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Sample Information

Patient Name: 黃德貞 Gender: Female ID No.: Q220929888 History No.: 39693408

Age: 55

Ordering Doctor: DOC3153J 黃煦晴 Ordering REQ.: D6DECGF Signing in Date: 2021/08/19

Path No.: S110-99319 **MP No.:** F21068

Assay: Oncomine Focus Assay

Sample Type: FFPE Block No.: S110-22078A Percentage of tumor cells: 40%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

- 3 Relevant Biomarkers
- 2 Therapies Available
- 1 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	KRAS p.(Q61L) c.182A>T, KRAS amplification	ROS1	None detected
MET	None detected		

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	KRAS p.(Q61L) c.182A>T KRAS proto-oncogene, GTPase Allele Frequency: 11.60%	None	cabozantinib	1
IIC	AR amplification androgen receptor	None	hormone therapy	0
IIC	KRAS amplification KRAS proto-oncogene, GTPase	None	None	1

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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 CDK4 amplification

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

DNA	A Sequence varia	ants						
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KRAS	p.(Q61L)	c.182A>T	COSM553	chr12:25380276	11.60%	NM_033360.4	missense	2000
ALK	p.(*1621R)	c.4861T>C		chr2:29416092	4.51%	NM_004304.5	stoploss	1287

Copy Number Variations		
Gene	Locus	Copy Number
KRAS	chr12:25364761	11.98
CDK4	chr12:58142052	38.42
AR	chrX:66776186	6.28
ERBB3	chr12:56477590	13.68

Biomarker Descriptions

AR (androgen receptor)

Background: The AR gene encodes the androgen receptor protein (AR), a ligand-activated transcription factor regulated by the binding of the hormones testosterone and dihydrotestosterone^{1,2}. Hormone binding to AR results in receptor dimerization, nuclear translocation, and target gene transcription, thus activating the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR signaling pathways, which promote cell proliferation and survival^{2,3,4}.

Alterations and prevalence: Alterations in AR function can result from overexpression, gene amplification, or mutations. AR mutations, including L702H, W742C/L, H875Y, and T878A, are commonly observed in 10-30% of castration-resistant prostate cancer and result in decreased ligand specificity, allowing other nuclear hormones to activate AR⁵. Androgen receptor splice variants have been reported in castration resistant prostate cancer^{6,7}. The androgen receptor splice variant 7 (AR-V7) is a result of aberrant mRNA splicing of AR exons 1-3 and a cryptic exon 3, resulting in the expression of a constitutively active protein⁷.

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Biomarker Descriptions (continued)

Potential relevance: The FDA has granted fast track designation (2016) to seviteronel for AR-positive triple-negative breast cancer (TNBC) patients⁸. Androgen deprivation therapy (ADT) such as abiraterone⁹ (2011) and enzalutamide¹⁰ (2011) are FDA approved for use in locally advanced and metastatic prostate cancers. Although many men initially respond to ADT, most will develop hormone resistance. Resistance to ADT is also associated with other aberrations of the AR gene including mutations within the ligand binding domain and gene amplification^{5,11,12}. The androgen receptor splice variant, AR-V7, lacks the ligand binding domain, resulting in constitutive activation and is associated with resistance to androgen deprivation therapy (ADT) in advanced prostate cancer⁶.

CDK4 (cyclin dependent kinase 4)

<u>Background</u>: The CDK4 gene encodes the cyclin-dependent kinase 4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle^{13,14}. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression¹⁵. Germline mutations in CDK4 are associated with familial melanoma^{16,17,18}.

Alterations and prevalence: Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A^{19,20,21}. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)^{22,23,24,25}.

<u>Potential relevance:</u> Currently, no therapies are approved for CDK4 aberrations. Small molecule inhibitors targeting CDK4/6 including palbociclib (2015), abemaciclib (2017), and ribociclib (2017), are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

KRAS (KRAS proto-oncogene, GTPase)

<u>Background:</u> 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^{26,27,28}.

