康誠生技
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GUARDANT

Guardant360
基因檢測服務報告

醫師姓名：洪逸平

受檢者姓名：曾柏瑞

送檢編號：A1079314

檢測次數：第一次

提醒

基因數據乃屬個人隱私，切勿輕易向任何個人、團體或非您的授權者透漏本報告內容。若您有任何疑慮，歡迎來電洽詢，我們很樂意為您提供更詳細的諮詢服務。若因郵遞錯誤收此檔，請予銷毀，多謝合作。

詳細資訊

康誠生技股份有限公司 客戶服務中心

諮詢時間｜週一～週五 9:00～17:00 （國定假日除外）

諮詢專線｜02-55696099

客服信箱｜service.gb@healthconn.com

REPORTING

Report Date:	JUL-01-2024
Receipt Date:	JUN-25-2024
Collection Date:	JUN-24-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Yi-Ping Hung
Account: Genconn Biotech Co., LTD
Address: F15., No 207-5 Sec 3, Beixin Rd, Xindian Dist, New Taipei City, 23143, Taiwan
Ph: +886 963 820 633 | Fax: N/A
Additional Recipient: N/A

Complete Tumor Response Map on page 2

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY Approved in indication | Approved in other indication | Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 3)	% cfDNA or Amplification
BRCA2 S1882*	Niraparib, Olaparib, Rucaparib, Talazoparib	Yes	1.1%
TP53 R273G	None	Yes	2.4%
GNAS R201H	None	Yes	0.3%

Variants of Uncertain Clinical Significance
CDK12 K1372E (1.4%), *BRCA2* S1882T (0.7%), *BRAF* T651S (0.7%), *SMAD4* S504R (0.2%), *ATM* V1073L (0.2%), *KRAS* V45fs (0.6%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
FGFR2 I422I (0.8%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Comments

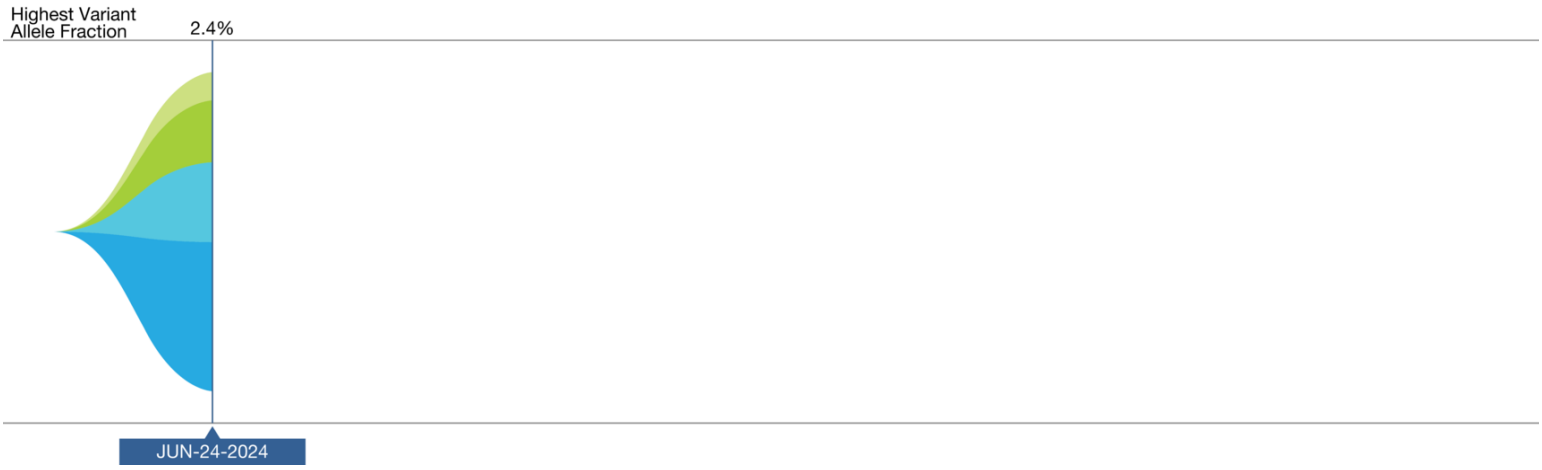
Multiple alterations in BRCA2 were detected in close proximity to one another in this sample. In some cases, this may indicate BRCA2 reversion, which is associated with resistance to PARP inhibitors and platinum agents. Clinical correlation is suggested.
Reported by: NT3,JP1

Additional Biomarkers

Biomarker	Additional Details
MSI-High	NOT DETECTED

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	
TP53 R273G	2.4%	
BRCA2 S1882*	1.1%	
FGFR2 I422I	0.8%	Synonymous Alteration §
GNAS R201H	0.3%	
ATM V1073L	0.2%	Variants of Uncertain Clinical Significance §
BRAF T651S	0.7%	Variants of Uncertain Clinical Significance §
BRCA2 S1882T	0.7%	Variants of Uncertain Clinical Significance §
CDK12 K1372E	1.4%	Variants of Uncertain Clinical Significance §
KRAS V45fs	0.6%	Variants of Uncertain Clinical Significance §
SMAD4 S504R	0.2%	Variants of Uncertain Clinical Significance §

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Available Clinical Trials (within the same state as the ordering physician)

There may be additional trials not listed here. Visit: **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1079314 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
BRCA2 S1882*	NCT04434482 Min Song,min.song@impacttherapeutics.com,021 68411121	IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer	Phase 1 /Phase 2	Taipei, Taiwan Taoyuan, Taiwan Taichung, Taiwan Tainan, Taiwan (2)
	NCT05269316 Xiangna Chen,xiangna.chen@impacttherapeutics.com,+86-021-68411121	Study to Evaluate IMP9064 as a Monotherapy or in Combination in Patients With Advanced Solid Tumors	Phase 1	Taipei, Taiwan
	NCT05797168 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Phase I/IIa Study for AZD5335 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Solid Tumors	Phase 1 /Phase 2	Tainan City, Taiwan Taichung, Taiwan Taipei, Taiwan (2)
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 R273G	NCT04768868 Jian Wang,Jian.wang@impacttherapeutics.com,+86 18613056501	The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients With Advanced Solid Tumors	Phase 1	Taipei, Taiwan Taoyuan, Taiwan Taichung, Taiwan Tainan, Taiwan (2)
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
GNAS R201H	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			

More clinical trial options available at **portal.guardanthealth.com**

Definitions

Variants of Uncertain Clinical Significance: The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alteration: This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Deletion (Del): The following alteration was detected in this patient: *KRAS* V45fs. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

***Nonsense mutation:** A point mutation that results in a premature stop codon.

Interpretation

Somatic alterations were detected in the circulating cell-free DNA isolated from this patient's blood specimen. These genomic alterations are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatments. The percentage of altered cell-free DNA circulating (% cfDNA) in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn over, size, heterogeneity, vascularization, disease progression, and treatment.

