REPORTING

Report Date:	MAY-01-2024
Receipt Date:	APR-23-2024
Collection Date:	APR-22-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Chih-Hsueh Chen
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
BRAF G265R	~ Trametinib	Yes	10.4%
TP53 V272L	None	Yes	12.7%
TP53 N131Y	None	Yes	12.2%
CCNE1 Amplification	None	Yes	Low (+)

Variants of Uncertain Clinical Significance
FGFR2 L753F (10.8%), *BRCA1* R959I (10.7%), *CDK4* V77I (1.4%), *ROS1* T2045K (0.5%), *EGFR* Y69C (0.3%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
NTRK1 Y681Y (0.1%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

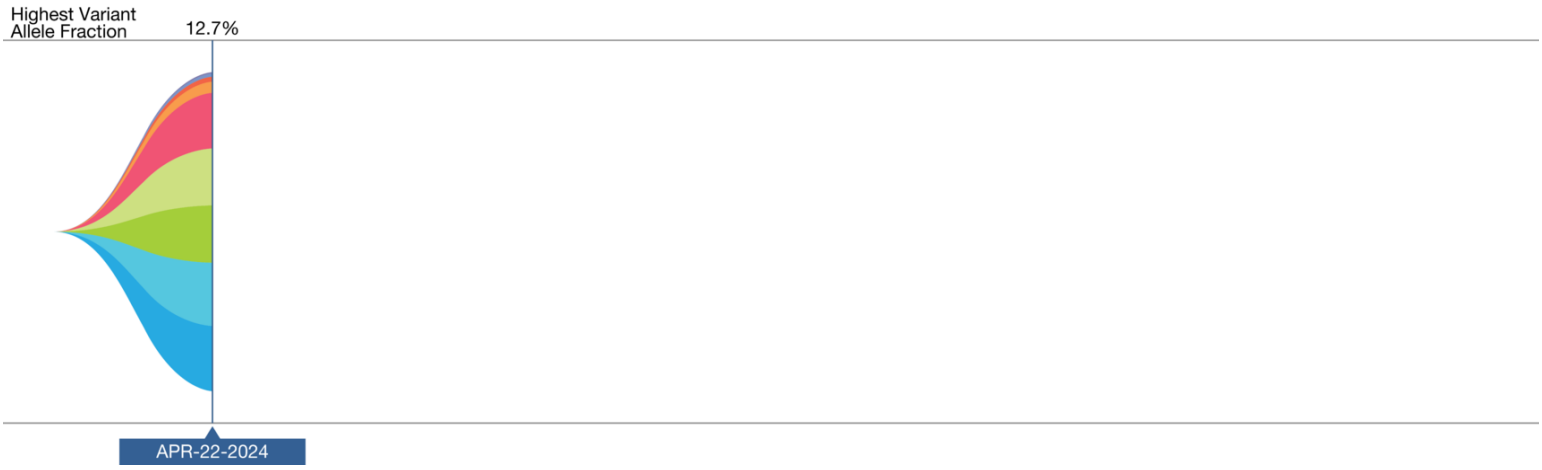
Comments
Reported by: MY3

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 V272L	12.7%	
TP53 N131Y	12.2%	
FGFR2 L753F	10.8%	Variants of Uncertain Clinical Significance §
BRCA1 R959I	10.7%	Variants of Uncertain Clinical Significance §
BRAF G265R	10.4%	
CDK4 V77I	1.4%	Variants of Uncertain Clinical Significance §
ROS1 T2045K	0.5%	Variants of Uncertain Clinical Significance §
EGFR Y69C	0.3%	Variants of Uncertain Clinical Significance §
NTRK1 Y681Y	0.1%	Synonymous Alteration §
CCNE1 Amplification Amplifications not graphed above	Low (+) Plasma Copy Number 2.5	

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 A1024384 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
TP53 V272L	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			
TP53 N131Y	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			
BRAF G265R	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
CCNE1 Amplification	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.

Amplification: Guardant360 detects amplifications in the genes listed in Table 1. Gene amplification results in increased copies of the gene present in the cfDNA. The reported absolute copy number value represents the average copy number for the detected gene that was detected in circulating cfDNA. With the exception of sex-linked genes such as *AR*, 2 copies are expected in the absence of amplification. As the absolute number of copies in circulation is dependent on both tumor fraction and the magnitude of the tumor amplification, amplifications are reported on a semi-quantitative scale.
For *CCNE1*, *EGFR* and *FGFR1*, three levels are reported:
Low (+): Amplification magnitude is below the 50th percentile of amplifications detected by Guardant360.
Medium (++): Amplification magnitude is between the 50th and 90th percentiles.
High (+++): Amplification magnitude is above the 90th percentile.

For *BRAF*, *CCND1*, *CCND2*, *CDK4*, *CDK6*, *ERBB2*, *FGFR2*, *KIT*, *KRAS*, *MET*, *PDGFRA*, *RAF1*, *MYC*, *PIK3CA* and *AR*, two levels are reported:
Medium (++): Amplification magnitude is below the 50th percentile of amplifications detected by Guardant360.
High (+++): Amplification magnitude is above the 50th percentile.

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.

Amplification was detected in the circulating cell-free DNA isolated from this patient's blood specimen for the annotated gene(s). Unlike tissue-based gene amplification tests (e.g. IHC or FISH), Guardant360 assesses the total representation of a given gene in all circulating cell-free DNA present in the patient's blood sample including material derived from the tumor and healthy tissue alike. As such, the absolute level of amplification present in the blood depends both on the tumor-derived cfDNA content and on the degree of amplification within that fraction and cannot be inferred from bulk cfDNA interrogation. For example, a positive Guardant360 test could represent a small population of cells with extremely high levels of the detected gene amplification. Alternatively, it could represent a large population of cells with low to medium levels of the detected gene amplifications. The exact correlation between amplification detected by Guardant360 compared to IHC or FISH and how each test differentially guides patient management is an area of active investigation.

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 A1024384 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)
TP53 V272L	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)
	NCT04855656 Nathan Hawkey, MD, MBA, clininfo@reparerx.com,+1 (857) 340-5402	Study of RP-6306 Alone or in Combination With RP-3500 or Debio 0123 in Patients With Advanced Solid Tumors	Phase 1	Houston, TX; Saint Louis, MO; Boston, MA; New Haven, CT; Salt Lake City, UT; Charlottesville, VA; Providence, RI (2); New York, NY (2); Denmark; Canada (2)
	NCT04869475 Min Shi, MD & Ph. D,sm11998@rjh.com.cn,+86-21-64370045	Arsenic Trioxide in Refractory Solid Tumors With Rescuable p53 Mutation	Phase 2	China
	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)
TP53 N131Y	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)
	NCT04855656 Nathan Hawkey, MD, MBA, clininfo@reparerx.com,+1 (857) 340-5402	Study of RP-6306 Alone or in Combination With RP-3500 or Debio 0123 in Patients With Advanced Solid Tumors	Phase 1	Houston, TX; Saint Louis, MO; Boston, MA; New Haven, CT; Salt Lake City, UT; Charlottesville, VA; Providence, RI (2); New York, NY (2); Denmark; Canada (2)
	NCT04869475 Min Shi, MD & Ph. D,sm11998@rjh.com.cn,+86-21-64370045	Arsenic Trioxide in Refractory Solid Tumors With Rescuable p53 Mutation	Phase 2	China
	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)
BRAF G265R	NCT02407509 Taleen Shakouri, PhD,DDU3808@icr.ac.uk,02034376629	Phase I Trial of VS-6766 Alone and in Combination With Everolimus	Phase 1	United Kingdom (3)
	NCT04116541 Jean-Yves BLAY, MD,jean-yves.blay@lyon.unicancer.fr,+33478785126	A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/Characteristics in Advanced /	Phase 2	France (8)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
		Metastatic Tumors.		
	NCT04913285 Kinnate Clinical Operations, clinicaltrials@kinnate.com,858.252.2723	A Study to Evaluate KIN-2787 in Participants With BRAF and/or NRAS Mutation Positive Solid Tumors	Phase 1	Los Angeles, CA; Cleveland, OH; Stanford, CA; La Jolla, CA; Nashville, TN; Tampa, FL; Fairfax, VA; Orlando, FL (2); New York, NY (2); France (5); Australia (2); Spain (5)
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05355701 Pfizer CT.gov Call Center,ClinicalTrials.gov_Inquiries@pfizer.com,1-800-718-1021	A Study to Learn About the Study Medicine Called PF-07799933 in People With Advanced Solid Tumors With BRAF Alterations.	Phase 1	Newton, MA; Miami, FL; Novi, MI; Rogers, AR; Springdale, AR; Fayetteville, AR; San Antonio, TX; Middletown, NJ; Detroit, MI (2); Cleveland, OH (3); Boston, MA (2); New York, NY (3); Portland, OR (2); TN (6); CO (6); Canada (5); Israel (6)
CCNE1 Amplification	NCT04855656 Nathan Hawkey, MD, MBA, clininfo@reparerx.com,+1 (857) 340-5402	Study of RP-6306 Alone or in Combination With RP-3500 or Debio 0123 in Patients With Advanced Solid Tumors	Phase 1	Houston, TX; Saint Louis, MO; Boston, MA; New Haven, CT; Salt Lake City, UT; Charlottesville, VA; Providence, RI (2); New York, NY (2); Denmark; Canada (2)
	NCT05238922 Incyte Corporation Call Center (US), medinfo@incyte.com,1.855.463.3463	Study of INCB123667 in Subjects With Advanced Solid Tumors	Phase 1	Duarte, CA; Philadelphia, PA; Atlanta, GA; Pittsburgh, PA; Irvine, CA; Lone Tree, CO; Fort Worth, TX; New York, NY (2); Netherlands (2); Japan (5); United Kingdom (4); Italy (5); France (4); Switzerland (3)
	NCT05252416 Blueprint Medicines, medinfo@blueprintmedicines.com,617-714-6707	(VELA) Study of BLU-222 in Advanced Solid Tumors	Phase 1 /Phase 2	Oklahoma City, OK; Philadelphia, PA; Stanford, CA; Chicago, IL; Baltimore, MD; San Francisco, CA; Little Rock, AR; Houston, TX; Detroit, MI; Chapel Hill, NC; Sarasota, FL; Salt Lake City, UT; Nashville, TN; Charlottesville, VA; New York, NY (3); Boston, MA (2); United Kingdom; Italy (3)
	NCT05262400 Pfizer CT.gov Call Center,ClinicalTrials.gov_Inquiries@pfizer.com,1-800-718-1021	A Study to Learn About the Study Medicine (Called PF-07220060 in Combination With PF-07104091) In Participants With Breast Cancer and Solid Tumors	Phase 1 /Phase 2	Houston, TX; Boston, MA; Grand Rapids, MI; Dallas, TX; Kansas City, MO; Seattle, WA (2); CA (5); Argentina (4); Czechia (3); China (7); Brazil (5); South Africa (6); Mexico (3); Bulgaria (5); Spain (6)
	NCT05867251 Medical Information, ClinicalTrials@avenzotx.com,(858) 239-2944	Study of ARTS-021 in Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Oklahoma City, OK; Philadelphia, PA; Cleveland, OH; New Haven, CT; Sarasota, FL; Fairfax, VA

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
BRAF G265R	ASN007		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	ASTX029		ERK1/2 kinase inhibitor.	Phase 2 (Solid Tumor)
	Avutometinib		Dual Raf/MEK kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Non-small cell lung carcinoma (NSCLC), Uveal melanoma, Ovarian carcinoma)
	BDTX-4933		Braf class 1, 2, and 3 inhibitor.	Phase 1 (Solid Tumor)
	Belvarafenib		Pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor)
	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)
	Brimarafenib		Braf class 1, 2, and 3 inhibitor.	Phase 2 (Solid Tumor) Phase 1 (Pancreatic ductal adenocarcinoma, Colorectal carcinoma (CRC))
	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)
	Defactinib		Focal adhesion kinase (FAK) inhibitor, upstream of MAPK pathway.	Phase 2 (Solid Tumor) Phase 2 (Lymphoma, Multiple myeloma (MM))
	Donafenib		Deuterium labeled sorafenib.	Phase 1 (Solid Tumor) Phase 3 (Hepatocellular carcinoma (HCC), Thyroid carcinoma, Colorectal carcinoma (CRC))
	E6201		MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	HMPL-295		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	IMM-1-104		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Non-small cell lung carcinoma (NSCLC), Pancreatic ductal adenocarcinoma)
	JZP815		pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor)
	KIN-2787		Pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Lifirafenib		Dual Braf/Egfr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	LTT462		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	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))
	MK-8353		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	Naporafenib		Pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor)
	PF-07799544		MEK Brain Penetrant Inhibitor.	Phase 1 (Glioma, Melanoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma, Colorectal carcinoma (CRC))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	PF-07799933		BRAF class 2 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))
	Plixorafenib		Braf mutant kinase inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Glioma, Hairy cell leukemia)
	QLH11906		pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor)
	Regorafenib	Stivarga	Multi-kinase inhibitor targeting VEGFR-2 and 3, Ret, Kit, Pdgfrs, Fgfrs, Tie2, and Raf.	Phase 2 (Lung carcinoid) FDA Approved in other indications (GIST (Gastrointestinal stromal tumor), Hepatocellular carcinoma (HCC), 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)
	Sorafenib	Nexavar	Raf kinase inhibitor, also inhibits VEGFR-2/Pdgfr-beta/Kit.	Phase 2 (Neuroendocrine carcinoma) FDA Approved in other indications (Hepatocellular carcinoma (HCC), Renal cell carcinoma, Thyroid carcinoma)
	Temuterkib		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Pancreatic ductal adenocarcinoma)
	Tizaterkib		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Hematologic malignancies)
	Tovorafenib	Ojemda	Pan-Raf kinase inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (Low-grade glioma with BRAF V600 mutation or BRAF fusion/rearrangement)
	Trametinib	Mekinist	MEK1,2 inhibitor.	Phase 2 (Solid Tumor) FDA Approved in other indications (Melanoma with BRAF V600 mutation)
	Ulixertinib		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, Melanoma, Histiocytic and dendritic cell neoplasms, Langerhans cell histiocytosis (LCH), Uveal melanoma, Acute myeloid leukemia (AML), Gastrointestinal carcinoma, Non-Hodgkin lymphoma (NHL), Myelodysplastic Syndrome (MDS))
	XP-102		pan-Raf kinase inhibitor.	Phase 2 (Melanoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma, Colorectal carcinoma (CRC))
TP53 V272L N131Y	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))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	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.	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-))
	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))
CCNE1 Amplification	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))
	ARTS-021		Cdk2 inhibitor.	Phase 2 (Solid Tumor)
	BLU-222		Cdk2 inhibitor.	Phase 2 (Solid Tumor)
	Dinaciclib		Cdk inhibitor targeting several Cdks, including Cdk1, Cdk2, Cdk5, and Cdk9.	Phase 1 (Solid Tumor) Phase 3 (Chronic lymphocytic leukemia (CLL))
	INCB0123667		Cdk2 inhibitor.	Phase 1 (Solid Tumor)
	PF-07104091		Cdk2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC), Ovarian carcinoma, Small cell lung carcinoma

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				(SCLC), Breast carcinoma)
	RGT-419B		CDK2/4/6 inhibitor.	Phase 1 (Solid Tumor)
	RP-6306		Myt1 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors, Uterine carcinoma)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
BRAF G265R	BRAF activating mutations or amplification have been reported to result in uncontrolled cell growth and tumorigenesis. [1,2]. BRAF alterations have been reported to be most common in colorectal neuroendocrine carcinoma compared with other types of neuroendocrine cancers, where they have been associated with advanced tumor stage. [3,4].	Braf signals upstream of the MAPK pathway, and BRAF amplification or activating mutations may confer sensitivity to inhibitors of Braf and/or components of the MAPK pathway, including MEK. [5]. The BRAF V600-specific inhibitors vemurafenib and dabrafenib have been approved for the treatment of BRAF V600E-positive melanoma. [6,7]. In addition, the MEK inhibitors trametinib and cobimetinib (in combination with vemurafenib) have been FDA-approved for BRAF V600E- and V600K-positive melanoma as has the encorafenib-binimetinib combination. [8-10]. Vemurafenib has additionally been approved for BRAF V600-positive Erdheim-Chester disease. [11]. Encorafenib in combination with cetuximab has been FDA-approved for the treatment of pretreated adult colorectal cancer patients with metastatic disease and harboring a BRAF V600E mutation, as detected by an FDA-approved test. [12-14]. The triple combination of atezolizumab plus cobimetinib and vemurafenib has also been FDA-approved for the treatment of V600E/K-positive melanoma. [15]. The combination of dabrafenib and trametinib has been FDA-approved for V600E/K-positive melanoma as well as V600E-positive solid tumor (excluding CRC), V600E-positive non-small cell lung carcinoma, and V600E-positive anaplastic thyroid carcinoma. [7,16-21]. Additional drug candidates targeting Raf-1 and/or components of the downstream MAPK pathway, such as MEK, are under clinical investigation in the context of non-V600 BRAF mutations. [22-25]. While the type of BRAF mutation reported here is not expected to respond to Braf V600 inhibitors, it may predict sensitivity to MEK or Raf/pan-Raf inhibitors. [26-31].	
TP53 V272L	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [32]. 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. [33-35]. Expression of p53 in normal cells is low; however, TP53 alterations,	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. [54-56]. Inhibition of components of the DNA damage checkpoint, including Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical	Mutations in TP53 may increase resistance to ionizing radiation therapy. [66,67].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	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. [36-40]. Typical and atypical lung carcinoid samples have been reported to exhibit lower rates of TP53 mutation and reduced p53 expression as compared with other subtypes of lung neuroendocrine carcinoma, such as small cell lung carcinoma (SCLC) or lung large cell neuroendocrine carcinoma. [41-45]. TP53 is one of the most commonly mutated genes in SCLC, and alterations of TP53 have been reported to be important for SCLC carcinogenesis. [46,47]. In a study of 110 SCLC samples, nearly all tumors were found to have biallelic inactivation of both TP53 and RB1; tumors lacking RB1 mutation were found to have loss of Rb due to another mechanism, revealing all SCLC tumors to have functional loss of p53 and Rb. [48]. TP53 mutation has been significantly associated with advanced stage in a study of 51 SCLC cases. [49]. Preclinical studies have reported that disruption of TP53 and RB1 in pulmonary neuroendocrine cells can give rise to neuroendocrine lesions and SCLC in mouse models. [50-53].	cancer models with deficiency of p53 function. [57-59]. 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. [60-65]. TP53 mutation in prostate small cell carcinoma cells has been reported to result in expression of Aurora kinase A, which is involved in cell proliferation and small cell neuroendocrine tumorigenesis; this study suggests Aurora kinase inhibitors may be therapeutic for small cell neuroendocrine tumors harboring TP53 mutation. [61].	
TP53 N131Y	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [32]. 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. [33-35]. Expression of p53 in normal 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. [36-40]. Typical and atypical lung carcinoid samples have been reported to exhibit lower rates of TP53 mutation and reduced p53 expression as compared with other subtypes of lung neuroendocrine carcinoma, such as small cell lung carcinoma (SCLC) or lung large cell	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. [54-56]. Inhibition of components of the DNA damage checkpoint, including Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function. [57-59]. 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. [60-65]. TP53 mutation in prostate small cell	Mutations in TP53 may increase resistance to ionizing radiation therapy. [66,67].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	neuroendocrine carcinoma. [41-45]. TP53 is one of the most commonly mutated genes in SCLC, and alterations of TP53 have been reported to be important for SCLC carcinogenesis. [46,47]. In a study of 110 SCLC samples, nearly all tumors were found to have biallelic inactivation of both TP53 and RB1; tumors lacking RB1 mutation were found to have loss of Rb due to another mechanism, revealing all SCLC tumors to have functional loss of p53 and Rb. [48]. TP53 mutation has been significantly associated with advanced stage in a study of 51 SCLC cases. [49]. Preclinical studies have reported that disruption of TP53 and RB1 in pulmonary neuroendocrine cells can give rise to neuroendocrine lesions and SCLC in mouse models. [50-53].	carcinoma cells has been reported to result in expression of Aurora kinase A, which is involved in cell proliferation and small cell neuroendocrine tumorigenesis; this study suggests Aurora kinase inhibitors may be therapeutic for small cell neuroendocrine tumors harboring TP53 mutation. [61].	
CCNE1 Amplification	Increased Cyclin E1 levels have been reported to enhance cell proliferation, which is likely due to its key role in the cell cycle. [68-70]. Scientific studies have reported that a number of cancers show CCNE1 amplification, overexpression of Cyclin E1, or increased Cyclin E1-Cdk2 activity. [71-77]. One study of lung neuroendocrine tumors reported that high Cyclin E expression was significantly associated with advanced stages 3-4 and nodal metastasis. [78].	At present there are no drugs that directly target Cyclin E1. However, tumors with CCNE1 amplification or activating mutations may be sensitive to inhibitors of Cdk2, the protein that Cyclin E1 binds and activates. Cyclin-dependent kinase (Cdk) inhibitors that target a variety of Cdks, including Cdk2, are under investigation in early phase clinical trials. [75,79]. The efficacy of this therapeutic approach has been reported in preclinical studies of breast and ovarian cancer cells with CCNE1 amplification or Cyclin E1 overexpression, in which treatment with Cdk2 inhibitors resulted in decreased proliferation and increased apoptosis in the cancer cells and reduced metastatic colonization in xenograft models. [80,81]. The combination of Cdk2 and either Akt or PI3K inhibitors in cancer cells with CCNE1 amplification has also been reported to be effective in preclinical studies. [82,83]. In addition, preliminary results from a Phase 2 trial of the Wee1 inhibitor adavosertib in patients with platinum-resistant ovarian cancer indicated that CCNE1 amplification may be positively associated with response. [84].	CCNE1 amplification has been implicated in resistance to Cdk4/6 inhibition in preclinical models of breast and ovarian cancer. [85,86].

References

1. Davies H, Bignell G, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett M, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson B, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins G, Bigner D, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho J, Leung S, Yuen S, Weber B, Seigler H, Darrow T, Paterson H, Marais R, Marshall C, Wooster R, Stratton M, Futreal P "Mutations of the BRAF gene in human cancer." Nature(2002): 949-54
2. Vultur A, Villanueva J, Herlyn M "Targeting BRAF in advanced melanoma: a first step toward manageable disease." Clinical cancer research : an official journal of the American Association for Cancer Research(2011): 1658-63
3. Dizdar L, Werner T, Drusenheimer J, Möhlendick B, Raba K, Boeck I, Anlauf M, Schott M, Göring W, Esposito I, Stoecklein N, Knoefel W, Krieg A "BRAFV600E mutation: A promising target in colorectal neuroendocrine carcinoma." International journal of cancer(2019): 1379-1390
4. Chetty R, Capo-Chichi J, Serra S "Colorectal large-cell neuroendocrine carcinoma with lymphoid stroma: further evidence confirming a unique subtype associated with MLH1/PMS2 loss, BRAF mutation, Epstein-Barr virus negativity, and the possibility of a better prognosis." Histopathology(2019): 247-253
5. Solit D, Garraway L, Pratilas C, Sawai A, Getz G, Basso A, Ye Q, Lobo J, She Y, Osman I, Golub T, Sebolt-Leopold J, Sellers W, Rosen N "BRAF mutation predicts sensitivity to MEK inhibition." Nature(2006): 358-62
6. Flaherty K, Puzanov I, Kim K, Ribas A, McArthur G, Sosman J, O'Dwyer P, Lee R, Grippo J, Nolop K, Chapman P "Inhibition of mutated, activated BRAF in metastatic melanoma." The New England journal of medicine(2010): 809-19
7. Flaherty K, Infante J, Daud A, Gonzalez R, Kefford R, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, Kudchadkar R, Burris H, Falchook G, Algazi A, Lewis K, Long G, Puzanov I, Lebowitz P, Singh A, Little S, Sun P, Allred A, Ouellet D, Kim K, Patel K, Weber J "Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations." The New England journal of medicine(2012): 1694-703
8. Flaherty K, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, Demidov L, Hassel J, Rutkowski P, Mohr P, Dummer R, Trefzer U, Larkin J, Utikal J, Dreno B, Nyakas M, Middleton M, Becker J, Casey M, Sherman L, Wu F, Ouellet D, Martin A, Patel K, Schadendorf D "Improved survival with MEK inhibition in BRAF-mutated melanoma." The New England journal of medicine(2012): 107-14
9. Larkin J, Ascierto P, Dréno B, Atkinson V, Liszkay G, Maio M, Mandalà M, Demidov L, Stroyakovskiy D, Thomas L, de la Cruz-Merino L, Dutriaux C, Garbe C, Sovak M, Chang I, Choong N, Hack S, McArthur G, Ribas A "Combined vemurafenib and cobimetinib in BRAF-mutated melanoma." The New England journal of medicine(2014): 1867-76
10. Dummer R, Ascierto P, Gogas H, Arance A, Mandala M, Liszkay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R, Chiarion-Sileni V, Dutriaux C, de Groot J, Yamazaki N, Loquai C, Moutouh-de Parseval L, Pickard M, Sandor V, Robert C, Flaherty K "Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial." The Lancet. Oncology(2018): 603-615
11. Diamond E, Subbiah V, Lockhart A, Blay J, Puzanov I, Chau I, Raje N, Wolf J, Erinjeri J, Torrisi J, Lacouture M, Elez E, Martínez-Valle F, Durham B, Arcila M, Ulaner G, Abdel-Wahab O, Pitcher B, Makrutzki M, Riehl T, Baselga J, Hyman D "Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study." JAMA oncology(2018): 384-388
12. "A Multicenter, Randomized, Open-label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA) /Irinotecan (FOLFIRI)/Cetuximab With a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With BRAF V600E-mutant Metastatic Colorectal Cancer" (2019)
13. Kopetz S, Grothey A, Cutsem EV, et al. "Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC)." J Clin Onc(2020): suppl 8
14. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong Y, Steeghs N, Guren T, Arkenau H, Garcia-Alfonso P, Pfeiffer P, Orlov S, Lonardi S, Elez E, Kim T, Schellens J, Guo C, Krishnan A, Dekervel J, Morris V, Calvo Ferrandiz A, Tarpgaard L, Braun M, Gollerkeri A, Keir C, Maharry K, Pickard M, Christy-Bittel J, Anderson L, Sandor V, Tabernero J "Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer." The New England journal of medicine(2019): 1632-1643
15. McArthur GA, Stroyakovskiy D, Gogas H, et al. "Evaluation of atezolizumab (A), cobimetinib (C), and vemurafenib (V) in previously untreated patients with BRAFV600 mutation-positive advanced melanoma: Primary results from the phase 3 IMspire150 trial" AACR 2020 Online Proceedings(2020): CT012
16. Hyman D, Puzanov I, Subbiah V, Faris J, Chau I, Blay J, Wolf J, Raje N, Diamond E, Hollebecque A, Gervais R, Elez-Fernandez M, Italiano A, Hofheinz R, Hidalgo M, Chan E, Schuler M, Lasserre S, Makrutzki M, Sirzen F, Veronese M, Tabernero J, Baselga J "Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations." The New England journal of medicine(2015): 726-36
17. Planchard D, Besse B, Groen H, Souquet P, Quoix E, Baik C, Barlesi F, Kim T, Mazieres J, Novello S, Rigas J, Upalawanna A, D'Amelio A, Zhang P, Mookerjee B, Johnson B "Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial." The Lancet. Oncology(2016): 984-993
18. Long G, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob J, Chiarion-Sileni V, Lebbe C, Mandalà M, Millward M, Arance A, Bondarenko I, Haanen J, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini D, Irani J, Swann S, Legos J, Jin F, Mookerjee B, Flaherty K "Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial." Lancet (London, England)(2015): 444-51
19. Subbiah V, Kreitman R, Wainberg Z, Cho J, Schellens J, Soria J, Wen P, Zielinski C, Cabanillas M, Urbanowitz G, Mookerjee B, Wang D, Rangwala F, Keam B "Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer." Journal of clinical oncology : official journal of the American Society of Clinical Oncology(2018): 7-13
20. Salama A, Li S, Macrae E, Park J, Mitchell E, Zwiebel J, Chen H, Gray R, McShane L, Rubinstein L, Patton D, Williams P, Hamilton S, Armstrong D, Conley B, Arteaga C, Harris L, O'Dwyer P, Chen A, Flaherty K "Dabrafenib and Trametinib in Patients With Tumors With BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H." Journal of clinical oncology : official journal of the American Society of Clinical Oncology(2020): 3895-3904
21. Subbiah V, Lassen U, Élez E, Italiano A, Curigliano G, Javle M, de Braud F, Prager G, Greil R, Stein A, Fasolo A, Schellens J, Wen P, Viele K, Boran A, Gasal E, Burgess P, Ilankumaran P, Wainberg Z "Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial." The Lancet. Oncology(2020): 1234-1243
22. Noeparast A, Teugels E, Giron P, Verschelden G, De Brakeleer S, Decoster L, De Grève J "Non-V600 BRAF mutations recurrently found in lung cancer predict sensitivity to the combination of Trametinib and Dabrafenib." Oncotarget(2017): 60094-60108

References

23. Molnár E, Rittler D, Baranyi M, Grusch M, Berger W, Döme B, Tóvári J, Aigner C, Tímár J, Garay T, Hegedűs B "Pan-RAF and MEK vertical inhibition enhances therapeutic response in non-V600 BRAF mutant cells." BMC cancer(2018): 542
24. Noeparast A, Giron P, De Brakeleer S, Eggermont C, De Ridder U, Teugels E, De Grève J "Type II RAF inhibitor causes superior ERK pathway suppression compared to type I RAF inhibitor in cells expressing different BRAF mutant types recurrently found in lung cancer." Oncotarget(2018): 16110-16123
25. Sullivan R, Infante J, Janku F, Wong D, Sosman J, Keedy V, Patel M, Shapiro G, Mier J, Tolcher A, Wang-Gillam A, Sznol M, Flaherty K, Buchbinder E, Carvajal R, Varghese A, Lacouture M, Ribas A, Patel S, DeCrescenzo G, Emery C, Groover A, Saha S, Varterasian M, Welsch D, Hyman D, Li B "First-in-Class ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study." Cancer discovery(2018): 184-195
26. Cotto-Rios X, Agianian B, Gitego N, Zacharioudakis E, Giricz O, Wu Y, Zou Y, Verma A, Poulikakos P, Gavathiotis E "Inhibitors of BRAF dimers using an allosteric site." Nature communications(2020): 4370
27. Yaeger R, Corcoran R "Targeting Alterations in the RAF-MEK Pathway." Cancer discovery(2019): 329-341
28. Yao Z, Torres N, Tao A, Gao Y, Luo L, Li Q, de Stanchina E, Abdel-Wahab O, Solit D, Poulikakos P, Rosen N "BRAF Mutants Evade ERK-Dependent Feedback by Different Mechanisms that Determine Their Sensitivity to Pharmacologic Inhibition." Cancer cell(2015): 370-83
29. Karoulia Z, Wu Y, Ahmed T, Xin Q, Bollard J, Krepler C, Wu X, Zhang C, Bollag G, Herlyn M, Fagin J, Lujambio A, Gavathiotis E, Poulikakos P "An Integrated Model of RAF Inhibitor Action Predicts Inhibitor Activity against Oncogenic BRAF Signaling." Cancer cell(2016): 485-498
30. Falchook G, Long G, Kurzrock R, Kim K, Arkenau T, Brown M, Hamid O, Infante J, Millward M, Pavlick A, O'Day S, Blackman S, Curtis C, Lebowitz P, Ma B, Ouellet D, Kefford R "Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial." Lancet (London, England)(2012): 1893-901
31. Röring M, Herr R, Fiala G, Heilmann K, Braun S, Eisenhardt A, Halbach S, Capper D, von Deimling A, Schamel W, Saunders D, Brummer T "Distinct requirement for an intact dimer interface in wild-type, V600E and kinase-dead B-Raf signalling." The EMBO journal(2012): 2629-47
32. Brown C, Lain S, Verma C, Fersht A, Lane D "Awakening guardian angels: drugging the p53 pathway." Nature reviews. Cancer(2009): 862-73
33. 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
34. 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
35. 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
36. 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
37. 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
38. 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
39. 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
40. 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
41. Naranjo Gómez J, Bernal J, Arranz P, Fernández S, Roman J "Alterations in the expression of p53, KLF4, and p21 in neuroendocrine lung tumors." Archives of pathology & laboratory medicine(2014): 936-42
42. Onuki N, Wistuba I, Travis W, Virmani A, Yashima K, Brambilla E, Hasleton P, Gazdar A "Genetic changes in the spectrum of neuroendocrine lung tumors." Cancer(1999): 600-7
43. Vollbrecht C, Werner R, Walter R, Christoph D, Heukamp L, Peifer M, Hirsch B, Burbat L, Mairinger T, Schmid K, Wohlschlaeger J, Mairinger F "Mutational analysis of pulmonary tumours with neuroendocrine features using targeted massive parallel sequencing: a comparison of a neglected tumour group." British journal of cancer(2015): 1704-11
44. Simbolo M, Mafficini A, Sikora K, Fassan M, Barbi S, Corbo V, Mastracci L, Rusev B, Grillo F, Vicentini C, Ferrara R, Pilotto S, Davini F, Pelosi G, Lawlor R, Chilosi M, Tortora G, Bria E, Fontanini G, Volante M, Scarpa A "Lung neuroendocrine tumours: deep sequencing of the four World Health Organization histotypes reveals chromatin-remodelling genes as major players and a prognostic role for TERT, RB1, MEN1 and KMT2D." The Journal of pathology(2017): 488-500
45. Walter R, Vollbrecht C, Christoph D, Werner R, Schmeller J, Flom E, Trakada G, Rapti A, Adamidis V, Hohenforst-Schmidt W, Kollmeier J, Mairinger T, Wohlschlaeger J, Zarogoulidis P, Porpodis K, Schmidt K, Mairinger F "Massive parallel sequencing and digital gene expression analysis reveals potential mechanisms to overcome therapy resistance in pulmonary neuroendocrine tumors." Journal of Cancer(2016): 2165-2172
46. Takahashi T, Takahashi T, Suzuki H, Hida T, Sekido Y, Ariyoshi Y, Ueda R "The p53 gene is very frequently mutated in small-cell lung cancer with a distinct nucleotide substitution pattern." Oncogene(1991): 1775-8
47. Kitamura H, Yazawa T, Sato H, Okudela K, Shimoyamada H "Small cell lung cancer: significance of RB alterations and TTF-1 expression in its carcinogenesis, phenotype, and biology." Endocrine pathology(2009): 101-7
48. George J, Lim J, Jang S, Cun Y, Ozretić L, Kong G, Leenders F, Lu X, Fernández-Cuesta L, Bosco G, Müller C, Dahmen I, Jahchan N, Park K, Yang D, Karnezis A, Vaka D, Torres A, Wang M, Korbel J, Menon R, Chun S, Kim D, Wilkerson M, Hayes N, Engelmann D, Pützer B, Bos M, Michels S, Vlasic I, Seidel D, Pinther B, Schaub P, Becker C, Altmüller J, Yokota J, Kohno T, Iwakawa R, Tsuta K, Noguchi M, Muley T, Hoffmann H, Schnabel P, Petersen I, Chen Y, Soltermann A, Tischler V, Choi C, Kim Y, Massion P, Zou Y, Jovanovic D, Kontic M, Wright G, Russell P, Solomon B, Koch I, Lindner M, Muscarella L, la Torre A, Field J, Jakopovic M, Knezevic J, Castaños-Vélez E, Roz L, Pastorino U, Brustugun O, Lund-Iversen M, Thunnissen E, Köhler J, Schuler M, Botling J, Sandelin M, Sanchez-Cespedes M, Salvesen H, Achter V, Lang U, Bogus M, Schneider P, Zander T, Ansén S, Hallek M, Wolf J, Vingron M, Yatabe Y, Travis W, Nürnberg P, Reinhardt C, Perner S, Heukamp L, Büttner R, Haas S, Brambilla E, Peifer M, Sage J, Thomas R "Comprehensive genomic profiles of small cell lung cancer." Nature(2015): 47-53

References

49. Hu J, Wang Y, Zhang Y, Yu Y, Chen H, Liu K, Yao M, Wang K, Gu W, Shou T "Comprehensive genomic profiling of small cell lung cancer in Chinese patients and the implications for therapeutic potential." Cancer medicine(2019): 4338-4347
50. Meuwissen R, Linn S, Linnoila R, Zevenhoven J, Mooi W, Berns A "Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model." Cancer cell(2003): 181-9
51. Park K, Liang M, Raiser D, Zamponi R, Roach R, Curtis S, Walton Z, Schaffer B, Roake C, Zmoos A, Kriegel C, Wong K, Sage J, Kim C "Characterization of the cell of origin for small cell lung cancer." Cell cycle (Georgetown, Tex.)(2011): 2806-15
52. Sutherland K, Proost N, Brouns I, Adriaensen D, Song J, Berns A "Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung." Cancer cell(2011): 754-64
53. Akeno N, Reece A, Callahan M, Miller A, Kim R, He D, Lane A, Moulton J, Wikenheiser-Brokamp K "TRP53 Mutants Drive Neuroendocrine Lung Cancer Through Loss-of-Function Mechanisms with Gain-of-Function Effects on Chemotherapy Response." Molecular cancer therapeutics(2017): 2913-2926
54. 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
55. 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
56. 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
57. Ma C, Janetka J, Piwnica-Worms H "Death by releasing the breaks: CHK1 inhibitors as cancer therapeutics." Trends in molecular medicine(2011): 88-96
58. 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
59. 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
60. 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
61. 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
62. 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
63. 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
64. 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
65. 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
66. El-Deiry W "The role of p53 in chemosensitivity and radiosensitivity." Oncogene(2003): 7486-95
67. 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
68. Ohtsubo M, Roberts J "Cyclin-dependent regulation of G1 in mammalian fibroblasts." Science (New York, N.Y.)(1993): 1908-12
69. Resnitzky D, Gossen M, Bujard H, Reed S "Acceleration of the G1/S phase transition by expression of cyclins D1 and E with an inducible system." Molecular and cellular biology(1994): 1669-79
70. Möröy T, Geisen C "Cyclin E." The international journal of biochemistry & cell biology(2004): 1424-39
71. Akama Y, Yasui W, Yokozaki H, Kuniyasu H, Kitahara K, Ishikawa T, Tahara E "Frequent amplification of the cyclin E gene in human gastric carcinomas." Japanese journal of cancer research : Gann(1995): 617-21
72. Keyomarsi K, Conte D, Toyofuku W, Fox M "Deregulation of cyclin E in breast cancer." Oncogene(1995): 941-50
73. Nielsen N, Arnerlöv C, Emdin S, Landberg G "Cyclin E overexpression, a negative prognostic factor in breast cancer with strong correlation to oestrogen receptor status." British journal of cancer(1996): 874-80
74. Georgieva J, Sinha P, Schadendorf D "Expression of cyclins and cyclin dependent kinases in human benign and malignant melanocytic lesions." Journal of clinical pathology(2001): 229-35
75. Akli S, Keyomarsi K "Cyclin E and its low molecular weight forms in human cancer and as targets for cancer therapy." Cancer biology & therapy(2003): S38-47
76. Li J, Miki H, Ohmori M, Wu F, Funamoto Y "Expression of cyclin E and cyclin-dependent kinase 2 correlates with metastasis and prognosis in colorectal carcinoma." Human pathology(2001): 945-53
77. Wang A, