged During Transfection (RET)-Positive Cancer
Treatment	Alectinib| Crizotinib
Location	United States, China, France, Hong Kong, Italy, Korea, Republic of, Poland, Russian Federation, Spain, Turkey

NCT05341583	**Phase 3**
Title	Ensartinib as Adjuvant Treatment in Anaplastic Lymphoma Kinase (ALK) Positive Non-small Cell Lung Cancer

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Treatment	Ensartinib| Placebo
Location	China

NCT05351320	**Phase 2**
Title	WX-0593 Combined With Concurrent Chemoradiotherapy in Unresectable Locally Advanced NSCLC
Treatment	WX-0593 Tablets| chemotherapy| Thoracic Radiation Therapyï¼ˆTRTï¼‰
Location	China

NCT05284539	**Phase 2**
Title	Efficacy of Platinum-based Chemotherapy Plus Immune Checkpoint Inhibitors for EGFR/ALK/ROS1 Mutant Lung Cancer
Treatment	Pemetrexed, Cisplatin, Bevacizumab Plus Pembrolizumab
Location	China

NCT06378892	**Phase 2**
Title	A Study to Evaluate the Combination of Platinum-pemetrexed Based Chemotherapy Plus Lorlatinib in ALK Positive Non-Small Cell Lung Cancer (NSCLC) With Exclusively Extracranial Disease Progression on Lorlatinib
Treatment	Lorlatinib
Location	Italy

NCT04840004	**Phase 2**
Title	Efficacy and Safety of PVT-1 Treatment in Patients With Advanced Non-Small Cell Lung Cancer
Treatment	PVT-1
Location	Turkey

NCT04802876	**Phase 2**
Title	Efficacy of Tislelizumab and Spartalizumab Across Multiple Cancer-types in Patients With PD1-high mRNA Expressing Tumors
Treatment	Spartalizumab| Tislelizumab
Location	Spain

NCT04042558	**Phase 2**
Title	A Study Evaluating Platinum-Pemetrexed-Atezolizumab (+/-Bevacizumab) for Patients With Stage IIIB/IV Non-squamous Non-small Cell Lung Cancer With EGFR Mutations, ALK Rearrangement or ROS1 Fusion Progressing After Targeted Therapies
Treatment	Carboplatin + Pemetrexed + Atezolizumab + Bevacizumab| Carboplatin + Pemetrexed + Atezolizumab

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Location	France

NCT06092086	**Phase 2**
Title	Lorlatinib as the First-line Treatment in China Advanced ALK+ NSCLC
Treatment	Loratinib
Location	China

NCT05869162	**Phase 2**
Title	Phase II Study of SY-3505 in Patients With ALK-positive NSCLC Who Have Failed Prior Second-Generation ALK TKI
Treatment	SY-3505
Location	China

NCT06322095	**Phase 2**
Title	A Study of GH21 Combined With Previous Target Therapy or Immunotherapy in Patients With Advanced Solid Tumors
Treatment	PD-1| MET inhibitor| ALK inhibitor| BRAF Inhibito| EGFR Monoclonal antibody| GH21| MEK Inhibitor
Location	China

NCT06311981	**Phase 2**
Title	Carbon Ion Radiotherapy for Locally Advanced Lung Cancer in Elderly Patients
Treatment	carbon ion radiotherapy| targeted therapy| single regimen chemotherapy in sequence with radiotherapy
Location	China

NCT04302025	**Phase 2**
Title	A Study of Multiple Therapies in Biomarker-Selected Patients With Resectable Stages IB-III Non-Small Cell Lung Cancer
Treatment	Alectinib| Entrectinib| Vemurafenib (Enrollment closed)| Cobimetinib (Enrollment closed)| Pralsetinib (Enrollment closed)| Atezolizumab| SBRT| Resection| Chemotherapy| Divarasib
Location	United States

NCT05955391	**Phase 2**
Title	TGRX-326 Chinese Phase II for Advanced Non-small Cell Lung Cancer (NSCLC)
Treatment	TGRX-326
Location	China

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NCT04116541	Phase 2
Title	A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/characteristics in Advanced / Metastatic Tumors.
Treatment	HDM201| Ribociclib| Cabozantinib| Alectinib| Regorafenib| Trametinib| Dabrafenib| Avapritinib
Location	France

