Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 陳許壽美
Gender: Female
ID No.: F226091152
History No.: 32627944
Age: 78

Ordering Doctor: DOC3016D 江起陸
Ordering REQ.: 0BHDYQC
Signing in Date: 2021/06/25

Path No.: S110-98989
MP No.: F21050
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-18571A
Percentage of tumor cells: 40%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page
Variant Details	2
Biomarker Descriptions	2
Relevant Therapy Summary	3
Relevant Therapy Details	6
Clinical Trials Summary	6
Alert Details	10

Report Highlights

2 Relevant Biomarkers
1 Therapies Available
61 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	***KRAS p.(G12C) c.34G>T***	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*KRAS p.(G12C) c.34G>T* KRAS proto-oncogene, GTPase Allele Frequency: 22.72%	None	cabozantinib	55
IIC	*KIT p.(M541L) c.1621A>C* KIT proto-oncogene, receptor tyrosine kinase Allele Frequency: 47.82%	None	None	6

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KIT	p.(M541L)	c.1621A>C	.	chr4:55593464	47.82%	NM_000222.3	missense	1997
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	22.72%	NM_033360.4	missense	1994
JAK1	p.(P733=)	c.2199A>G	.	chr1:65310489	47.35%	NM_002227.4	synonymous	1998
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.05%	NM_213647.3	missense	2000
EGFR	p.(Q787=)	c.2361G>A	.	chr7:55249063	47.42%	NM_005228.5	synonymous	1999

Biomarker Descriptions

KIT (KIT proto-oncogene, receptor tyrosine kinase)

Background: The KIT gene, also known as CD117, encodes the KIT proto-oncogene receptor tyrosine kinase (c-KIT), a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, CSF1R, FLT1, FLT3, FLT4 and KDR[1,2]. KIT is a receptor for stem cell factor, important in regulating growth and development of hematopoietic cells[3]. The KIT gene is flanked by the PDGFRA and KDR genes on chromosome 4q12. Ligand binding to KIT results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways promoting cell proliferation and survival[4].

Alterations and prevalence: Recurrent somatic KIT alterations are observed in both solid and hematological cancers and include activating mutations such as single nucleotide variants, small duplications, and complex in-frame insertions or deletions (indels). Mutations in KIT exons 8, 9, 11, and 17 disrupt auto-inhibitory mechanisms and lead to constitutive activity[5]. Gain of function mutations are found in up to 70% of mast cell tumors, 17% of nasal T-cell lymphomas, and 9% of dysgerminoma[6]. Somatic mutations in exon 11 occur in 60-70% of all gastrointestinal stromal tumor (GIST), whereas alterations in exons 8 and 17 are more common in myeloid cancers[5,6,7]. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80-93% of aggressive forms of mastocytosis[8,9].

Potential relevance: Imatinib[10] (2001) is approved for KIT positive malignant GIST and adult patients with aggressive systemic mastocytosis (SM) harboring D816V mutations. Imatinib is also recommended for KIT activating mutations in melanoma and exon 9 and 11 mutations in GIST[11,12,13]. Mutations in exon 17 have been identified to confer resistance to imatinib and sunitinib[14]. Patients with acute myeloid leukemia (AML) that harbor KIT activating mutations with t(8;21) and inv(16) have an increased risk of relapse[15]. KIT D816V mutation is associated with the diagnosis of SM and aggressiveness of the disease[16,17].

Biomarker Descriptions (continued)

KRAS (KRAS proto-oncogene, GTPase)

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS 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[18,19,20].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[21]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[21,22,23]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,24].

Potential relevance: Currently, no therapies are approved for KRAS aberrations. However, the KRAS G12C inhibitor, sotorasib (AMG-510), was granted fast track (2019) and breakthrough (2020) therapy designation for previously treated non-small cell lung cancer (NSCLC) patients with KRAS G12C mutation[25,26]. Additionally, onvansertib[27] was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[28] and panitumumab[29], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[24]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[30].