Method and Limitations

Guardant360 sequences 74 cancer-associated genes to identify somatic alterations. Cell-free DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using the Illumina platform and hg19 as the reference genome. All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Guardant360 include single nucleotide variants, gene amplifications, fusions, short insertions/deletions (longest detected, 70 base pairs), and splice site disrupting events (see Table 1). Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Guardant360 panel. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue. MSI status is currently not reported for earlier panel versions. This version of the Guardant360 test is not validated for the detection of other types of genomic alterations, such as complex rearrangements or gene deletions. Certain sample or variant characteristics, such as low cfDNA concentration, may result in reduced analytic sensitivity. Guardant360 cannot discern the source of circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot easily distinguish germline variants from somatic alterations. Guardant360 is not validated for the detection of germline or de novo variants that are associated with hereditary cancer risk. Tissue genotyping should be considered when plasma genotyping is negative, if clinically appropriate.

Table 1: Genes on the Guardant360 Panel

Guardant360 reports single nucleotide variants, splice site mutations, and insertion and deletion variants (indels) in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

AKT1	*ALK* #	*APC*	*AR* †	*ARAF*	*ARID1A*	*ATM*	*BRAF* †	*BRCA1*
BRCA2	*CCND1* †	*CCND2* †	*CCNE1* †	*CDH1*	*CDK12*	*CDK4* †	*CDK6* †	*CDKN2A*
CTNNB1	*DDR2*	*EGFR* †	*ERBB2* †	*ESR1*	*EZH2*	*FBXW7*	*FGFR1* †	*FGFR2* † #
FGFR3 #	*GATA3*	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*IDH2*
JAK2	*JAK3*	*KIT* †	*KRAS* †	*MAP2K1*	*MAP2K2*	*MAPK1*	*MAPK3*	*MET* †
MLH1	*MPL*	*MTOR*	*MYC* †	*NF1*	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*
NTRK1 #	*NTRK3*	*PDGFRA* †	*PIK3CA* †	*PTEN*	*PTPN11*	*RAF1* †	*RB1*	*RET* #
RHEB	*RHOA*	*RIT1*	*ROS1* #	*SMAD4*	*SMO*	*STK11*	*TERT* ‡	*TP53*
TSC1	*VHL*							

‡ Guardant360 reports alterations in the promoter region of this gene.

† Guardant360 reports amplifications of this gene.

Guardant360 reports fusion events involving this gene.

About the Test

The Guardant360 assay was developed and its performance characteristics were determined by Guardant Health, Inc. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test may be used for clinical purposes and should not be regarded as investigational or for research only. Guardant Health's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing. The laboratory report should be interpreted in the context of other clinical information and laboratory, pathology, and imaging studies by a qualified medical professional prior to initiating or changing a patient's treatment plan. The selection of any, all, or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) is entirely at the discretion of the treating medical professional. Drug and trial information are based on the diagnosis written on the submitted test request form; this information is not based on any supplemental information provided by the requesting medical professional, including pathology reports or other molecular studies. Some drugs listed in this report may not be approved or cleared by the FDA for the indicated use. Guardant Health makes no endorsement, express or implied, of any product, physician, or procedure contained in this report. This report makes no promises or guarantees that a particular medication will affect (or not affect) the clinical outcome of any patient.

Testing Performed at: Guardant Health

Laboratory Director: Martina Lefterova, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, USA

Additional information is available

Any therapeutic annotations are based on publicly available information. This information is described in the "Detailed Therapy Results" and "Relevance of Detected Alterations" sections.

Visit **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1079314 in the subject line of the email for:

- Additional clinical trials
- Detailed Therapy Results
- Relevance of Detected Alterations
- References

If you would like to receive this additional information with every Guardant360 report, please call client services at **855.698.8887** to opt-in.

Additional information begins on the next page.