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

NCT05740943	Phase 2
Title	Induction Lorlatinib in Stage III Non-small Cell Lung Cancer
Treatment	Lorlatinib
Location	China

NCT05456256	Phase 2
Title	A Study of LP-300 with Carboplatin and Pemetrexed in Never Smokers with Advanced Lung Adenocarcinoma
Treatment	LP-300| Pemetrexed| Carboplatin
Location	United States, Japan, Taiwan

NCT05014464	Phase 2
Title	ALK Tyrosine Kinase Inhibitors in ALK-rearranged Advanced Squamous Cell Carcinoma
Treatment	Crizotinib
Location	China

NCT05296278	Phase 2
Title	Efficacy and Biomarker Explanation of IBI-323 + Bevacizumab Plus Platinum Based Chemotherapy on ALK-Rearranged NSCLC
Treatment	IBI-323 combined with bevacizumab plus Platinum
Location	China

NCT05178511	Phase 2

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Title	Ensatinib Treat Second-generation ALK-TKI Resistance After Second-generation ALK-TKI Resistance
Treatment	Ensartinib
Location	China

Press here for a live search of clinical trials for ALK

FGFR3 associated clinical trials

NCT05004974	**Phase 2**
Title	Sintilimab With Pemigatinib in Patients With PD-L1-positive and FGFR Mutated Advanced Non-small Cell Lung Cancer
Treatment	Sintilimab| Pemigatinib
Location	China

NCT06632262	**Phase 2**
Title	A Phase 2 Clinical Study of ABSK061 and ABSK043
Treatment	ABSK061 + ABSK043| ABSK061+ABSK043 in combination with CAPOX
Location	China

NCT05544552	**Phase 1|Phase 2**
Title	Safety and Preliminary Anti-Tumor Activity of TYRA-300 in Advanced Urothelial Carcinoma and Other Solid Tumors With FGFR3 Gene Alterations
Treatment	TYRA-300
Location	United States, Australia, France, Spain

NCT05614739	**Phase 1**
Title	A Study of LOXO-435 in Participants With Cancer With a Change in a Gene Called FGFR3
Treatment	LOXO-435| Pembrolizumab
Location	United States, Australia, Canada, China, France, Germany, Israel, Italy, Japan, Korea, Republic of, Netherlands, Norway, Spain, United Kingdom

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12. Appendix

12.a. Immune checkpoint inhibitors predictive biomarkers

Tumor Mutation Burden (TMB)

bTMB (blood-based tumor mutational burden) usually refers to the number of somatic nonsynonymous mutations or all mutations per megabase in the gene region examined by whole exome sequencing or targeted sequencing in a tumor peripheral blood sample. bTMB is derived from DNA released into blood circulation by tumor cells (circulating tumor - ctDNA). Tissue TMB (tTMB) is approved as a tumor agnostic biomarker for immunotherapy in patients with metastatic solid tumors. bTMB is positively correlated with tTMB, which can reflect the level of TMB in tumor tissues to some extent. Studies have shown that bTMB is not correlated with the expression of PD-L1 in tumor tissues (PMID: 30082870).

A retrospective analysis confirmed correlation between tTMB and bTMB in patients with NSCLC included in the OAK (NCT02008227, n=850) and Poplar (NCT01903993, n=287) clinical trials of Atezolizumab in second-line treatment for advanced non-small cell lung cancer. High TMB was associated with response to immunotherapy in both trials. A different study successfully correlated blood and tissue TMB results on 2000 NSCLC samples from Geneplus database. The correlation of bTMB with outcomes after front line treatment with Pembrolizumab and Pembrolizumab plus Chemotherapy was also evaluated, at a cutoff of ≥16 mut/Mb, in 66 pts with mNSCLC. Early results suggested that bTMB may predict therapeutic outcomes after first line Pembrolizumab based therapy in mNSCLC. However, the prospective phase III BFAST trial concluded that bTMB at a cut-off of ≥16 mut/Mb was not a predictive biomarker for clinical outcomes with atezolizumab in patients with previously untreated metastatic NSCLC, although the 18-month PFS and OS both numerically favored atezolizumab in this bTMB group (PMID: 35995953).