Relevant Therapy Summary

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

KRAS p.(G12C) c.34G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
adagrasib	✖	✖	✖	✖	● (III)
bevacizumab, chemotherapy	✖	✖	✖	✖	● (III)
pembrolizumab, lenvatinib, chemotherapy	✖	✖	✖	✖	● (III)
adagrasib, pembrolizumab	✖	✖	✖	✖	● (II)
atezolizumab, cobimetinib	✖	✖	✖	✖	● (II)
ceralasertib + durvalumab	✖	✖	✖	✖	● (II)
regorafenib, chemotherapy	✖	✖	✖	✖	● (II)
RO-5126766, defactinib	✖	✖	✖	✖	● (II)
sintilimab, anlotinib hydrochloride	✖	✖	✖	✖	● (II)
spartalizumab	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)
TVB-2640	✖	✖	✖	✖	● (II)
ulixertinib	✖	✖	✖	✖	● (II)
adagrasib, pembrolizumab, cetuximab, afatinib	✖	✖	✖	✖	● (I/II)
afatinib, selumetinib	✖	✖	✖	✖	● (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

KRAS p.(G12C) c.34G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ASTX029	✖	✖	✖	✖	● (I/II)
binimetinib + palbociclib, binimetinib, palbociclib	✖	✖	✖	✖	● (I/II)
D-1553	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
JDQ-443, TNO-155, spartalizumab	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
rigosertib, nivolumab	✖	✖	✖	✖	● (I/II)
RMC-4630, cobimetinib	✖	✖	✖	✖	● (I/II)
selinexor, chemotherapy	✖	✖	✖	✖	● (I/II)
selumetinib, durvalumab, tremelimumab	✖	✖	✖	✖	● (I/II)
sotorasib	✖	✖	✖	✖	● (I/II)
telaglenastat, palbociclib	✖	✖	✖	✖	● (I/II)
TNO-155, adagrasib	✖	✖	✖	✖	● (I/II)
AZD-0364	✖	✖	✖	✖	● (I)
BBP-398	✖	✖	✖	✖	● (I)
BGB-3245	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
DAY-101	✖	✖	✖	✖	● (I)
FCN-437	✖	✖	✖	✖	● (I)
GDC-6036	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	✖	✖	● (I)
mRNA-5671, pembrolizumab	✖	✖	✖	✖	● (I)
NBF-006	✖	✖	✖	✖	● (I)
neratinib, trametinib	✖	✖	✖	✖	● (I)
pembrolizumab + trametinib	✖	✖	✖	✖	● (I)

* 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

KRAS p.(G12C) c.34G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
PF-07284892, binimetinib	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RMC-4630, pembrolizumab	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (I)
sotorasib, PD-1 Inhibitor, Pan-ErbB tyrosine kinase inhibitor, chemotherapy, anti-PD-L1 antibody	✖	✖	✖	✖	● (I)
TAK 659, chemotherapy	✖	✖	✖	✖	● (I)
TAS-0612	✖	✖	✖	✖	● (I)
TNO-155, spartalizumab	✖	✖	✖	✖	● (I)

KIT p.(M541L) c.1621A>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avapritinib	✖	✖	✖	✖	● (II)
cabozantinib	✖	✖	✖	✖	● (II)
dasatinib, sunitinib	✖	✖	✖	✖	● (II)
nilotinib, pazopanib	✖	✖	✖	✖	● (II)
ponatinib	✖	✖	✖	✖	● (II)
sunitinib, regorafenib	✖	✖	✖	✖	● (II)

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

Relevant Therapy Details

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 2021-04-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12C) c.34G>T

○ **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 (First-line therapy)