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
BRCA2 S1882*	NCT02925234 E.E. Voest, prof.,DRUP@nki.nl, 0031205129111	The Drug Rediscovery Protocol (DRUP Trial)	Phase 2	Netherlands (35)
	NCT03742895 Toll Free Number,Trialsites@merck.com, 1-888-577-8839	Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)	Phase 2	Harrison, NY; Seattle, WA; New York, NY; Baltimore, MD; Middletown, NJ; Colombia; Argentina; United Kingdom; Canada; Ireland; Denmark; Israel; Australia; Spain (2); Turkey (7); Korea, Republic of (2); Guatemala (4); Mexico (2); France (2); Peru (5)
	NCT04434482 Min Song,min.song@impacttherapeutics.com,021 68411121	IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer	Phase 1 /Phase 2	Evergreen Park, IL; Canton, OH; Columbus, OH; Tennessee, TN; China (4); Taiwan (5); Korea, Republic of (4); Australia (4)
	NCT04972110 Gabriela Gomez, MD, MBA, clininfo@reparerx.com,1 (857) 340-5402	Study of RP-3500 (Camonsertib) With Niraparib or Olaparib in Advanced Solid Tumors	Phase 1 /Phase 2	Houston, TX; Rochester, MN; Eugene, OR; Phoenix, AZ; New Haven, CT; Baltimore, MD; Aurora, CO; Jacksonville, FL; Salt Lake City, UT; San Francisco, CA; Ann Arbor, MI; New York, NY (2)
	NCT05269316 Xiangna Chen,xiangna.chen@impacttherapeutics.com,+86-021-68411121	Study to Evaluate IMP9064 as a Monotherapy or in Combination in Patients With Advanced Solid Tumors	Phase 1	Greenville, SC; New York, NY; Dallas, TX; Hackensack, NJ; China; Taiwan; Australia (2)
	NCT05327010 See https://clinicaltrials.gov/ct2/show/NCT05327010	Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial	Phase 2	New Haven, CT; Chicago, IL; Houston, TX; Lee's Summit, MO; Chapel Hill, NC; North Kansas City, MO; Atlanta, GA; Pittsburgh, PA; Aurora, CO; Gainesville, FL; Galveston, TX; Salt Lake City, UT; Trumbull, CT; Lexington, KY; Charlottesville, VA; Kansas City, MO; Bethesda, MD (2); KS (5); CA (8)
	NCT05338346 Edwin Hoe,edwin.hoe@antengene.com, +61 497 390477	A Study of ATG-018 (ATR Inhibitor) Treatment in Patients With Advanced Solid Tumors and Hematological Malignancies	Phase 1	Australia (5)
	NCT05797168 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Phase I/IIa Study for AZD5335 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Solid Tumors	Phase 1 /Phase 2	Houston, TX; Duarte, CA; Louisville, KY; Boston, MA; Columbus, OH; Irvine, CA; Portland, OR; Aurora, CO; Providence, RI (2); Canada (5); Japan (2); China (5); Taiwan (4); United Kingdom (4); Israel (2); Australia (2); Spain (4)
TP53 R273G	NCT02769962 Danielle F Pinkiert, R.N.,danielle.pinkiert@nih.gov,(240) 858-7566	Trial of EP0057, a Nanoparticle Camptothecin With Olaparib in People With Relapsed /Refractory Small Cell Lung Cancer	Phase 1 /Phase 2	Bethesda, MD
	NCT03968653 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors	Phase 1	Spain; Netherlands (3)
	NCT04768868 Jian Wang,Jian.wang@impacttherapeutics.com,+86 18613056501	The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients With Advanced Solid Tumors	Phase 1	Louisville, KY; Boston, MA; Atlanta, GA; Dallas, TX; Fairway, KS; San Antonio, TX; China (4); Taiwan (5)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	NCT05109975 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	A Study to Evaluate Safety and Preliminary Anti-tumor Activity of Debio 0123 as Monotherapy in Adult Participants With Advanced Solid Tumors	Phase 1	Grand Rapids, MI; San Antonio, TX; Switzerland; Spain (7)
	NCT05253053 Caixia Sun, Ph.D., clinicaltrial@transtherabio.com,025-58216298	To Evaluate Efficacy and Safety of TT-00420 (Tinengotinib) as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors	Phase 1 /Phase 2	China (9)
GNAS R201H	NCT02925234 E.E. Voest, prof.,DRUP@nki.nl, 0031205129111	The Drug Rediscovery Protocol (DRUP Trial)	Phase 2	Netherlands (35)
	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
	NCT04341181 Ulrik Lassen, Prof.,ulrik.lassen@regionh.dk,+45 3545 8923	ProTarget - A Danish Nationwide Clinical Trial on Targeted Cancer Treatment Based on Genomic Profiling	Phase 2	Denmark (7)
	NCT04720976 Jacobio Pharmaceuticals, clinicaltrials@jacobiopharma.com,86 10 56315466	JAB-3312 Based Combination Therapy in Adult Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Oklahoma City, OK; Saint Louis, MO; Phoenix, AZ; New York, NY; Chicago, IL; New Haven, CT; Jacksonville, FL; Los Angeles, CA; Houston, TX; Detroit, MI; Rochester, MN; Indianapolis, IN; Scottsdale, AZ; Orange City, FL; Salt Lake City, UT
	NCT05111561 See https://clinicaltrials.gov/ct2/show/NCT05111561	Testing the Combination of the Anticancer Drugs ZEN003694 and Binimetinib in Patients With Advanced/Metastatic or Unresectable Solid Tumors With RAS Alterations and Triple Negative Breast Cancer	Phase 1	Houston, TX; Boston, MA; Galveston, TX

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
BRCA2 S1882*	AMXI-5001		Dual PARP1/2 and microtubule polymerization inhibitor.	Phase 2 (Solid Tumor)
	ATG-018		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Marginal zone lymphoma (MZL), Diffuse large B-cell lymphoma (DLBCL))
	AZD9574		PARP1 inhibitor (brain penetrant).	Phase 2 (Glioma, Pancreatic carcinoma, Prostate carcinoma, Ovarian carcinoma, Breast carcinoma)
	Camonsertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Fluzoparib		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Pancreatic carcinoma, Ovarian carcinoma, Breast carcinoma)
	IDX-1197		PARP inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	Niraparib	Zejula	PARP inhibitor.	Phase 2 (Esophageal carcinoma) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma with BRCA1/2 mutation)
	Nivolumab+ipilimumab	Opdivo+Yervoy	Anti-PD-1 monoclonal antibody + anti-CTLA-4 monoclonal antibody combination.	Phase 3 (Esophageal carcinoma) FDA Approved in other indications (NSCLC with high PD-L1 expression, Hepatocellular carcinoma (HCC), Melanoma, Non-small cell lung carcinoma (NSCLC), Renal cell carcinoma, Esophageal squamous cell carcinoma, CRC with MSI-H or dMMR, Mesothelioma)
	NMS-03305293		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma)
	Olaparib	Lynparza	PARP inhibitor.	Phase 2 (Esophageal carcinoma) FDA Approved in other indications (Pancreatic adenocarcinoma with germline BRCA1/2 mutation, Prostate cancer with HRR gene mutation, Ovarian carcinoma with BRCA1/2 mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Pamiparib		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Gastric carcinoma, Gastroesophageal junction carcinoma)
	RP12146		PARP inhibitor.	Phase 1 (Gastric carcinoma, Pancreatic carcinoma, Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Breast carcinoma, Cholangiocarcinoma, Colorectal carcinoma (CRC))
	Rucaparib	Rubraca	PARP inhibitor.	Phase 2 (Esophageal carcinoma) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma)
	Saruparib		PARP1 inhibitor.	Phase 2 (Solid Tumor) Phase 3 (Prostate carcinoma)
	Senaparib		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Small cell