Evaluation of tissue- and plasma-derived TMB from the CheckMate 848 clinical trial, showed that at the prespecified cutoff of 10 mut/Mb, 15.8% and 20.7% of samples had high tTMB and bTMB, respectively; the positive (PPA), negative and overall percentage agreements between assays were 60%, 88%, and 84%, respectively. TMB correlation (Spearman's r, 0.54; P < 0.0001) and PPA (66%) were improved among 806 (79.3%) sample pairs with plasma maximum somatic allele frequency ≥ 1% (https://doi.org/10.1158/1538-7445.AM2022-2139).

Plasma samples with high bTMB values are highly correspondent with tTMB, whereas bTMB low results may also be the result of low tumor burden at earlier stages of disease as well as poorly shedding tumors (PMID: 35217576). Typically, bTMB reports higher than tTMB, as reported in Drusbosky et al, who analyzed 5610 blood specimens with the 80th percentile bTMB being ≥16 mut/Mb tissue equivalency (PMID: 35274716).

At present, there is no consensus on the application of bTMB in clinical cancer treatment.

Table S1. TMB interpretation and cut-offs.

Tumour Type	Immunotherapy agent	Study/Trial	TMB high cut-off	Type of benefit
NSCLC	Anti PD-L1	B1FIRST [1]	**≥16 Muts/Mb**	ORR
NSCLC	Anti PD-L1	BFAST Cohort C [2]	**≥16 Muts/Mb**	-
NSCLC	Anti PD-L1	MYSTIC [3]	**≥20 Muts/Mb**	OS
NSCLC	Anti PD-L1	OAK [4]	**≥16 Muts/Mb**	PFS
NSCLC	Anti PD-L1	POPLAR [4]	**≥16 Muts/Mb**	PFS

1. Mok, Tony & Gadgeel, S. & Kim, et al. Blood first line ready screening trial (B-F1RST) and blood first assay screening trial (BFAST) enable clinical development of novel blood-based biomarker assays for tumor mutational burden (TMB) and somatic mutations in 1L advanced or metastatic NSCLC. 2017. Annals of Oncology. 28. 10.1093/annonc/mdx380.084.| **2**. Peters S, et al. Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational burden: primary analysis of BFAST cohort C randomized phase 3 trial. Nat Med. 2022 Sep;28(9):1831-1839. | **3**. Rizvi NA, et al. MYSTIC Investigators. Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized

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Clinical Trial. JAMA Oncol. 2020 May 1;6(5):661-674. doi: 10.1001/jamaoncol.2020.0237. | **4.** Gandara DR, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med. 2018 Sep;24(9):1441-1448. doi: 10.1038/s41591-018-0134-3.

Microsatellite Instability (MSI)

MSI (microsatellite instability, MSI) refers to the phenomenon that the sequence of microsatellites increases or decreases. Microsatellite (MS), also called Short Tandem Repeats (STRs) or Simple Sequence Repeat (SSRs), consists of repeated sequences of 1-6 nucleotides. This report uses NGS panel detection and is based on the 1021 Panel platform. The results of MSI are divided into three types: MSI-H, which means microsatellites are highly unstable; MSS, which means microsatellites are stable; MSI-U, which means that the sample does not meet the MSI evaluation conditions (tissues or pleural fluid samples may not have passed the MSI indicator calculation quality control due to the low DNA and/or content of tumor cells).

FDA approved pembrolizumab for solid tumors with MSI-H or dMMR (highly unstable microsatellites or MMR defects) and approved for MSI-H or dMMR colorectal cancer as the first-line treatment (PMID: 35680043, 33264544). FDA approved nivolumab for the treatment of children or adults who have progressed after 5-FU/oxaliplatin/irinotecan treatment with MSI-H or dMMR metastatic colorectal cancer. The NCCN clinical practice guidelines for colorectal cancer indicate that pembrolizumab/nivolumab can be used for the treatment of patients with dMMR/MSI-H colorectal cancer (PMID: 28734759).

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12.c. Methodology

ctDNA analysis was performed using plasma-extracted cfDNA, in combination with DNA extracted from leukocytes as a control to avoid the detection of false positive results due to clonal hematopoiesis mutations. The MagMAX Cell-Free DNA Isolation Kit (Thermofischer Scientific) and the MagCore Genomic DNA Whole Blood Kit (RBC Bioscience) were used for cfDNA and genomic DNA extraction respectively. A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology Multi-Gene Variant Assay (GenePlus) which is a qualitative test that detects variants in 1021 tumor-related genes and gene rearrangements / fusions in 38 genes. Sequencing was carried out on an MGI sequencing platform (DNBSEQ-G400). The analysis includes the entire exon regions of 312 genes, introns/promoters/fusion breakpoint regions of 38 genes and partial coding exons of 709 genes. The test also reports 30+ immune response biomarkers, including Tumor Mutational Burden (TMB) score and Microsatellite Instability (MSI) status.

Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system.

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 100%. Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 100%.

Limit of Detection (LoD): The limit of detection (LoD) of this assay is listed in the table below. The LoD is based on as low as 30 ng of gDNA input for library preparation.

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	VAF ≥0.3%
Insertions/deletions (Indel)	VAF ≥0.3%
Fusion (or rearrangement)	VAF ≥0.5%

Disclaimer

1. This test is mainly used to assist clinical decision-making and the result does not represent clinical decision.
2. The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
3. The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: https://clinicaltrials.gov/.
4. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
5. 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), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).
6. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

Limitations

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1. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Limited cell free tumor DNA (ctDNA) amount could result in false negative results.
3. Germline variants in *PMS2* gene with VAF>25% are reported.
4. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
5. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
6. Fraction of base quality ≥ Q30: 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%.
7. 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.

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12.d. Quality Control Results

Quality Control Index		Result	Criterion
Sequencing Quality Assessment	Average effective sequencing depth[1]	2361	≥ 1000
	Fraction of target covered with ≥ 50x[2]	100%	≥99%
	Fraction of base quality ≥ Q30[3]	96%	≥80%
Overall Assessment[4]		PASS	

Note：

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. Fraction of target covered with ≥ 50x: The proportion of bases that sequencing depth reach or above 50x on target, this index reflecting the coverage uniformity of sequencing.
3. Fraction of base quality ≥ Q30: The proportion of base quality in sequencing data that reach or above Q30, that is the probability of base recognition accuracy rate exceeds 99.9%.
4. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.

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12.e. Genes Analyzed

312 genes including all exon regions and available for detecting SNV / Indel / CNV									
ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	APC	AR	ARAF	ARID1A
ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2
AXL	B2M	BAP1	BARD1	BCL2	BCL2L1	BCOR	BLM	BMPR1A	BRAF
BRCA1	BRCA2	BRD4	BRIP1	BTK	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD274	CDC73	CDH1	CDK12	CDK4	CDK6	CDK8
CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP
CRKL	CSF1R	CTCF	CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDR1	DDR2
DICER1	DNMT3A	DOT1L	EGFR	EIF1AX	EMSY	EP300	EPAS1	EPCAM	EPHA2
EPHA3	EPHA5	EPHB1	EPHB6	ERBB2	ERBB3	ERBB4	ERCC1	ERCC3	ERCC4
ERCC5	ERG	ERRFI1	ESR1	EXT1	EXT2	EZH2	FAM123B	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FANCM	FAS	FAT1	FAT2
FBXW7	FGF19	FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN
FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXP1	FUBP1	GALNT12	GATA3	GNA11
GNAQ	GNAS	GRIN2A	GRM3	HDAC1	HGF	HNF1A	HOXB13	HRAS	IDH1
IDH2	IFNG	IFNGR1	IGF1R	IKBKE	IKZF1	IL7R	INPP4B	IRF2	IRS2
JAK1	JAK2	JAK3	JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT
KRAS	LRP1B	MAF	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAPK1	MAX	MCL1
MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLH3	MLL
MLL2	MLL3	MPL	MRE11A	MS4A1	MSH2	MSH3	MSH6	MST1R	MTOR
MUTYH	MYC	MYCL1	MYCN	MYD88	NBN	NCOR1	NF1	NF2	NFE2L2
NFKB1A	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NSD1	NTHL1	NTRK1
NTRK2	NTRK3	PALB2	PARK2	PARP1	PAX5	PBRM1	PCK1	PDCD1	PDCD1LG2
PDGFRA	PDGFRB	PDK1	PIK3CA	PIK3CB	PIK3CG	PIK3R1	PIK3R2	PMS1	PMS2
POLD1	POLE	POT1	PPP2R1A	PRDM1	PRKAR1A	PTCH1	PTCH2	PTEN	PTPN11
PTPRD	RAC1	RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1
RARA	RB1	RBM10	RECQL	RECQL4	RET	RHOA	RICTOR	RINT1	RNF43
ROS1	RPTOR	RUNX1	SDHA	SDHAF2	SDHB	SDHC	SDHD	SERPINB3	SERPINB4
SETD2	SF3B1	SLX4	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1
SOX2	SOX9	SPOP	SRC	STAG2	STAT3	STK11	SUFU	SYK	TBX3
TCF7L2	TERC	TET2	TGFBR2	TMEM127	TMPRSS2	TNFAIP3	TNFRSF14	TOP1	TOP2A
TP53	TSC1	TSC2	TSHR	U2AF1	VEGFA	VHL	WRN	WT1	XPO1
XRCC2	ZMAT3								