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 cancer²³. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61^{23,29,30}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{22,31}.

Potential relevance: The KRAS inhibitor, sotorasib³², is approved (2021) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The small molecular inhibitor, RO-5126766, was granted breakthrough designation (2021) alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer³³. Additionally, onvansertib³⁴ was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab³⁵ and panitumumab³⁶, 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)³¹. Additionally, KRAS mutations are associated with poor prognosis in NSCLC³⁷.

Relevant Therapy Summary

In this cancer type	In other cancer type	In this cancer	type and other car	ncer types	× No eviden	ce
KRAS p.(Q61L)	c.182A>T					
Relevant Therapy		FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib		×	×	×	0	×
RMC-4630, pembroliz	zumab	×	×	×	×	(I)

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

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Relevant Therapy Summary (continued)

■ In this cancer type
O In other cancer type
In this cancer type and other cancer types
X No evidence

AR amplification					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
androgen receptor therapy	×	0	×	×	×
bicalutamide	×	0	×	×	×
leuprorelin	×	0	×	×	×

KRAS amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
RMC-4630, pembrolizumab	×	×	×	×	(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 NCCN Information

In this cancer type In other cancer type In this cancer type and other cancer types

NCCN information is current as of 2021-07-01. For the most up-to-date information, search www.nccn.org. For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

AR amplification

androgen receptor therapy

Cancer type: Head and Neck Cancer Variant class: AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

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

O bicalutamide

Cancer type: Head and Neck Cancer Variant class: AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

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

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AR amplification (continued)

O leuprorelin

Cancer type: Head and Neck Cancer Variant class: AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

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

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Current ESMO Information

In this cancer type

O In other cancer type

In this cancer type and other cancer types

ESMO information is current as of 2021-07-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(Q61L) c.182A>T

O 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]

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Clinical Trials in Taiwan region:

Clinical Trials Summary

KRAS p.(Q61L) c.182A>T

NCT ID	Title	Phase
NCT04418661	A Phase I, Open-label, Multicenter, Safety Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I

KRAS amplification

NCT ID	Title	Phase
NCT04418661	A Phase I, Open-label, Multicenter, Safety Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I

Alerts Informed By Public Data Sources

Current FDA Information











FDA information is current as of 2021-07-14. For the most up-to-date information, search www.fda.gov.

KRAS p.(Q61L) c.182A>T

cetuximab

Cancer type: Colorectal Cancer Label as of: 2021-04-06 Variant class: KRAS 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 platinumbased 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

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KRAS p.(Q61L) c.182A>T (continued)

panitumumab

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

Cancer type: Endometrial Carcinoma Variant class: KRAS mutation

Supporting Statement:

The FDA has granted Breakthrough Designation to the small molecule inhibitor, RO-5126766 alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer.

Reference:

https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-receives-breakthrough-therapy-designation-vs

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

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AR amplification

seviteronel

Cancer type: Triple Negative Breast Cancer Variant class: AR positive

Supporting Statement:

The FDA has granted Fast Track Designation to the small-molecule CYP17 lyase-selective inhibitor, seviteronel, for:

- Androgen receptor (AR) positive advanced triple negative breast cancer (TNBC).
- Estrogen receptor (ER) positive advanced breast cancer.

Reference:

https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA

Current NCCN Information

NCCN information is current as of 2021-07-01. 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.(Q61L) c.182A>T

cetuximab

Cancer type: Colon Cancer Variant class: KRAS 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 2.2021]

cetuximab

Cancer type: Rectal Cancer Variant class: KRAS 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 1.2021]

panitumumab

Cancer type: Colon Cancer Variant class: KRAS 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 2.2021]

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KRAS p.(Q61L) c.182A>T (continued)

panitumumab

Cancer type: Rectal Cancer Variant class: KRAS 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 1.2021]

Current EMA Information

EMA information is current as of 2021-07-14. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(Q61L) c.182A>T

cetuximab, cetuximab + oxaliplatin

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

Reference:

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

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Current ESMO Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

ESMO information is current as of 2021-07-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(Q61L) c.182A>T

cetuximab

Cancer type: Colorectal Cancer Variant class: KRAS 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: KRAS 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)]

panitumumab

Cancer type: Colorectal Cancer Variant class: KRAS 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)]

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KRAS p.(Q61L) c.182A>T (continued)

panitumumab + chemotherapy

Cancer type: Colorectal Cancer Variant class: KRAS 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)]

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Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

Date: 19 Aug 2021

References

- Lu et al. International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. Pharmacol. Rev. 2006 Dec;58(4):782-97. PMID: 17132855
- 2. Davey et al. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. Clin Biochem Rev. 2016 Feb;37(1):3-15. PMID: 27057074
- Crumbaker et al. AR Signaling and the PI3K Pathway in Prostate Cancer. Cancers (Basel). 2017 Apr 15;9(4). PMID: 28420128
- 4. Leung et al. Non-Genomic Actions of the Androgen Receptor in Prostate Cancer. . Front Endocrinol (Lausanne). 2017 Jan 17;8:2. . PMID: 28144231
- 5. Waltering et al. Androgen receptor (AR) aberrations in castration-resistant prostate cancer. Mol. Cell. Endocrinol. 2012 Sep 5;360(1-2):38-43. PMID: 22245783
- Antonarakis et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N. Engl. J. Med. 2014 Sep 11;371(11):1028-38. PMID: 25184630
- 7. Zhu et al. Novel Junction-specific and Quantifiable In Situ Detection of AR-V7 and its Clinical Correlates in Metastatic Castration-resistant Prostate Cancer. Eur. Urol. 2018 May;73(5):727-735. PMID: 28866255
- 8. https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202379s031s033lbl.pdf
- 10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203415s016lbl.pdf
- 11. Lallous et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. Genome Biol. 2016 Jan 26;17:10. PMID: 26813233
- 12. Robinson et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015 May 21;161(5):1215-1228. PMID: 26000489
- 13. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
- 14. Sherr et al. Targeting CDK4 and CDK6: From Discovery to Therapy. Cancer Discov. 2016 Apr;6(4):353-67. PMID: 26658964
- 15. Weinberg. The retinoblastoma protein and cell cycle control. Cell. 1995 May 5;81(3):323-30. PMID: 7736585
- 16. Rane et al. Germ line transmission of the Cdk4(R24C) mutation facilitates tumorigenesis and escape from cellular senescence. Mol. Cell. Biol. 2002 Jan;22(2):644-56. PMID: 11756559
- 17. Zuo et al. Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. Nat. Genet. 1996 Jan;12(1):97-9. PMID: 8528263
- 18. Molven et al. A large Norwegian family with inherited malignant melanoma, multiple atypical nevi, and CDK4 mutation. Genes Chromosomes Cancer. 2005 Sep;44(1):10-8. PMID: 15880589
- 19. Ceha et al. Several noncontiguous domains of CDK4 are involved in binding to the P16 tumor suppressor protein. Biochem. Biophys. Res. Commun. 1998 Aug 19;249(2):550-5. PMID: 9712735
- 20. Tsao et al. Novel mutations in the p16/CDKN2A binding region of the cyclin-dependent kinase-4 gene. Cancer Res. 1998 Jan 1;58(1):109-13. PMID: 9426066
- 21. Sotillo et al. Invasive melanoma in Cdk4-targeted mice. Proc. Natl. Acad. Sci. U.S.A. 2001 Nov 6;98(23):13312-7. PMID: 11606789
- 22. 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
- 23. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
- 24. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
- 25. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
- 26. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
- 27. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
- 28. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PP0.00000000000187. PMID: 27341593
- 29. 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
- 30. 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

References (continued)

- 31. 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
- 32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf
- 33. https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-receives-breakthrough-therapy-designation-vs
- 34. 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
- 35. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf
- 36. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf
- 37. 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