Taipei Veterans General Hospital

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Sample Information

Patient Name: 胡淑娟
Gender: Female
ID No.: A201592153
History No.: 8553295
Age: 66

Ordering Doctor: DOC1885G楊慕華
Ordering REQ.: 0AXYUQC
Signing in Date: 2020/11/04

Path No.: S109-89815
MP No.: TM20005
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-42700A
Percentage of tumor cells: 90%
Note:

Sample Cancer Type: Melanoma

Report Highlights

2 Relevant Biomarkers
7 Therapies Available
31 Clinical Trials

Relevant Melanoma Findings

Gene	Finding
BRAF	Not detected
KIT	Not detected
NTRK1	Not detected
NTRK3	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*NRAS p.(Q61R) c.182A>G* NRAS proto-oncogene, GTPase Allele Fraction: 0.459	anti-CTLA-4 + anti-PD-1 anti-PD-1 binimetinib	cabozantinib	20

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], 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
	Tumor Mutational Burden 2.5 Mut/Mb measured	**pembrolizumab** [1]	ipilimumab + nivolumab nivolumab pembrolizumab	11

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, 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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
NRAS	p.(Q61R)	c.182A>G	COSM584	chr1:115256529	0.459	NM_002524.4	missense	85
PDE4DIP	p.(K17R)	c.50A>G	.	chr1:144994682	0.055	NM_001198834.3	missense	2000
IKBKE	p.(R49L)	c.146G>T	.	chr1:206647732	0.285	NM_014002.3	missense	2000
MSH6	p.(P1082S)	c.3244C>T	.	chr2:48030630	0.508	NM_000179.2	missense	1806
LRP1B	p.(=)	c.4392A>G	.	chr2:141625346	0.526	NM_018557.2	synonymous	2000
FN1	p.(S2296L)	c.6887C>T	.	chr2:216232717	0.403	NM_212482.2	missense	2000
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	1.000	NM_002343.5	nonframeshift Insertion	553
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	1.000	NM_006206.5	synonymous	1988
FLT4	p.(R1354H)	c.4061G>A	.	chr5:180030223	0.524	NM_182925.4	missense	1998
NOTCH4	p.(L13_L16del)	c.36_47delGCTGCTGCTGCT	.	chr6:32191658	0.283	NM_004557.3	nonframeshift Deletion	
SYNE1	p.(L5015M)	c.15043T>A	.	chr6:152647681	1.000	NM_182961.3	missense	1997
SYNE1	p.(M1443I)	c.4329G>A	.	chr6:152755062	0.242	NM_182961.3	missense	1999
ADGRA2	p.(A1098G)	c.3293C>G	.	chr8:37699149	0.032	NM_032777.9	missense	63
PRKDC	p.(H3747R)	c.11242A>G	.	chr8:48695092	0.524	NM_006904.6	missense	1998
PRKDC	p.(=)	c.6479C>T	.	chr8:48769846	0.576	NM_006904.6	synonymous	1994
PTPRD	p.(=)	c.3624C>T	.	chr9:8465556	0.320	NM_002839.3	synonymous	1445
SYK	p.(=)	c.1770G>A	.	chr9:93650844	0.288	NM_003177.6	synonymous	2000
RET	p.(T278N)	c.833C>A	.	chr10:43600607	0.550	NM_020975.4	missense	1997
KAT6B	p.(=)	c.369C>T	.	chr10:76602984	0.078	NM_012330.3	synonymous	51
MAML2	p.(S462A)	c.1384T>G	.	chr11:95825811	0.516	NM_032427.3	missense	1998
MDM2	p.(P320S)	c.958C>T	.	chr12:69233093	0.677	NM_002392.5	missense	2000

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
EP400	p.(V1678M)	c.5032G>A	.	chr12:132511999	0.243	NM_015409.4	missense	2000
MMP2	p.(=)	c.51C>T	.	chr16:55513442	0.556	NM_004530.5	synonymous	543
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	0.473	NM_001795.4	missense	1966
HLF	p.(?)	c.-47T>TCTTTT	.	chr17:53342799	0.098	NM_002126.4	unknown	1101
MALT1	p.(=)	c.1164A>G	.	chr18:56390425	0.317	NM_006785.3	synonymous	1503
MALT1	p.(H778R)	c.2333A>G	.	chr18:56414932	0.695	NM_006785.3	missense	1998
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	1.000	NM_001136139.3	missense	673
PIK3R2	p.(P151S)	c.451C>T	.	chr19:18271764	0.498	NM_005027.3	missense	771
PIK3R2	p.(R508H)	c.1523G>A	.	chr19:18277076	0.500	NM_005027.3	missense	1997
CIC	p.(=)	c.4374G>A	.	chr19:42798802	0.313	NM_015125.4	synonymous	1481
PTPRT	p.(G938R)	c.2812G>A	.	chr20:40770570	0.354	NM_133170.3	missense	2000
RUNX1	p.(Q397R)	c.1190A>G	.	chr21:36164685	0.509	NM_001754.4	missense	905
MN1	p.(Q529R)	c.1586A>G	.	chr22:28194946	0.055	NM_002430.2	missense	55
CHEK2	p.(H371Y)	c.1111C>T	.	chr22:29091846	0.473	NM_007194.3	missense	607

Biomarker Descriptions

NRAS (NRAS proto-oncogene, GTPase)

Background: The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[1,2,3].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. NRAS mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers[4,5]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[4,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[9] and panitumumab[10], are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[8]. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[11] as well as melanoma[12]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[13].

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

Biomarker Descriptions (continued)

(mut/Mb) of DNA coding sequence[14]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[15,16,17,18,19]. 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[20,21,22,23].

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[24]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[21,24]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[21,24]. 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)[21,24,25]. 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[24,26,27]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[28,29,30,31].

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, and pembrolizumab also for advanced esophageal squamous cell carcinoma. In 2020, the indication for pembrolizumab[32] 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 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[29,33,34]. In contrast, several previously promising trials have 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 (pembroluzimab vs. chemotherapy), KEYNOTE 021 (pembroluzimab vs. pembroluzimab + 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[35]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[36]. TMB score estimation is affected by the utilized assays, therefore efforts are underway to develop a standardized approach to calculate with the aim to support consistent reporting of TMB values across laboratories[37,38,39,40].

Relevant Therapy Summary

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

NRAS p.(Q61R) c.182A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
binimetinib	✖	●	✖	✖	✖
anti-CTLA-4 + anti-PD-1	✖	✖	✖	●	✖
anti-PD-1	✖	✖	✖	●	✖
cabozantinib	✖	✖	✖	○	✖
selumetinib, ulixertinib	✖	✖	✖	✖	● (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

NRAS p.(Q61R) c.182A>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trametinib, dabrafenib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
trametinib, antimalarial	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
FCN-159	✖	✖	✖	✖	● (I)
IN10018, cobimetinib	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	✖	✖	● (I)
LXH254 , spartalizumab	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
MLN-2480	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (II)
ipilimumab + nivolumab	✖	○	✖	○	✖
nivolumab	✖	○	✖	✖	● (I/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

Tumor Mutational Burden (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BAY1905254	✖	✖	✖	✖	● (I)
BI 754091, BI 754111	✖	✖	✖	✖	● (I)
zimberelimab	✖	✖	✖	✖	● (I)

* 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 2020-09-16. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2020-06-29 **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®.

Small Cell Lung Cancer (SCLC)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1]

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 and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1]

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.[1]

Tumor Mutational Burden (continued)

- 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 cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1]
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- 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 Cancer 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] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[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 first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction 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 recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

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 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 and are not candidates for curative surgery or radiation.[1]

Tumor Mutational Burden-High (TMB-H) Cancer

Tumor Mutational Burden (continued)

- 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 cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

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/2020/125514s084lbl.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 2020-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NRAS p.(Q61R) c.182A>G

● binimetinib

Cancer type: Melanoma **Variant class:** NRAS mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy; Progression after prior immune checkpoint inhibitor therapy (Second-line or subsequent therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 3.2020]