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38 genes including specific intron, promoter and fusion breakpoint regions and available for detecting gene rearrangement or fusion									
ALK	BCL2L11	BRAF	BRCA1	BRD4	CD74	EGFR	EML4	ERG	ETV6
EZR	FGFR1	FGFR2	FGFR3	KIF5B	KIT	MAML2	MET	MSH2	MYC
MYCL1	NCOA4	NOTCH2	NTRK1	NTRK2	NTRK3	PDGFRA	RAF1	RET	ROS1
RSPO2	SDC4	SLC34A2	TERT	TFE3	TMPRSS2	TPM3	PMS2		
709 genes including partial exon regions and available for detecting SNV / Indel									
ABCA13	ABCB1	ABCC1	ABCC11	ABCC2	ABCG2	ABL2	ACACA	ACIN1	ACTB
ACTG1	ACTG2	ACVR2A	ACVRL1	ADAM29	ADAMTS5	ADCY1	AFF1	AFF2	AFF3
AHNAK	AKAP9	ALB	AMOT	ANGPT1	ANK3	ANKRD11	ANKRD30A	ANKRD30B	APEX1
APOBEC3B	ARAP3	ARFGEF1	ARFGEF2	ARHGAP29	ARHGAP35	ARID4B	ARID5B	ARNT	ASCL4
ASH1L	ASMTL	ASPM	ASTN1	ASXL2	ATIC	ATP11B	ATP12A	ATP1A1	ATP2B3
BAZ2B	BBC3	BBS9	BCAS1	BCL10	BCL11A	BCL11B	BCL2A1	BCL2L11	BCL3
BCL6	BCL9	BCORL1	BCR	BIRC3	BMPR2	BNC2	BPTF	BRD2	BRD3
BRSK1	BRWD1	BTLA	BUB1	C15orf23	C15orf55	C1QA	C1S	C3orf70	C7orf53
C8orf34	CACNA1E	CADM2	CALR	CAMTA1	CASP1	CASQ2	CBLB	CBR1	CBR3
CCDC168	CCNA1	CCNB3	CCT3	CCT5	CCT6B	CD22	CD33	CD5L	CD74
CDA	CDH11	CDH18	CDH23	CDK13	CHD1	CHD1L	CHD4	CHD6	CHD8
CHD9	CHFR	CHI3L1	CHN1	CIITA	CLDN18	CLP1	CLSPN	CLTC	CNOT3
CNOT4	CNTN1	CNTN5	CNTNAP1	CNTNAP5	COL1A1	COL2A1	COL5A1	COL5A2	COL5A3
COPS2	CPS1	CRIPAK	CRLF2	CRNKL1	CRTC1	CSF1	CSF3R	CSMD1	CSMD3
CSNK1A1	CSNK1G3	CTLA4	CTNNA2	CTNND1	CUX1	CXCR4	CYBA	CYP19A1	CYP1A1
CYP1B1	CYP2A13	CYP2C8	CYP2D6	CYP3A4	CYP3A5	DCC	DDX3X	DDX5	DEK
DHX35	DHX9	DIAPH1	DIS3L2	DLC1	DMD	DNAH6	DNAJB1	DNM2	DNMT1
DNMT3B	DOCK2	DOCK7	DPYD	DRGX	DTX1	DUSP22	DYSF	E2F3	EBF1
ECT2L	EED	EEF1A1	EGFL7	EGR3	EIF2AK3	EIF2C3	EIF3A	EIF4A2	EIF4G3
ELAC2	ELF1	ELF3	ELMO1	ELN	EME2	EMID2	EML4	EPC1	EPHA1
EPHA4	EPHA7	EPHB2	EPHB4	EPOR	EPPK1	EPS15	ERBB2IP	ERCC2	ESR2
ETS1	ETV1	ETV5	ETV6	EWSR1	EZR	F8	FAM131B	FAM135B	FAM157B
FAM46C	FAM5C	FAP	FASLG	FAT3	FAT4	FCGR1A	FCGR2A	FCGR2B	FCGR3A
FCRL4	FGF10	FGF12	FGF14	FGF23	FGF6	FLG	FLI1	FLNC	FMN2
FN1	FNDC4	FOXA2	FOXO1	FOXO3	FOXQ1	FRMPD4	FUS	FXR1	FYN
FZD1	G3BP1	G3BP2	GAB2	GABRA6	GATA1	GATA2	GFRAL	GIGYF1	GKN2
GLB1L3	GLI1	GLI2	GLI3	GMPS	GNA13	GNG2	GPC3	GPR124	GPS2
GPX1	GRB7	GSK3B	GSTM5	GSTP1	GUSB	H3F3A	H3F3B	H3F3C	HCLS1
HCN1	HDAC4	HDAC9	HECW1	HEY1	HIST1H1C	HIST1H1D	HIST1H1E	HIST1H2AC	HIST1H2AG
HIST1H2AL	HIST1H2AM	HIST1H2BC	HIST1H2BD	HIST1H2BJ	HIST1H2BK	HIST1H2BO	HIST1H3B	HIST1H3C	HIST1H3D

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HIST1H3F	HIST1H3G	HIST1H3H	HIST1H3I	HIST1H4I	HIST3H3	HLA-A	HLA-B	HLA-C	HLF
HMCN1	HNF1B	HNRPDL	HOXA11	HOXA13	HOXA3	HOXA9	HOXC13	HOXD11	HOXD13
HSD3B1	HSP90AA1	HSP90AB1	HSPA8	HSPD1	HSPH1	ICK	ICOSLG	ID3	IFITM3
IGF1	IGF2	IGF2R	IGLL5	IKZF2	IKZF3	IL10	IL1RAPL1	IL21R	IL6
IL6ST	IMPG1	ING1	INHBA	INPP4A	INPPL1	INSR	IRF4	IRF6	IRS1
ITGB3	ITK	ITSN1	JARID2	KALRN	KAT6A	KAT6B	KCNJ5	KCNQ2	KDM2B
KEL	KIF5B	KLF4	KLHL6	KLK1	KRTAP5-5	L3MBTL1	LAMA2	LATS1	LATS2
LCP1	LEF1	LGALS8	LIFR	LPHN2	LPP	LRP2	LRP4	LRP5	LRP6
LRRC7	LRRK2	LYN	LZTS1	MACF1	MAD1L1	MAGI2	MAML2	MAML3	MAP3K13
MAPK3	MCC	MCM3	MDC1	MECOM	MEF2C	MGA	MIB1	MIOS	MKL1
MLL4	MLLT3	MMP11	MMP2	MN1	MNDA	MNX1	MSH4	MSN	MSR1
MTHFR	MTRR	MUC5B	MYH11	MYH14	MYH9	MYO3A	MYOD1	NAP1L1	NAV3
NCAM2	NCF2	NCF4	NCK1	NCOA3	NCOA4	NCOR2	NCSTN	NDUFA13	NFATC4
NFE2L3	NKX3-1	NLRC3	NOD1	NOS3	NOTCH4	NQO1	NR1I2	NR2F2	NR4A2
NRG1	NRP2	NRXN1	NTM	NUMA1	NUP107	NUP210	NUP93	NUP98	OBSCN
OGDH	OMD	OPCML	OR11G2	OR2T4	OR4A15	OR4C6	OR5L2	OR6F1	P2RY8
P4HB	PABPC1	PABPC3	PAG1	PAK1	PAK3	PASK	PAX3	PAX7	PC
PCDH18	PCSK6	PCSK7	PDCD11	PDE4DIP	PDGFB	PDILT	PER1	PGR	PHF1
PHF6	PIK3C2A	PIK3C2B	PIK3C2G	PIK3C3	PIM1	PKD1L2	PKHD1	PLAG1	PLCB1
PLCG1	PLCG2	PLK1	PLXNA1	PLXNB2	PNRC1	POLQ	POM121	POM121L12	POU2AF1
PPM1D	PPP1R17	PPP6C	PRDM16	PREX2	PRF1	PRKAA1	PRKCB	PRKCI	PRKDC
PRRX1	PRX	PSG2	PSIP1	PSMB1	PSMB5	PTGS1	PTGS2	PTPN13	PTPN2
PTPRB	PTPRK	PTPRO	PTPRS	PTPRT	PTPRU	RAB35	RAC2	RAD21	RAD54B
RANBP2	RASA1	RASGRP1	RBL1	REL	RELN	RFC1	RGS3	RHEB	RHOH
RHOT1	RIT1	RNASEL	ROBO1	ROBO2	ROBO3	ROCK1	RPGR	RPS6KB1	RPS6KB2
RSPO2	RSPO3	RUNX1T1	RUNX2	RXRA	RYR1	RYR2	SBDS	SCUBE2	SDC4
SEC31A	SEMA3A	SEMA3E	SEMA6A	SERPINA7	SETBP1	SETDB1	SF1	SF3A1	SFPQ
SGCZ	SGK1	SH2B3	SH2D1A	SH3PXD2A	SHH	SI	SIN3A	SLC16A1	SLC1A2
SLC22A16	SLC22A18	SLC22A2	SLC22A3	SLC34A2	SLCO1B3	SLIT1	SLIT2	SMARCD1	SMARCE1
SMC1A	SMC1B	SNCAIP	SNTG1	SNX29	SOD2	SOS1	SOX10	SOX17	SPEN
SPRR3	SPSB4	SPTA1	SRD5A2	SRGAP1	SRGAP3	SRSF2	SRSF7	STAG1	STAT1
SUCLG1	SUCLG2	SULT1A1	SUZ12	SVEP1	SYNCRIP	SYNE1	TAF1	TAF15	TAF1L
TAL1	TBL1XR1	TBX15	TBX22	TCEB1	TCF12	TCF3	TCF4	TCL1A	TEC
TENM3	TERT	TET1	TFDP1	TFDP2	TFE3	TGFBR1	THBS2	TJP1	TLE1
TLL2	TLR4	TLX3	TMEM132D	TNFSF11	TNN	TP53BP1	TP63	TP73	TPM3
TPR	TRAF2	TRAF7	TRIM24	TRIM58	TRIO	TRPC5	TRRAP	TSHZ2	TSHZ3
TTF1	TUBA3C	TUBB3	TUSC3	TXNIP	TYMS	TYR	UBE2D2	UBR5	UGT1A1