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				lung carcinoma (SCLC))
	Stenoparib		PARP inhibitor.	Phase 1 (Pancreatic carcinoma, Non-small cell lung carcinoma (NSCLC), Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma, Colorectal carcinoma (CRC))
	Talazoparib	Talzenna	PARP inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (Prostate cancer with HRR gene mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Veliparib		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Glioblastoma, Non-small cell lung carcinoma (NSCLC), Ovarian carcinoma, Ovarian carcinosarcoma, Breast carcinoma, Lung cancer)
TP53 R273G	Adavosertib		Wee1 tyrosine kinase inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Lymphoma, Embryonal tumor with multi-layered rosettes (ETMR), Medulloblastoma, Small cell lung carcinoma (SCLC), Primary myelofibrosis (PMF), Ovarian carcinosarcoma, Acute myeloid leukemia (AML), MDS/MPN, unclassifiable, Chronic myelomonocytic leukemia (CMML), Peritoneal papillary serous carcinoma, Myelodysplastic Syndrome (MDS))
	AL8326		Aurora kinase B/VEGFRs/Fgfr multi-kinase inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Small cell lung carcinoma (SCLC))
	Alisertib		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	ATO	Trisenox	PML-RARA inhibitor. Inhibits multiple signaling pathways, including the Hedgehog pathway.	Phase 2 (Esophageal carcinoma) FDA Approved in other indications (Acute myeloid leukemia (AML), Acute promyelocytic leukemia (APL))
	AZD2811		Nanoparticle formulation of Aurora kinase B inhibitor barasertib (AZD1152).	Phase 1 (Solid Tumor) Phase 2 (Acute myeloid leukemia (AML), Myelodysplastic Syndrome (MDS))
	Azenosertib		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (High-grade serous ovarian carcinoma, Uterine serous/clear cell carcinoma, Osteosarcoma, Ovarian epithelial carcinoma, Colorectal adenocarcinoma, Acute myeloid leukemia (AML), Fallopian tube carcinoma, Peritoneal carcinoma, Pancreatic adenocarcinoma)
	Debio 0123		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	EP0042		Aurora kinase A/B and Flt3 inhibitor.	Phase 2 (Acute myeloid leukemia (AML), Chronic myelomonocytic leukemia (CMML), Myelodysplastic Syndrome (MDS))
	IMP7068		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	JAB-2485		Aurora kinase A inhibitor.	Phase 2 (Solid Tumor)
	LY3295668		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Small cell lung carcinoma (SCLC), Breast carcinoma (triple negative), Breast carcinoma (hormone receptor +, HER2-))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	SGT-53		TP53 gene therapy delivered via transferrin-targeted nanoparticles.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma, Pancreatic carcinoma)
	SY-4835		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	TAS-119		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor)
	Tinengotinib		Aurora kinase A/B inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Breast carcinoma (triple negative))
GNAS R201H	BI 3011441		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Binimetinib	Mektovi	MEK1,2 inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	Cobimetinib	Cotellic	MEK1,2 inhibitor.	Phase 2 (Solid Tumor) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation, Histiocytic and dendritic cell neoplasms)
	E6201		MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	IMM-1-104		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Non-small cell lung carcinoma (NSCLC), Pancreatic ductal adenocarcinoma)
	Mirdametinib		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioma, Non-small cell lung carcinoma (NSCLC), Neurofibroma, Breast carcinoma, Glioneuronal tumor, Neurofibromatosis type 1, Lung cancer, Colorectal carcinoma (CRC))
	PF-07799544		MEK Brain Penetrant Inhibitor.	Phase 1 (Glioma, Melanoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma, Colorectal carcinoma (CRC))
	Pimasertib		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Pancreatic ductal adenocarcinoma, Ovarian carcinoma, Hematologic malignancies, Colorectal carcinoma (CRC))
	Selumetinib	Koselugo	MEK1,2 inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (NF1-related plexiform neurofibroma)
	SHR7390		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Trametinib	Mekinist	MEK1,2 inhibitor.	Phase 2 (Solid Tumor) FDA Approved in other indications (Melanoma with BRAF V600 mutation)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
BRCA2 S1882*	Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis. [1,2]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers. [3-11]. The risk of developing breast or ovarian carcinoma in BRCA2 mutation carriers has been reported to be 45-69% and 11-17%, respectively. [12-14].	Inactivating BRCA2 alterations have been reported to predict sensitivity to platinum-based chemotherapy and PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, which are FDA-approved in specific indications. [15-19]. The PARP inhibitor olaparib has been approved by the FDA for use in advanced ovarian cancer, metastatic Her2 negative breast cancer, and pancreatic adenocarcinoma patients with germline BRCA1/2 mutations as well as for castration-resistant adult prostate cancer patients with tumors harboring germline or somatic alteration in one or more homologous recombination repair genes, including BRCA1/2 mutations; rucaparib has been approved by the FDA for advanced ovarian cancer and castration-resistant prostate cancer patients with either germline or somatic BRCA1/2 mutations. [18,18-26]. Olaparib in combination with abiraterone and prednisone or prednisolone has been approved by the FDA for the treatment of adult patients with metastatic castration-resistant prostate cancer with deleterious BRCA mutation as determined by an FDA-approved companion diagnostic test. [27]. In addition, talazoparib in combination with enzalutamide has been FDA-approved for the treatment of metastatic castration-resistant prostate cancer patients with tumors harboring germline or somatic alteration in one or more homologous recombination repair genes, including BRCA2 mutation. [28-30]. Furthermore, niraparib in combination with abiraterone acetate plus prednisone has been approved by the FDA for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) harboring deleterious or suspected deleterious BRCA1/2 mutations. [31,32].	
TP53 R273G	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [33]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias. [34-36]. Expression of p53 in normal	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines. [57-59]. Inhibition of components of the DNA damage checkpoint, including Wee1, has been reported to enhance the activity of	Mutations in TP53 may increase resistance to ionizing radiation therapy. [69,70]. Wild-type TP53 status and little or no expression of p53 have been correlated with response to chemotherapy in esophageal carcinoma; one study of ESCC patients treated with 5-fluorouracil plus cisplatin reported a response rate of 32% (14/44) in patients harboring wild-

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects. [37-41]. TP53 mutation and accumulation of the p53 protein have been found to occur early in esophageal cancer and to play a role in tumorigenesis, with studies reporting increased mutation and expression rates in esophagitis, dysplasia, and esophageal adenocarcinoma and squamous cell carcinoma (ESCC) cases, as compared with controls. [42-50]. A meta-analysis of 4577 esophageal carcinoma cases reported a significant correlation between p53 expression and increased TNM stage, as well as the presence of lymph node and distant metastasis. [51]. TP53 mutation and p53 expression have also been associated with poorly differentiated ESCC. [52-56].	DNA-damaging agents in preclinical cancer models with deficiency of p53 function. [60-62]. Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors. [63-68].	type TP53, as compared with 0% (0 /20) in patients with TP53 mutation. [71-75].
GNAS R201H	Activating mutations in GNAS occur predominantly at R201. GNAS R201H and R201C are mutations commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with activating GNAS mutations. [76-78].	At present there are no clinical studies or therapies directly targeted to GNAS mutation in cancer. However, based on preclinical evidence, tumors with GNAS mutations may be sensitive to inhibitors of the MAPK pathway, which are currently under clinical investigation. [79].	

References

1. Holloman W "Unraveling the mechanism of BRCA2 in homologous recombination." Nature structural & molecular biology(2011): 748-54
2. Kolinjivadi A, Sannino V, de Antoni A, Técher H, Baldi G, Costanzo V "Moonlighting at replication forks - a new life for homologous recombination proteins BRCA1, BRCA2 and RAD51." FEBS letters(2017): 1083-1100
3. Bougie O, Weberpals J "Clinical Considerations of BRCA1- and BRCA2-Mutation Carriers: A Review." International journal of surgical oncology(2011): 374012
4. Nathanson K, Domchek S "Therapeutic approaches for women predisposed to breast cancer." Annual review of medicine(2011): 295-306
5. "Cancer risks in BRCA2 mutation carriers." Journal of the National Cancer Institute(1999): 1310-6
6. Hahn S, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, Gerdes B, Kress R, Ziegler A, Raeburn J, Campra D, Grützmann R, Rehder H, Rothmund M, Schmiegel W, Neoptolemos J, Bartsch D "BRCA2 germline mutations in familial pancreatic carcinoma." Journal of the National Cancer Institute(2003): 214-21
7. Monnerat C, Chompret A, Kannengiesser C, Avril M, Janin N, Spatz A, Guinebretière J, Marian C, Barrois M, Boitier F, Lenoir G, Bressac-de Paillerets B "BRCA1, BRCA2, TP53, and CDKN2A germline mutations in patients with breast cancer and cutaneous melanoma." Familial cancer(2007): 453-61
8. Zhang L, Bacares R, Boyar S, Hudis C, Nafa K, Offit K "cDNA analysis demonstrates that the BRCA2 intronic variant IVS4-12del5 is a deleterious mutation." Mutation research(2009): 84-9
9. Casula M, Muggiano A, Cossu A, Budroni M, Caracò C, Ascierto P, Pagani E, Stanganelli I, Canzanella S, Sini M, Palomba G, Palmieri G "Role of key-regulator genes in melanoma susceptibility and pathogenesis among patients from South Italy." BMC cancer(2009): 352
10. Moran A, O'Hara C, Khan S, Shack L, Woodward E, Maher E, Lalloo F, Evans D "Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations." Familial cancer(2012): 235-42
11. Cruz C, Teule A, Caminal J, Blanco I, Piulats J "Uveal melanoma and BRCA1/BRCA2 genes: a relationship that needs further investigation." Journal of clinical oncology : official journal of the American Society of Clinical Oncology(2011): e827-9
12. Antoniou A, Pharoah P, Narod S, Risch H, Eyfjord J, Hopper J, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles D, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi O, Thompson D, Evans C, Peto J, Lalloo F, Evans D, Easton D "Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies." American journal of human genetics(2003): 1117-30
13. Lee A, Moon B, Kim T "BRCA1/BRCA2 Pathogenic Variant Breast Cancer: Treatment and Prevention Strategies." Annals of laboratory medicine(2020): 114-121