Tumor Mutational Burden

○ ipilimumab + nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2020]

○ nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2020]

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent or Metastatic Cervical Cancer; Progressed on prior treatment and does not have satisfactory alternative treatment options; Tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] as determined by an FDA-approved test (Second-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 2.2020]

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pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Unresectable locoregional recurrent/persistent disease not amenable to RAI therapy (Not specified)
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; CNS or soft tissue or bone metastases not amenable to RAI therapy (Not specified)
- Thyroid Gland Medullary Carcinoma; Locoregional recurrent/persistent disease (Not specified) (Useful in Certain Circumstances)
- Thyroid Gland Medullary Carcinoma; Recurrent or persistent disease; Distant metastases; Asymptomatic, symptomatic or progression of disease (Not specified) (Useful in Certain Circumstances)
- Thyroid Gland Anaplastic Carcinoma; Metastatic (Not specified) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

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pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable or Metastatic Endometrial Carcinoma or Uterine Sarcoma; Progressed on prior treatment and does not have satisfactory alternative treatment options; Tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] as determined by an FDA-approved test (Not specified) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2020]

Current ESMO Information

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

ESMO information is current as of 2020-09-01. For the most up-to-date information, search www.esmo.org.

NRAS p.(Q61R) c.182A>G

● anti-CTLA-4 + anti-PD-1

Cancer type: Melanoma **Variant class:** NRAS mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz41]

● anti-PD-1

Cancer type: Melanoma **Variant class:** NRAS mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz41]

○ cabozantinib

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** RAS mutation

ESMO Level of Evidence/Grade of Recommendation: II / C

Population segment (Line of therapy):
- Metastatic Thyroid Gland Medullary Carcinoma (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology 30: 1856–1883, 2019 doi:10.1093/annonc/mdz400]

Tumor Mutational Burden

ipilimumab + nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage IV Squamous and Non-squamous (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance

FDA information is current as of 2020-09-16. For the most up-to-date information, search www.fda.gov.

NRAS p.(Q61R) c.182A>G

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2019-04-23 **Variant class:** NRAS Q61 mutation

Indications and usage:

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer
- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test
- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf

NRAS p.(Q61R) c.182A>G (continued)

panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2017-06-29 **Variant class:** NRAS Q61 mutation

Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.
- Limitation of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf

Current NCCN Information

Contraindicated Not recommended Resistance

NCCN information is current as of 2020-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NRAS p.(Q61R) c.182A>G

cetuximab

Cancer type: Colon Cancer **Variant class:** NRAS exon 3 mutation

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

- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

cetuximab

Cancer type: Rectal Cancer **Variant class:** NRAS exon 3 mutation

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

- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 6.2020]

NRAS p.(Q61R) c.182A>G (continued)

panitumumab

Cancer type: Colon Cancer **Variant class:** NRAS exon 3 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

panitumumab

Cancer type: Rectal Cancer **Variant class:** NRAS exon 3 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 6.2020]

Current EMA Information

Contraindicated Not recommended Resistance

EMA information is current as of 2020-09-16. For the most up-to-date information, search www.ema.europa.eu/ema.

NRAS p.(Q61R) c.182A>G

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-30 **Variant class:** NRAS exon 3 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-24 **Variant class:** NRAS exon 3 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf

Current ESMO Information

Contraindicated Not recommended Resistance

ESMO information is current as of 2020-09-01. For the most up-to-date information, search www.esmo.org.

NRAS p.(Q61R) c.182A>G

cetuximab

Cancer type: Colorectal Cancer **Variant class:** NRAS exon 3 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

cetuximab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** NRAS exon 3 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

NRAS p.(Q61R) c.182A>G (continued)

panitumumab

Cancer type: Colorectal Cancer **Variant class:** NRAS exon 3 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

panitumumab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** NRAS exon 3 mutation

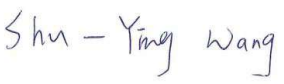
Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

Signatures

Testing Personnel:



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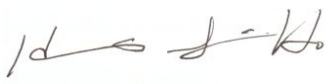
Laboratory Supervisor:



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Pathologist:

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