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

Clinical Trials Summary

KRAS p.(G12C) c.34G>T

NCT ID	Title	Phase
NCT04685135	A Randomized Phase III Study of MRTX849 Versus Docetaxel in Patients With Previously Treated Non-Small Cell Lung Cancer With KRAS G12C Mutation	III
NCT04613596	A Phase II Trial of MRTX849 in Combination With Pembrolizumab in Patients With Advanced Non-Small Cell Lung Cancer With KRAS G12C Mutation	II
NCT03785249	A Phase I/II Multiple Expansion Cohort Trial of MRTX849 in Patients With Advanced Solid Tumors With KRAS G12C Mutation KRYSTAL-1	I/II
NCT04699188	A Phase Ib/II Open-label, Multi-center Dose Escalation Study of JDQ443 in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation	I/II
NCT03600883	A Phase I/II, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With KRAS p.G12C	I/II
NCT04330664	A Phase 1/2 Trial of MRTX849 in Combination With TNO155 in Patients With Advanced Solid Tumors With KRAS G12C Mutation KRYSTAL 2.	I/II
NCT04528836	A Phase I/IB First-in-Human Study of the SHP2 Inhibitor BBP-398 (Formerly Known as IACS-15509) in Patients With Advanced Solid Tumors	I
NCT03948763	A Phase I, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT04185883	A Phase Ib, Protocol Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 (pINN) Sotorasib Monotherapy and in Combination With Other Anti-cancer Therapies in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101)	I

Clinical Trials Summary (continued)

KRAS p.(G12C) c.34G>T (continued)

NCT ID	Title	Phase
NCT04000529	A Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability, and Preliminary Efficacy of TNO155 in Combination With Spartalizumab or Ribociclib in Selected Malignancies	I
NCT03808558	A Phase II Single-Center Pharmacodynamic Study of TVB-2640 In KRAS Mutant Non-Small Cell Lung Carcinomas	II
NCT03095612	An Investigator-Sponsored, Phase I/II Trial of the Oral XPO1 Inhibitor Selinexor (KPT-330) in Combination With Docetaxel for Previously Treated, Advanced KRAS Mutant Non-small Cell Lung Cancer (NSCLC)	I/II
NCT04045496	A Phase I, Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Evidence of Antitumor Activity of JAB-3312 in Adult Patients With Advanced Solid Tumors	I
NCT02450656	Phase I/II Study With the Combination of Afatinib and Selumetinib in Advanced KRAS Mutant Positive and PIK3CA Wildtype Non-small Cell Lung Cancer	I/II
NCT02743923	Chemotherapy in KRAS Mutated Chemotherapy Naive Non-small Cell Lung Cancer Patients: a Phase III Study Comparing Cisplatin-pemetrexed With Carboplatin-paclitaxel-bevacizumab: NVALT 22	III
NCT04716933	A Phase III Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) With or Without Lenvatinib (E7080/MK-7902) as First-line Intervention in Participants With Metastatic Nonsquamous Non-small Cell Lung Cancer (LEAP-006)	III
NCT03600701	A Phase II Study of Atezolizumab and Cobimetinib in PD-1/PD-L1 Inhibitor Resistant or Refractory Non-Small Cell Lung Cancer	II
NCT02664935	National Lung Matrix Trial: Multi-drug, Genetic Marker-directed, Non-comparative, Multi-centre, Multi-arm Phase II Trial in Non-small Cell Lung Cancer	II
NCT03520842	Study of Regorafenib in Combination With Oral Methotrexate for KRAS Mutated Non-Small Cell Lung Cancer (NSCLC)	II
NCT04620330	A Phase II Study of VS-6766 (Dual RAF/MEK Inhibitor) as a Single Agent and In Combination With Defactinib (FAK Inhibitor) in Recurrent KRAS-Mutant (KRAS-MT) Non-Small Cell Lung Cancer (NSCLC)	II
No NCT ID	Safety and Efficacy of Sintilimab Combined With Anlotinib in Patients With KRAS Mutant Advanced / Metastatic Non-Small Cell Lung Cancer: a Prospective, Single-Arm Study	II
NCT04790409	A Single-Arm, Open-Label, Phase II Study of PD-1 Monoclonal Antibody Combined with Anlotinib in the Treatment of Advanced Rare-Mutant Non-Small Cell Lung Cancer (NSCLC)	II
NCT03693326	An Open-Label, Multicenter, Phase II Study of PDR001 in Patients with Non-Small Cell Lung Cancer Harboring KRAS/NRAS Mutation or Without Actionable Genetic Abnormalities, Detected Using NGS Platform	II
No NCT ID	A Single-center, Open-label , Non-randomized Control Clinical Trial On Clinical Features and Medical Treatment of Advanced NSCLC With Rare Gene Mutations	II
NCT03170206	Phase I/II Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor Binimetinib (MEK162) for Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer	I/II
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II
NCT04263090	A Phase I/IIa Study of Rigosertib Plus Nivolumab in Stage IV Lung Adenocarcinoma Patients With KRAS Mutation Who Progressed on First-Line Treatment	I/II