14. Kuchenbaecker K, Hopper J, Barnes D, Phillips K, Mooij T, Roos-Blom M, Jervis S, van Leeuwen F, Milne R, Andrieu N, Goldgar D, Terry M, Rookus M, Easton D, Antoniou A, McGuffog L, Evans D, Barrowdale D, Frost D, Adlard J, Ong K, Izatt L, Tischkowitz M, Eeles R, Davidson R, Hodgson S, Ellis S, Nogues C, Lasset C, Stoppa-Lyonnet D, Fricker J, Faivre L, Berthet P, Hooning M, van der Kolk L, Kets C, Adank M, John E, Chung W, Andrulis I, Southey M, Daly M, Buys S, Osorio A, Engel C, Kast K, Schmutzler R, Caldes T, Jakubowska A, Simard J, Friedlander M, McLachlan S, Machackova E, Foretova L, Tan Y, Singer C, Olah E, Gerdes A, Arver B, Olsson H "Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers." JAMA(2017): 2402-2416
15. Litton J, Rugo H, Ettl J, Hurvitz S, Gonçalves A, Lee K, Fehrenbacher L, Yerushalmi R, Mina L, Martin M, Roché H, Im Y, Quek R, Markova D, Tudor I, Hannah A, Eiermann W, Blum J "Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation." The New England journal of medicine(2018): 753-763
16. Hollis R, Churchman M, Gourley C "Distinct implications of different BRCA mutations: efficacy of cytotoxic chemotherapy, PARP inhibition and clinical outcome in ovarian cancer." OncoTargets and therapy(2017): 2539-2551
17. Kim G, Ison G, McKee A, Zhang H, Tang S, Gwise T, Sridhara R, Lee E, Tzou A, Philip R, Chiu H, Ricks T, Palmby T, Russell A, Ladouceur G, Pfuma E, Li H, Zhao L, Liu Q, Venugopal R, Ibrahim A, Pazdur R "FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy." Clinical cancer research : an official journal of the American Association for Cancer Research(2015): 4257-61
18. Swisher E, Lin K, Oza A, Scott C, Giordano H, Sun J, Konecny G, Coleman R, Tinker A, O'Malley D, Kristeleit R, Ma L, Bell-McGuinn K, Brenton J, Cragun J, Oaknin A, Ray-Coquard I, Harrell M, Mann E, Kaufmann S, Floquet A, Leary A, Harding T, Goble S, Maloney L, Isaacson J, Allen A, Rolfe L, Yelensky R, Raponi M, McNeish I "Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial." The Lancet. Oncology (2017): 75-87
19. Scott L "Niraparib: First Global Approval." Drugs(2017): 1029-1034
20. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, Meier W, Shapira-Frommer R, Safra T, Matei D, Macpherson E, Watkins C, Carmichael J, Matulonis U "Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer." The New England journal of medicine(2012): 1382-92
21. Balasubramaniam S, Beaver J, Horton S, Fernandes L, Tang S, Horne H, Liu J, Liu C, Schrieber S, Yu J, Song P, Pierce W, Robertson K, Palmby T, Chiu H, Lee E, Philip R, Schuck R, Charlab R, Banerjee A, Chen X, Wang X, Goldberg K, Sridhara R, Kim G, Pazdur R "FDA Approval Summary: Rucaparib for the Treatment of Patients with Deleterious BRCA Mutation-Associated Advanced Ovarian Cancer." Clinical cancer research : an official journal of the American Association for Cancer Research(2017): 7165-7170
22. Coleman R, Oza A, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals J, Clamp A, Scambia G, Leary A, Holloway R, Gancedo M, Fong P, Goh J, O'Malley D, Armstrong D, Garcia-Donas J, Swisher E, Floquet A, Konecny G, McNeish I, Scott C, Cameron T, Maloney L, Isaacson J, Goble S, Grace C, Harding T, Raponi M, Sun J, Lin K, Giordano H, Ledermann J "Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet (London, England)(2017): 1949-1961
23. Robson M, Im S, Senkus E, Xu B, Domchek S, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P "Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation." The New England journal of medicine(2017): 523-533
24. Robson M, Tung N, Conte P, Im S, Senkus E, Xu B, Masuda N, Delaloge S, Li W, Armstrong A, Wu W, Goessl C, Runswick S, Domchek S "OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer." Annals of oncology : official journal of the European Society for Medical Oncology(2019): 558-566
25. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall M, Park J, Hochhauser D, Arnold D, Oh D, Reinacher-Schick A, Tortora G, Algül H, O'Reilly E, McGuinness D, Cui K, Schlienger K, Locker G, Kindler H "Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer." The New England journal of medicine (2019): 317-327

References

26. Abida W, Patnaik A, Campbell D, Shapiro J, Bryce A, McDermott R, Sautois B, Vogelzang N, Bambury R, Voog E, Zhang J, Piulats J, Ryan C, Merseburger A, Daugaard G, Heidenreich A, Fizazi K, Higano C, Krieger L, Sternberg C, Watkins S, Despain D, Simmons A, Loehr A, Dowson M, Golsorkhi T, Chowdhury S "Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration." Journal of clinical oncology : official journal of the American Society of Clinical Oncology(2020): 3763-3772
27. Saad F, Armstrong AJ, Thiery-Vuillemin A, et al. "PROpel: Phase III trial of olaparib (ola) and abiraterone (abi) versus placebo (pbo) and abi as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)." J Clin Oncol(2022): Abstract 11
28. "A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TALAZOPARIB WITH ENZALUTAMIDE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER" (2023)
29. Agarwal N, Azad A, Carles J, et al. "TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)." J Clin Oncol(2023): LBA17
30. Agarwal N, Azad A, Carles J, Fay A, Matsubara N, Heinrich D, Szczylik C, De Giorgi U, Young Joung J, Fong P, Voog E, Jones R, Shore N, Dunshee C, Zschäbitz S, Oldenburg J, Lin X, Healy C, Di Santo N, Zohren F, Fizazi K "Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial." Lancet (London, England)(2023): 291-303
31. Chi K, Rathkopf D, Smith M, Efstathiou E, Attard G, Olmos D, Lee J, Small E, Pereira de Santana Gomes A, Roubaud G, Saad M, Zurawski B, Sakalo V, Mason G, Francis P, Wang G, Wu D, Diorio B, Lopez-Gitlitz A, Sandhu S "Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer." Journal of clinical oncology : official journal of the American Society of Clinical Oncology(2023): 3339-3351
32. "A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Metastatic Prostate Cancer" (2023)
33. Brown C, Lain S, Verma C, Fersht A, Lane D "Awakening guardian angels: drugging the p53 pathway." Nature reviews. Cancer(2009): 862-73
34. Malkin D, Li F, Strong L, Fraumeni J, Nelson C, Kim D, Kassel J, Gryka M, Bischoff F, Tainsky M "Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms." Science (New York, N.Y.)(1990): 1233-8
35. Srivastava S, Zou Z, Pirollo K, Blattner W, Chang E "Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome." Nature(1991): 747-9
36. Santibáñez-Koref M, Birch J, Hartley A, Jones P, Craft A, Eden T, Crowther D, Kelsey A, Harris M "p53 germline mutations in Li-Fraumeni syndrome." Lancet (London, England)(1991): 1490-1
37. Wang Y, Lin R, Tan Y, Chen J, Chen C, Wang Y "Wild-type p53 overexpression and its correlation with MDM2 and p14ARF alterations: an alternative pathway to non-small-cell lung cancer." Journal of clinical oncology : official journal of the American Society of Clinical Oncology(2005): 154-64
38. Koga T, Hashimoto S, Sugio K, Yoshino I, Nakagawa K, Yonemitsu Y, Sugimachi K, Sueishi K "Heterogeneous distribution of P53 immunoreactivity in human lung adenocarcinoma correlates with MDM2 protein expression, rather than with P53 gene mutation." International journal of cancer(2001): 232-9
39. Kato S, Han S, Liu W, Otsuka K, Shibata H, Kanamaru R, Ishioka C "Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis." Proceedings of the National Academy of Sciences of the United States of America(2003): 8424-9
40. Houben R, Hesbacher S, Schmid C, Kauczok C, Flohr U, Haferkamp S, Müller C, Schrama D, Wischhusen J, Becker J "High-level expression of wild-type p53 in melanoma cells is frequently associated with inactivity in p53 reporter gene assays." PloS one(2011): e22096
41. Olivier M, Petitjean A, Marcel V, Pétré A, Mounawar M, Plymoth A, de Fromentel C, Hainaut P "Recent advances in p53 research: an interdisciplinary perspective." Cancer gene therapy(2009): 1-12
42. Stachler M, Camarda N, Deitrick C, Kim A, Agoston A, Odze R, Hornick J, Nag A, Thorner A, Ducar M, Noffsinger A, Lash R, Redston M, Carter S, Davison J, Bass A "Detection of Mutations in Barrett's Esophagus Before Progression to High-Grade Dysplasia or Adenocarcinoma." Gastroenterology(2018): 156-167
43. Mandard A, Hainaut P, Hollstein M "Genetic steps in the development of squamous cell carcinoma of the esophagus." Mutation research(2000): 335-42
44. Bellini M, Cadamuro A, Succi M, Proença M, Silva A "Alterations of the TP53 gene in gastric and esophageal carcinogenesis." Journal of biomedicine & biotechnology (2012): 891961
45. Taghavi N, Biramijamal F, Sotoudeh M, Moaven O, Khademi H, Abbaszadegan M, Malekzadeh R "Association of p53/p21 expression with cigarette smoking and prognosis in esophageal squamous cell carcinoma patients." World journal of gastroenterology(2010): 4958-67
46. Taghavi N, Biramijamal F, Sotoudeh M, Khademi H, Malekzadeh R, Moaven O, Memar B, A'rabi A, Abbaszadegan M "p16INK4a hypermethylation and p53, p16 and MDM2 protein expression in esophageal squamous cell carcinoma." BMC cancer(2010): 138
47. Bellini M, Leite K, Cury P, Silva A "p53, p16 and Fhit proteins expressions in chronic esophagitis and Chagas disease." Anticancer research(2008): 3793-9
48. Parenti A, Rugge M, Frizzera E, Ruol A, Noventa F, Ancona E, Ninfo V "p53 overexpression in the multistep process of esophageal carcinogenesis." The American journal of surgical pathology(1995): 1418-22
49. Bian Y, Osterheld M, Bosman F, Benhattar J, Fontolliet C "p53 gene mutation and protein accumulation during neoplastic progression in Barrett's esophagus." Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc(2001): 397-403
50. Davelaar A, Calpe S, Lau L, Timmer M, Visser M, Ten Kate F, Parikh K, Meijer S, Bergman J, Fockens P, Krishnadath K "Aberrant TP53 detected by combining immunohistochemistry and DNA-FISH improves Barrett's esophagus progression prediction: a prospective follow-up study." Genes, chromosomes & cancer(2015): 82-90
51. Wang L, Yu X, Li J, Zhang Z, Hou J, Li F "Prognostic significance of p53 expression in patients with esophageal cancer: a meta-analysis." BMC cancer(2016): 373
52. Niyaz M, Ainiwaer J, Abudureheman A, Zhang L, Sheyhidin I, Turhong A, Cai R, Hou Z, Awut E "Association between TP53 gene deletion and protein expression in esophageal squamous cell carcinoma and its prognostic significance." Oncology letters(2020): 1855-1865
53. Jin Y, Zhao X, Song X, Wang R, Fan Z, Wang P, Yang M, Zhou F, Bao Q, Wang L "The High Expression of p53 Is Predictive of Poor Survival Rather TP53 Mutation in Esophageal Squamous Cell Carcinoma." Journal of oncology(2023): 3801526
54. Madani K, Zhao R, Lim H, Casson A "Prognostic value of p53 mutations in oesophageal adenocarcinoma: final results of a 15-year prospective study." European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery(2010): 1427-32