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UMPS	UPF3B	USH2A	USP6	USP8	VEZF1	VIM	VTCN1	WASF3	WDR90
WDTC1	WHSC1	WHSC1L1	WIPF1	WNK1	WNT5A	WSCD2	WWOX	WWP1	WWP2
XIAP	XPC	XRCC1	XRCC3	YAP1	YY1AP1	ZBTB16	ZC3H11A	ZFHX3	ZFP36L1
ZFP36L2	ZFPM2	ZIC3	ZNF217	ZNF384	ZNF521	ZNF638	ZNF750	ZNF804B	
36 HRR genes analyzed									
ATM	ATR	ATRX	BAP1	BARD1	BLM	BRCA1	BRCA2	BRIP1	CDK12
CHEK1	CHEK2	C11orf30	ERCC1	FAM175A	FANCA	FANCC	FANCD2	FANCE	FANCF
FANCG	FANCL	FANCM	MRE11	NBN	PALB2	RAD50	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RECQL	RECQL4	WRN				
49 genes analyzed for germline mutations									
APC	ATM[1]	ATR[1]	AXIN2	BAP1[1]	BARD1[1]	BLM[1]	BMPR1A	BRCA1[1,2]	BRCA2[1,2]
BRIP1[1]	CDH1	CDK4	CDKN2A	CHEK2[1,2]	EPCAM[2]	FAM175A[1]	FANCA[1]	FANCL[1]	FANCM[1]
GALNT12	HOXB13	MEN1	MITF	MLH1	MRE11[1]	MSH2[2]	MSH3	MSH6[2]	MUTYH[2]
NBN[1]	NF1	NTHL1	PALB2[1,2]	PMS2	POLD1	POLE	PTEN	RAD50[1,2]	RAD51B[1]
RAD51C[1,2]	RAD51D[1,2]	RET	RNF43	SMAD4	SMARCA4	STK11	TP53[2]	VHL	

Note :

1. Genes of the homologous recombination (HR) complex
2. Unless otherwise noted analysis of large rearrangement was performed on the following genes: *BRCA1, BRCA2, CHEK2, EPCAM (Exons 8, 9), MLH1, MSH2, MSH6, MUTYH, PALB2, RAD50 (Exons 1, 2, 4, 10, 14, 21, 23 and 25), RAD51C, RAD51D, and TP53*

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12.f. Levels of Evidence for Genomic Biomarkers

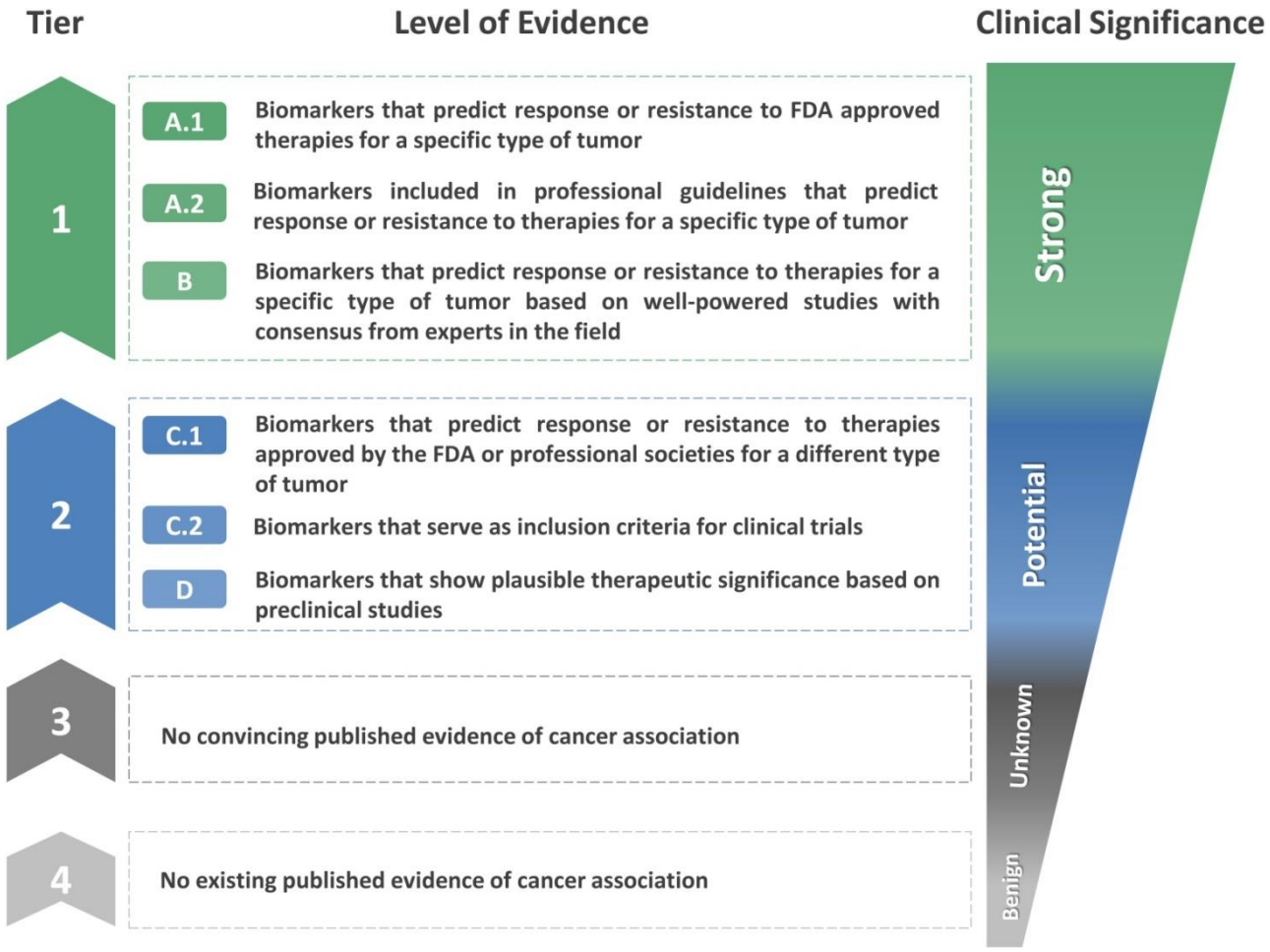

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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