Clinical Trials Summary (continued)

KRAS p.(G12C) c.34G>T (continued)

NCT ID	Title	Phase
NCT03875820	FRAME: A Phase I Trial Of The Combination Of VS-6063 (FAK Inhibitor) And RO5126766 (CH5126766) (A Dual RAF/MEK Inhibitor) In Patients With Advanced Solid Tumours.	I/II
NCT03965845	A Phase Ib/II, Open Label, Dose Escalation and Expansion Study of the Glutaminase Inhibitor Telaglenastat (CB-839) in Combination With CDK4/6 Inhibitor Palbociclib in Patients With Advanced or Metastatic Solid Tumors	I/II
NCT03284502	A Phase Ib, Open-label, Multicenter, Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of HM95573 in Combination With Either Cobimetinib or Cetuximab in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT03951116	Phase I Study of FCN-437c in Patients with Advanced Solid Tumors	I
NCT02974725	A Phase Ib, Open-label, Multicenter Study of Oral LXH254-centric Combinations in Adult Patients With Advanced or Metastatic KRAS or BRAF Mutant Non-Small Cell Lung Cancer or NRAS Mutant Melanoma	I
NCT03819387	A Phase I/Ib Open-Label, Multi-Center, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics and Preliminary Efficacy of Intravenous NBF 006 in Patients With Non-Small Cell Lung, Pancreatic, or Colorectal Cancer	I
NCT03299088	A Phase Ib Trial of Pembrolizumab (MK-3475) and Trametinib Focused on Advanced KRAS Mutant Non-small Cell Lung Cancer	I
NCT04418661	A Phase I, Open-label, Multicenter, Safety Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I
NCT03581487	Phase I/II Trial Immunotherapy With Durvalumab and Tremelimumab With Continuous or Intermittent MEK Inhibitor Selumetinib in NSCLC	I/II
NCT04585035	A Phase I/II, Open Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of D-1553 in Subjects With Advanced or Metastatic Solid Tumors With KRasG12C Mutation	I/II
NCT04449874	A Phase I Dose-Escalation and Dose-Expansion Study Evaluating the Safety, Pharmacokinetics, and Activity of GDC-6036 in Patients With Advanced or Metastatic Solid Tumors With a KRAS G12C Mutation	I
NCT04380753	A Phase I, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 (pINN Sotorasib) in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With KRAS p.G12C Mutation (CodeBreak 105)	I
NCT04586270	A Phase I Study of TAS0612 in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT02079740	An Open Label, Two-Part, Phase Ib/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor Trametinib and the BCL2-Family Inhibitor Navitoclax (ABT-263) in Combination in Subjects With KRAS or NRAS Mutation-Positive Advanced Solid Tumors	I/II
NCT03919292	Phase 1/2 Study of Neratinib and Divalproex Sodium (Valproate) in Advanced Solid Tumors, With an Expansion Cohort in Ras-Mutated Cancers	I/II
NCT03989115	A Phase Ib/II, Open-Label, Multicenter Dose-Escalation and Dose-Expansion Study of the Combination of RMC-4630 and Cobimetinib in Adult Participants With Relapsed/Refractory Solid Tumors With Specific Genomic Aberrations	I/II
NCT04249843	A First-in-Human, Phase Ia/Ib, Open Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients With Advanced or Refractory Tumors	I
NCT04418167	A Phase I Study of ERK1/2 Inhibitor JSI-1187 Administered as Monotherapy and in Combination With Dabrafenib for the Treatment of Advanced Solid Tumors With MAPK Pathway Mutations	I

Clinical Trials Summary (continued)

KRAS p.(G12C) c.34G>T (continued)

NCT ID	Title	Phase
NCT03065387	Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib, or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/ Amplification, or HER3/4 Mutation or KRAS Mutation	I
NCT02407509	A Phase I Trial of RO5126766 (a Dual RAF/MEK Inhibitor) Exploring Intermittent, Oral Dosing Regimens in Patients With Solid Tumours or Multiple Myeloma, With an Expansion to Explore Intermittent Dosing in Combination With Everolimus	I
NCT03756818	A Phase I Study of TAK-659 and Paclitaxel in Patients With Advanced Solid Tumors	I
NCT04800822	A Phase I Open-Label, Multi-Center, Dose Escalation and Dose Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Evidence of Antitumor Activity of PF-07284892 (ARRY-558) as a Single Agent and in Combination Therapy in Participants With Advanced Solid Tumors	I
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT04198818	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients With Advanced Tumors	I/II
NCT03429803	A Phase I Study of TAK-580 (MLN2480) for Children With Low-Grade Gliomas and Other RAS/RAF/ MEK/ERK Pathway Activated Tumors	I
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT04305249	A Phase I, Open-Label, Multi-Center Dose Finding Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of ATG-017 Monotherapy in Patients With Advanced Solid Tumors and Hematological Malignancies	I

KIT p.(M541L) c.1621A>C

NCT ID	Title	Phase
NCT04771520	Phase II Study of Avapritinib in Patients With CKIT or PDGFRA Mutation-Positive Malignant Solid Tumors	II
NCT04116541	MegaMOST - A Multicenter, Open-label, Biology Driven, Phase II Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations /Characteristics in Advanced / Metastatic Tumors.	II
NCT02029001	A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT02272998	Phase II Study Of Ponatinib For Advanced Cancers With Genomic Alterations In Fibroblastic Growth Factor Receptor (FGFR) And Other Genomic Targets (KIT, Pdgfra, RET FLT3, ABL1)	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-04-14. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12C) c.34G>T

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2021-04-06 **Variant class:** KRAS G12 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/2021/125084s277s280lbl.pdf

panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2017-06-29 **Variant class:** KRAS G12 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

KRAS p.(G12C) c.34G>T (continued)

sotorasib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** KRAS G12C mutation

Supporting Statement:

The FDA has granted Breakthrough Therapy Designation to the small molecule inhibitor, sotorasib, for KRAS G12C mutation as determined by an FDA-approved test in locally advanced or metastatic non-small cell lung cancer following at least one prior systemic therapy.

Reference:

https://investors.amgen.com//news-releases/news-release-details/amgens-sotorasib-granted-breakthrough-therapy-designation

bevacizumab + onvansertib + FOLFIRI

Cancer type: Colorectal Cancer **Variant class:** KRAS mutation

Supporting Statement:
The FDA has granted Fast Track Designation to the Polo-like Kinase 1 (PLK1) inhibitor, onvansertib, in combination with FOLFIRI and bevacizumab, for KRAS mutations in metastatic colorectal cancer in the second line.

Reference:

https://cardiffoncology.investorroom.com/2020-05-28-Cardiff-Oncology-Announces-Fast-Track-Designation-Granted-by-the-FDA-to-Onvansertib-for-Second-Line-Treatment-of-KRAS-Mutated-Colorectal-Cancer

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-04-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KRAS p.(G12C) c.34G>T

cetuximab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 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 2.2021]

cetuximab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 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 1.2021]

KRAS p.(G12C) c.34G>T (continued)

panitumumab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 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 2.2021]

panitumumab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 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 1.2021]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2021-04-14. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12C) c.34G>T

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-30 **Variant class:** KRAS exon 2 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:** KRAS exon 2 mutation

Reference:

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

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2021-04-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12C) c.34G>T

cetuximab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 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:** KRAS exon 2 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)]

---

panitumumab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 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)]

KRAS p.(G12C) c.34G>T (continued)

⊘ panitumumab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 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]."

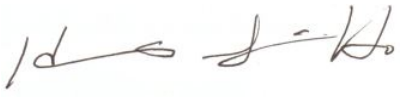
Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

Signatures

Testing Personnel:

2021.06.25
11:49:44 +08'00'

Laboratory Supervisor:



2021.06.25
11:49:54 +08'00'

Pathologist:

2021.06.25
11:50:05 +08'00'

References

1. Ségaliny et al. Receptor tyrosine kinases: Characterisation, mechanism of action and therapeutic interests for bone cancers. J Bone Oncol. 2015 Mar;4(1):1-12. PMID: 26579483
2. Berenstein. Class III Receptor Tyrosine Kinases in Acute Leukemia - Biological Functions and Modern Laboratory Analysis. Biomark Insights. 2015;10(Suppl 3):1-14. PMID: 26309392
3. Ashman. The biology of stem cell factor and its receptor C-kit. Int. J. Biochem. Cell Biol. 1999 Oct;31(10):1037-51. PMID: 10582338
4. Cardoso et al. The SCF/c-KIT system in the male: Survival strategies in fertility and cancer. Mol. Reprod. Dev. 2014 Dec;81(12):1064-79. PMID: 25359157
5. Abbaspour et al. Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. Drug Des Devel Ther. 2016;10:2443-59. PMID: 27536065
6. Liang et al. The C-kit receptor-mediated signal transduction and tumor-related diseases. Int. J. Biol. Sci. 2013;9(5):435-43. PMID: 23678293
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. Garcia-Montero et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. Blood. 2006 Oct 1;108(7):2366-72. PMID: 16741248
9. Chatterjee et al. Mastocytosis: a mutated KIT receptor induced myeloproliferative disorder. Oncotarget. 2015 Jul 30;6(21):18250-64. PMID: 26158763
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021588s056s057lbl.pdf
11. NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]
12. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2021]
13. Casali et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2018 Oct 1;29(Supplement_4):iv68-iv78. PMID: 29846513
14. KIT Oncogenic Mutations: Biologic Insights, Therapeutic Advances, and Future Directions. Cancer Res. 2016 Nov 1;76(21):6140-6142. PMID: 27803101
15. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2021]
16. Lim et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009 Jun 4;113(23):5727-36. PMID: 19363219
17. Verstovsek. Advanced systemic mastocytosis: the impact of KIT mutations in diagnosis, treatment, and progression. Eur. J. Haematol. 2013 Feb;90(2):89-98. PMID: 23181448
18. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
19. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
20. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
21. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
22. Román et al. KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. Mol Cancer. 2018 Feb 19;17(1):33. doi: 10.1186/s12943-018-0789-x. PMID: 29455666
23. Dinu et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. J Med Life. 2014 Oct-Dec;7(4):581-7. PMID: 25713627
24. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J. Clin. Oncol. 2016 Jan 10;34(2):179-85. PMID: 26438111
25. Amgen Announces New Clinical Data Evaluating Novel Investigational KRAS(G12C) Inhibitor In Larger Patient Group At WCLC 2019. https://investors.amgen.com/news-releases/news-release-details/amgen-announces-new-clinical-data-evaluating-novel
26. https://investors.amgen.com//news-releases/news-release-details/amgens-sotorasib-granted-breakthrough-therapy-designation
27. https://cardiffoncology.investorroom.com/2020-05-28-Cardiff-Oncology-Announces-Fast-Track-Designation-Granted-by-the-FDA-to-Onvansertib-for-Second-Line-Treatment-of-KRAS-Mutated-Colorectal-Cancer
28. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf
29. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf

References (continued)

30. Slebos et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N. Engl. J. Med. 1990 Aug 30;323(9):561-5. PMID: 2199829