References

55. Xu X, Zheng W, Tao K, Li X, Xu W, Wang Y, Zhu S, Mao W "p53 is an independent prognostic factor in operable esophageal squamous cell carcinoma: a large-scale study with a long follow-up." Medical oncology (Northwood, London, England)(2014): 257
56. Yao W, Qin X, Qi B, Lu J, Guo L, Liu F, Liu S, Zhao B "Association of p53 expression with prognosis in patients with esophageal squamous cell carcinoma." International journal of clinical and experimental pathology(2014): 7158-63
57. Schuler P, Harasymczuk M, Visus C, Deleo A, Trivedi S, Lei Y, Argiris A, Gooding W, Butterfield L, Whiteside T, Ferris R "Phase I dendritic cell p53 peptide vaccine for head and neck cancer." Clinical cancer research : an official journal of the American Association for Cancer Research(2014): 2433-44
58. Vermeij R, Leffers N, van der Burg S, Melief C, Daemen T, Nijman H "Immunological and clinical effects of vaccines targeting p53-overexpressing malignancies." Journal of biomedicine & biotechnology(2011): 702146
59. Saito H, Ando S, Morishita N, Lee K, Dator D, Dy D, Shigemura K, Adhim Z, Nibu K, Fujisawa M, Shirakawa T "A combined lymphokine-activated killer (LAK) cell immunotherapy and adenovirus-p53 gene therapy for head and neck squamous cell carcinoma." Anticancer research(2014): 3365-70
60. Ma C, Janetka J, Piwnica-Worms H "Death by releasing the breaks: CHK1 inhibitors as cancer therapeutics." Trends in molecular medicine(2011): 88-96
61. Hirai H, Arai T, Okada M, Nishibata T, Kobayashi M, Sakai N, Imagaki K, Ohtani J, Sakai T, Yoshizumi T, Mizuarai S, Iwasawa Y, Kotani H "MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil." Cancer biology & therapy(2010): 514-22
62. Bridges K, Hirai H, Buser C, Brooks C, Liu H, Buchholz T, Molkentine J, Mason K, Meyn R "MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells." Clinical cancer research : an official journal of the American Association for Cancer Research(2011): 5638-48
63. Vilgelm A, Pawlikowski J, Liu Y, Hawkins O, Davis T, Smith J, Weller K, Horton L, McClain C, Ayers G, Turner D, Essaka D, Stewart C, Sosman J, Kelley M, Ecsedy J, Johnston J, Richmond A "Mdm2 and aurora kinase a inhibitors synergize to block melanoma growth by driving apoptosis and immune clearance of tumor cells." Cancer research(2015): 181-93
64. Li Z, Sun Y, Chen X, Squires J, Nowroozizadeh B, Liang C, Huang J "p53 Mutation Directs AURKA Overexpression via miR-25 and FBXW7 in Prostatic Small Cell Neuroendocrine Carcinoma." Molecular cancer research : MCR(2015): 584-91
65. Katayama H, Sen S "Functional significance of Aurora kinase A regulatory interactions with p53-ERα complex in human breast cancer cells." Hormones & cancer(2011): 117-24
66. Tentler J, Ionkina A, Tan A, Newton T, Pitts T, Glogowska M, Kabos P, Sartorius C, Sullivan K, Espinosa J, Eckhardt S, Diamond J "p53 Family Members Regulate Phenotypic Response to Aurora Kinase A Inhibition in Triple-Negative Breast Cancer." Molecular cancer therapeutics(2015): 1117-29
67. Gully C, Velazquez-Torres G, Shin J, Fuentes-Mattei E, Wang E, Carlock C, Chen J, Rothenberg D, Adams H, Choi H, Guma S, Phan L, Chou P, Su C, Zhang F, Chen J, Yang T, Yeung S, Lee M "Aurora B kinase phosphorylates and instigates degradation of p53." Proceedings of the National Academy of Sciences of the United States of America(2012): E1513-22
68. Marxer M, Ma H, Man W, Poon R "p53 deficiency enhances mitotic arrest and slippage induced by pharmacological inhibition of Aurora kinases." Oncogene(2014): 3550-60
69. El-Deiry W "The role of p53 in chemosensitivity and radiosensitivity." Oncogene(2003): 7486-95
70. Miyasaka A, Oda K, Ikeda Y, Sone K, Fukuda T, Inaba K, Makii C, Enomoto A, Hosoya N, Tanikawa M, Uehara Y, Arimoto T, Kuramoto H, Wada-Hiraike O, Miyagawa K, Yano T, Kawana K, Osuga Y, Fujii T "PI3K/mTOR pathway inhibition overcomes radioresistance via suppression of the HIF1-α/VEGF pathway in endometrial cancer." Gynecologic oncology(2015): 174-80
71. Izutsu M, Domoto T, Kamoshida S, Ohsaki H, Matsuoka H, Umeki Y, Shiogama K, Hirayama M, Suda K, Uyama I "Expression status of p53 and organic cation transporter 1 is correlated with poor response to preoperative chemotherapy in esophageal squamous cell carcinoma." World journal of surgical oncology(2022): 105
72. Zhang S, Huang Q, Yang H, Xie X, Luo K, Wen J, Cai X, Yang F, Hu Y, Fu J "Correlation of p53 status with the response to chemotherapy-based treatment in esophageal cancer: a meta-analysis." Annals of surgical oncology(2013): 2419-27
73. Okumura H, Uchikado Y, Setoyama T, Matsumoto M, Owaki T, Ishigami S, Natsugoe S "Biomarkers for predicting the response of esophageal squamous cell carcinoma to neoadjuvant chemoradiation therapy." Surgery today(2014): 421-8
74. Yamasaki M, Miyata H, Fujiwara Y, Takiguchi S, Nakajima K, Nishida T, Yasuda T, Matsuyama J, Mori M, Doki Y "p53 genotype predicts response to chemotherapy in patients with squamous cell carcinoma of the esophagus." Annals of surgical oncology(2010): 634-42
75. Makino T, Yamasaki M, Miyata H, Yoshioka S, Takiguchi S, Fujiwara Y, Nakajima K, Nishida T, Mori M, Doki Y "p53 Mutation status predicts pathological response to chemoradiotherapy in locally advanced esophageal cancer." Annals of surgical oncology(2010): 804-11
76. Weinstein L, Shenker A, Gejman P, Merino M, Friedman E, Spiegel A "Activating mutations of the stimulatory G protein in the McCune-Albright syndrome." The New England journal of medicine(1991): 1688-95
77. Collins M, Sarlis N, Merino M, Monroe J, Crawford S, Krakoff J, Guthrie L, Bonat S, Robey P, Shenker A "Thyroid carcinoma in the McCune-Albright syndrome: contributory role of activating Gs alpha mutations." The Journal of clinical endocrinology and metabolism(2003): 4413-7
78. Nault J, Fabre M, Couchy G, Pilati C, Jeannot E, Tran Van Nhieu J, Saint-Paul M, De Muret A, Redon M, Buffet C, Salenave S, Balabaud C, Prevot S, Labrune P, Bioulac-Sage P, Scoazec J, Chanson P, Zucman-Rossi J "GNAS-activating mutations define a rare subgroup of inflammatory liver tumors characterized by STAT3 activation." Journal of hepatology(2012): 184-91
79. Wilson C, McIntyre R, Arends M, Adams D "The activating mutation R201C in GNAS promotes intestinal tumourigenesis in Apc(Min/+) mice through activation of Wnt and ERK1/2 MAPK pathways." Oncogene(2010): 4567-75