Taipei Veterans General Hospital

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Sample Information

Patient Name: 吳德卿
Gender: Male
ID No.: F101709768
History No.: 47876255
Age: 68

Ordering Doctor: DOC5390F 高冠鈞
Ordering REQ.: 0BPRKQX
Signing in Date: 2021/12/17

Path No.: S110-94848
MP No.: TM21014
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S110-36096A
Percentage of tumor cells: 20%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Other Solid Tumor

Table of Contents

Report Highlights

3 Relevant Biomarkers
1 Therapies Available
5 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*Tumor Mutational Burden* 8.35 Mut/Mb measured **Prognostic significance:** None **Diagnostic significance:** None	None	**pembrolizumab** [1]	3

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*NF1 p.(R816*) c.2446C>T* neurofibromin 1 Allele Frequency: 28.85% **Prognostic significance:** None **Diagnostic significance:** None	None	None	1
IIC	*TP53 p.(R273H) c.818G>A* tumor protein p53 Allele Frequency: 32.60% **Prognostic significance:** None **Diagnostic significance:** None	None	None	1

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

TSC2 p.(R1032) c.3094C>T, MSH2 p.(R929*) c.2785C>T, TET2 p.(F868L) c.2604T>G, MSH6 p.(L1081Afs*11) c.3240_3241delGT*

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
MSH2	p.(R929*)	c.2785C>T	.	chr2:47710068	35.14%	NM_000251.3	nonsense	1998
MSH6	p.(L1081Afs*11)	c.3240_3241delGT	.	chr2:48030625	26.49%	NM_000179.3	frameshift Deletion	1763
TET2	p.(F868L)	c.2604T>G	COSM87107	chr4:106157703	65.13%	NM_001127208.2	missense	1606
TSC2	p.(R1032*)	c.3094C>T	.	chr16:2129160	30.18%	NM_000548.5	nonsense	1173
TP53	p.(R273H)	c.818G>A	COSM10660	chr17:7577120	32.60%	NM_000546.5	missense	2000
NF1	p.(R816*)	c.2446C>T	.	chr17:29556079	28.85%	NM_001042492.3	nonsense	2000
ARID1A	p.(Q1334dup)	c.4001_4002insGCA	.	chr1:27100181	24.16%	NM_006015.6	nonframeshift Insertion	327
TAL1	p.(P276Rfs*4)	c.826_827insG	.	chr1:47685561	4.00%	NM_003189.5	frameshift Insertion	50
MSH2	p.(T564A)	c.1690A>G	.	chr2:47698132	39.19%	NM_000251.3	missense	1998
LRP1B	p.(R1464=)	c.4392A>G	.	chr2:141625346	65.85%	NM_018557.3	synonymous	1909
STK36	p.(A134T)	c.400G>A	.	chr2:219540162	63.90%	NM_015690.5	missense	1967
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.6	nonframeshift Insertion	1966
PHOX2B	p.(S286P)	c.856T>C	.	chr4:41747913	14.93%	NM_003924.4	missense	1822
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.90%	NM_006206.6	synonymous	1977
NOTCH4	p.(G534S)	c.1600G>A	.	chr6:32185796	14.21%	NM_004557.4	missense	1189

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency) (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
NOTCH4	p.(L13_L16del)	c.36_47delGCTGCTGCTGCT	.	chr6:32191658	46.77%	NM_004557.4	nonframeshift Deletion	
ROS1	p.(Y1353S)	c.4058A>C	.	chr6:117677875	36.18%	NM_002944.2	missense	1114
SYNE1	p.(D4661=)	c.13983C>T	.	chr6:152651837	36.37%	NM_182961.4	synonymous	1911
SYNE1	p.(K4121S)	c.12362_12363delAGinsGT	.	chr6:152658141	33.17%	NM_182961.4	missense	1993
SYNE1	p.(K4121R)	c.12362A>G	.	chr6:152658142	65.43%	NM_182961.4	missense	1993
SYNE1	p.(M3369V)	c.10105A>G	.	chr6:152686022	63.93%	NM_182961.4	missense	1999
IGF2R	p.(S1137=)	c.3411C>T	.	chr6:160482789	13.30%	NM_000876.3	synonymous	2000
POT1	p.(?)	c.-15T>G	.	chr7:124537242	24.16%	NM_015450.3	unknown	1668
ADGRA2	p.(A927T)	c.2779G>A	.	chr8:37698635	28.14%	NM_032777.10	missense	1997
ADGRA2	p.(R1277H)	c.3830G>A	.	chr8:37699686	5.56%	NM_032777.10	missense	126
NBN	p.(V346M)	c.1036G>A	.	chr8:90971041	37.75%	NM_002485.5	missense	2000
PTPRD	p.(A545V)	c.1634C>T	.	chr9:8507344	35.58%	NM_002839.4	missense	163
PTPRD	p.(G35=)	c.105G>T	.	chr9:8636804	33.42%	NM_002839.4	synonymous	1885
RET	p.(R189C)	c.565C>T	.	chr10:43598017	29.57%	NM_020975.6	missense	1197
KAT6B	p.(E1101Rfs*35)	c.3301_3302delGA	.	chr10:76781916	99.58%	NM_012330.4	frameshift Deletion	1443
FGFR2	p.(I422T)	c.1265T>C	.	chr10:123274653	29.54%	NM_000141.5	missense	1997
GUCY1A2	p.(G723=)	c.2169C>T	.	chr11:106558305	64.96%	NM_000855.3	synonymous	1618
ADAMTS20	p.(Y459=)	c.1377C>T	.	chr12:43858526	13.28%	NM_025003.5	synonymous	1958
HCAR1	p.(P283=)	c.849C>T	.	chr12:123214038	45.58%	NM_032554.4	synonymous	1744
EP400	p.(E1853D)	c.5559G>T	.	chr12:132514423	8.35%	NM_015409.5	missense	1832
IRS2	p.(Q1269P)	c.3806A>C	.	chr13:110434595	44.80%	NM_003749.3	missense	433
NKX2-1	p.(A302=)	c.906G>C	.	chr14:36986783	16.52%	NM_001079668.3	synonymous	666
MAP2K1	p.(A257=)	c.771G>A	.	chr15:66777405	28.75%	NM_002755.4	synonymous	2000
COL1A1	p.(S1199G)	c.3595A>G	.	chr17:48264220	68.82%	NM_000088.4	missense	1966
RNF213	p.(R4963C)	c.14887C>T	.	chr17:78360656	40.65%	NM_001256071.3	missense	2000
TCF3	p.(S253=)	c.759C>T	.	chr19:1622116	99.90%	NM_001136139.4	synonymous	959
AXL	p.(I708=)	c.2124C>T	.	chr19:41762444	64.20%	NM_021913.5	synonymous	2000
ITGB2	p.(V761=)	c.2283C>T	.	chr21:46306310	99.95%	NM_000211.5	synonymous	1999
MYH9	p.(T807=)	c.2421C>T	.	chr22:36698692	62.14%	NM_002473.6	synonymous	1474
KDM6A	p.(S418I)	c.1253G>T	.	chrX:44919325	41.60%	NM_021140.3	missense	1077
TFE3	p.(A474T)	c.1420G>A	.	chrX:48887977	26.74%	NM_006521.6	missense	258

Biomarker Descriptions

MSH2 (mutS homolog 2)

Background: The MSH2 gene encodes the mutS homolog 2 protein[1]. MSH2 is a tumor suppressor gene that heterodimerizes with MSH6 to form the MutSα complex or with MSH3 to form the MutSβ complex[2]. Both MutS complexes function in DNA damage recognition of base-base mismatches or insertion/deletion (indels) mispairs[2]. Specifically, the MutSα complex recognizes 1-2 nucleotide indels while MutSβ recognizes longer indel mispairs[2]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication. Mutations in MSH2 result in the degradation of MSH6[3]. Loss of MSH2 protein expression correlate to mutations in the genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[4]. MSH2, along with MLH1, MSH6, and PMS2 form the core components of the MMR pathway[5]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[2]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[5,6,7]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[5,8]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer.[6,8,9,10]. Specifically, MSH2 mutations are associated with increased risk of ovarian and pancreatic cancer[11].

Alterations and prevalence: Somatic mutations in MSH2 are observed in 8% of uterine corpus endometrial carcinoma, as well as 2-3% of bladder urothelial carcinoma, melanoma, and colorectal adenocarcinoma[12,13].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[14]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[15,16].

MSH6 (mutS homolog 6)

Background: The MSH6 gene encodes the mutS homolog 6 protein[1]. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex[2]. The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides[2]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication. Mutations in MSH2 result in the degradation of MSH6[3]. MSH6, along with MLH1, MSH2, and PMS2 form the core components of the MMR pathway[2]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[5,6,7]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[5,8]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[6,8,9,10]. Specifically, MSH6 mutations are associated with increased risk of ovarian and pancreatic cancer[11].

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma[12,13].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[14]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[15,16].

NF1 (neurofibromin 1)

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[17]. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state[17,18]. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival[17]. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)[17,19,20].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[17]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[17,21]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[17,20].

Biomarker Descriptions (continued)

Potential relevance: Somatic NF1 mutations are an ancillary diagnostic criteria for malignant peripheral nerve sheath tumor (MPNST) in soft tissue sarcoma[22,23].

TET2 (tet methylcytosine dioxygenase 2)

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[24]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[25,26]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[27]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[24,25,26]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[20]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[25,28]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[22,29]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[29,30]

TP53 (tumor protein p53)

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[31]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[32,33].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[12,13,34,35,36,37]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[12,13]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[38,39,40,41].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[42]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[43] and breakthrough designation[44] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[45,46]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),[20,29,47,48]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[49]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[50].

TSC2 (TSC complex subunit 2)

Background: The TSC2 gene encodes the tuberin protein. TSC2 and TSC1 (also known as hamartin) form a complex through their respective coiled-coil domains[51]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[52]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway[51,53]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[51].

Alterations and prevalence: Somatic mutations are observed in up to 8% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of cervical squamous cell carcinoma[12,13].

Potential relevance: Currently, no therapies are approved for TSC2 aberrations.

Biomarker Descriptions (continued)

Tumor Mutational Burden

Background: Tumor mutational burden (TMB), also known as tumor mutational load (TML), is the count of somatic mutations in the DNA of cancer cells. TMB is determined by next-generation sequencing and is expressed as the number of mutations per megabase (mut/Mb) of DNA coding sequence[54]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[55,56,57,58,59]. High TMB is associated with increased neo-antigen burden and has been linked to response to immune checkpoint inhibitors (ICIs) that target the cytotoxic T lymphocyte antigen-4 (CTLA4), programmed death protein 1 (PD1), and programmed death-ligand 1 (PD-L1) inhibitors[60,61,62,63].

Alterations and prevalence: In one study of over 100,000 tumor samples, the median TMB value was 3.6 mut/Mb although TMB values vary widely across cancers[64]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[61,64]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[61,64]. For example, within non-small cell lung cancer (NSCLC), higher TMB was observed in former/current smokers (10.5 mut/Mb) relative to never smokers (0.6 mut/Mb)[61,64,65]. There is no consensus around the definition of high and low TMB that could be applied universally to all tumor types, instead multiple sources suggest that TMB status is a cancer type specific attribute[64,66,67]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[68,69,70,71].

Potential relevance: ICIs stimulate a patient's own T-cells to kill tumors and have exhibited benefits in some patients. The first ICI to be approved by the FDA was ipilimumab (2011), an anti-CTLA4 antibody indicated for the treatment of metastatic melanoma. In 2014, anti-PD-1 antibodies, nivolumab (2014) and pembrolizumab (2014), were subsequently approved for the treatment of metastatic melanoma. Pembrolizumab was also approved (2014) for advanced esophageal squamous cell carcinoma. In 2020, the indication for pembrolizumab[14] was expanded to include TMB-H (>/= 10 mut/Mb) solid tumors that have progressed on prior therapy. Indications have been expanded for these ICIs to include several other cancer types including NSCLC, advanced renal cell carcinoma, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability (MSI)-High or mismatch repair deficient (dMMR) colorectal cancer, and hepatocellular carcinoma. Atezolizumab (2016), avelumab (2017), and durvalumab (2017), that target programmed death-ligand 1 (PD-L1), were subsequently approved by the FDA. However, the predictive biomarkers that underlie the clinical benefits of these approved immunotherapies, including TMB, are under active investigation. Several published studies including the CheckMate 586 and CheckMate 817 clinical trials have concluded that high TMB was associated with improved response to FDA approved checkpoint inhibitors[69,72,73]. In contrast, several promising previous trials failed to show an improvement in survival outcomes between high and low TMB including CheckMate 227 (ipilimumab + nivolumab vs. chemotherapy), CheckMate 026 (nivolumab vs. chemotherapy), KEYNOTE 189 (pembrolizumab vs. chemotherapy), KEYNOTE 021 (pembrolizumab vs. pembrolizumab + chemotherapy), and Lung-MAP (nivolumab + ipilimumab vs. nivolumab). In response, suggestions to combine TMB score with PD-L1 expression as a way to increase the predictive power for patient stratification have been reported[74]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[75]. Pembrolizumab is indicated for use in various cancer types with evidence of metastasis including Ewing sarcoma, salivary gland neoplasms, cervical cancer, uterine sarcoma, endometrial carcinoma, thyroid cancer, ovarian cancer, esophageal cancer, esophagogastric junction cancer, breast cancer, and germ cell tumors with high TMB[76,77,78,79,80,81,82,83,84]. TMB score estimation is affected by the utilized assays, therefore efforts are underway to develop a standardized approach for score calculation with the aim to support consistent reporting of TMB values across laboratories[85,86,87,88].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	○	○	✖	✖	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
pembrolizumab, quavonlimab, favezelimab, lenvatinib	✖	✖	✖	✖	○ (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

NF1 p.(R816*) c.2446C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
RMC-4630, pembrolizumab	✖	✖	✖	✖	● (I/II)

TP53 p.(R273H) c.818G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab, chemotherapy, radiation therapy	✖	✖	✖	✖	○ (III)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Details

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2021-10-13. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

○ pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2021-08-31 **Variant class:** Tumor Mutational Burden

Indications and usage:

KEYTRUDA® is a programmed death receptor-1 (PD-1)-blocking antibody indicated:

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma.
- for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

Non-Small Cell Lung Cancer (NSCLC)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC 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 receiving KEYTRUDA®.

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Limitations of Use: KEYTRUDA® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Tumor Mutational Burden (continued)

- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with MSI-H central nervous system cancers have not been established.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

- for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.[1]
- as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS)≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1]

Esophageal Cancer

- for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

Cervical Cancer

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.[1]

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1]

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1]

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of adult patients with advanced RCC.
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.

Endometrial Carcinoma

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Tumor Mutational Burden-High (TMB-H) Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma (cSCC)

- for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)

Tumor Mutational Burden (continued)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[2]

[1]This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

[2]This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s117,s118lbl.pdf

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2021-10-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

Tumor Mutational Burden

○ pembrolizumab

Cancer type: Chondrosarcoma, Osteosarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2022]

○ pembrolizumab

Cancer type: Breast Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IV; Invasive, Unresectable, Metastatic, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 8.2021]

○ pembrolizumab

Cancer type: Cervical Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Metastatic, Progression (Second-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2021]

○ pembrolizumab

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 4.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Gastric Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 4.2021]

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pembrolizumab

Cancer type: Head and Neck Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Nasopharyngeal; Recurrent, Unresectable, Metastatic (Subsequent therapy); Useful in certain circumstances
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

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pembrolizumab

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2021]

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pembrolizumab

Cancer type: Ovarian Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 3.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2022]

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pembrolizumab

Cancer type: Testicular Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Germ Cell Tumor; Metastatic (Third-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Testicular Cancer [Version 2.2021]

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pembrolizumab

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Locally Recurrent, Advanced, Metastatic (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2021]

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pembrolizumab

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Persistent, Local, Distant Metastases, Regional (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2021]

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pembrolizumab

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVC; Metastatic (Second-line therapy); Useful in certain circumstances, Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Endometrial Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 4.2021]

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pembrolizumab

Cancer type: Uterine Sarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Second-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 4.2021]

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pembrolizumab

Cancer type: Ewing Sarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2022]

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pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Adenocarcinoma; Visceral Metastases, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2022]

Clinical Trials in Taiwan region:

Clinical Trials Summary

Tumor Mutational Burden

NCT ID	Title	Phase
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158).	II
NCT03516981	A Phase II Precision Oncology Study of Biomarker-Directed, Pembrolizumab-(MK-3475, SCH 900475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (KEYNOTE-495; KeyImPaCT)	II

NF1 p.(R816*) c.2446C>T

NCT ID	Title	Phase
NCT04418661	A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I/II

TP53 p.(R273H) c.818G>A

NCT ID	Title	Phase
NCT04634877	A Phase III, Randomized, Double-Blind Study of Pembrolizumab Versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent (KEYNOTE-B21/ ENGOT-en11 / GOG-3053)	III

Alerts Informed By Public Data Sources

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-10-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

Tumor Mutational Burden

pembrolizumab

Cancer type: Giant Cell Tumor of Soft Tissue **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "NCCN does not recommend this systemic treatment for GCTB since it is not technically a malignant tumor."

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2022]

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2021-10-01. For the most up-to-date information, search www.esmo.org.

NF1 p.(R816*) c.2446C>T

imatinib

Cancer type: Gastrointestinal Stromal Tumor **Variant class:** NF1 mutation

Other criteria: SDH underexpression

ESMO Level of Evidence/Grade of Recommendation: IV / D

Summary:
ESMO™ Clinical Practice Guidelines include the following supporting statement:
- "Adjuvant treatment should be avoided in NF1-related and SDH expression negative GISTs [IV, D]."

Reference: ESMO Clinical Practice Guidelines - ESMO-EUROCAN-Gastrointestinal Stromal Tumours [Annals of Oncology (2021), doi: https://doi.org/10.1016/j.annonc.2021.09.005.]

Signatures

Testing Personnel:

2021.12.20
08:29:08 +08'00'

Laboratory Supervisor:

2021.12.20
08:29:22 +08'00'

Pathologist:

2021.12.20
08:29:37 +08'00'

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