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: 何再添
Gender: Male
ID No.: Q121002937
History No.: 17345389
Age: 61

Ordering Doctor: DOC1885G 楊慕華
Ordering REQ.: D5K38MJ
Signing in Date: 2020/12/10

Path No.: S109-96819
MP No.: F20107
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-78724C
Percentage of tumor cells: 90%
Note:

Sample Cancer Type: Melanoma

Report Highlights

1 Relevant Biomarkers
0 Therapies Available
12 Clinical Trials

Relevant Melanoma Findings

Gene	Finding
BRAF	Not detected
KIT	Not detected
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*GNA11 p.(Q209L) c.626A>T* G protein subunit alpha 11 Allele Fraction: 0.393	None	None	12

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 Fraction	Transcript	Variant Effect	Coverage
GNA11	p.(Q209L)	c.626A>T	COSM52969	chr19:3118942	0.393	NM_002067.4	missense	1999
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	0.485	NM_002227.3	synonymous	1993
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	0.475	NM_004304.4	missense	2000
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	0.998	NM_004304.4	missense	1998
ALK	p.(=)	c.3375C>A	.	chr2:29445458	0.468	NM_004304.4	synonymous	1960
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	0.999	NM_000142.4	synonymous	1679
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	0.996	NM_006206.5	synonymous	1998
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	0.992	NM_213647.2	missense	2000
RET	p.(=)	c.2307G>T	.	chr10:43613843	1.000	NM_020975.4	synonymous	1995
RET	p.(=)	c.2712C>G	.	chr10:43615633	0.382	NM_020975.4	synonymous	2000

Biomarker Descriptions

GNA11 (G protein subunit alpha 11)

Background: The GNA11 gene encodes an alpha subunit of heterotrimeric guanine nucleotide-binding proteins (G-proteins). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNA11 is closely related to GNAQ, another G-protein alpha subunit.

Alterations and prevalence: Somatic activating mutations in GNA11 and GNAQ at amino acids R183 and Q209 are common in uveal melanoma and are mutually exclusive. These mutations render the G protein constitutively active leading to the stimulation of MAP kinases, PI3K/AKT, and protein kinase C, which promote tumor growth and proliferation[1,2,3]. Approximately 45% of uveal melanoma cases contain activating mutations in GNA11 and up to 50% of cases contain activating mutations in GNAQ[4,5,6]. By contrast, GNA11 and GNAQ mutations are infrequent in cutaneous melanoma, with a combined prevalence of approximately 1%, and are infrequently observed in other cancers[5,6].

Potential relevance: Currently, no therapies are approved for GNA11 aberrations. In a randomized phase II clinical trial of MEK inhibitor selumetinib versus chemotherapy, GNA11 and GNAQ positive uveal melanoma patients demonstrated a median progression-free survival (PFS) of 15.9 weeks versus 7 weeks, respectively[7]. However, no statistically significant improvement in overall survival (OS) was observed and the improvement in outcomes was associated with a high rate of adverse events[7].

Relevant Therapy Summary

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

GNA11 p.(Q209L) c.626A>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selumetinib, ulixertinib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
LXS-196, binimetinib	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
MLN-2480	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (I)

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

Clinical Trials Summary

GNA11 p.(Q209L) c.626A>T

NCT ID	Title	Phase
NCT03947385	A Phase I/II Study of IDE196 in Patients With Solid Tumors Harboring GNAQ/11 Mutations or PRKC Fusions	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
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
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II

Clinical Trials Summary (continued)

GNA11 p.(Q209L) c.626A>T (continued)

NCT ID	Title	Phase
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
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
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	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
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
NCT02607813	A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations	I
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I

Signatures

Testing Personnel:

2020.12.11 13:35:27 +08'00'

Laboratory Supervisor:

2020.12.11 13:35:57 +08'00'

Pathologist:

2020.12.11 13:36:10 +08'00'

References

1. Luke et al. Biology of advanced uveal melanoma and next steps for clinical therapeutics. Pigment Cell Melanoma Res. 2015 Mar;28(2):135-47. PMID: 25113308
2. Amaro et al. The biology of uveal melanoma. Cancer Metastasis Rev. 2017 Mar;36(1):109-140. PMID: 28229253
3. Parish et al. GNAS, GNAQ, and GNA11 alterations in patients with diverse cancers. Cancer. 2018 Oct 15;124(20):4080-4089. PMID: 30204251
4. Van et al. Mutations in GNA11 in uveal melanoma. N. Engl. J. Med. 2010 Dec 2;363(23):2191-9. PMID: 21083380
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
6. 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
7. Carvajal et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA. 2014 Jun 18;311(23):2397-405. PMID: 24938562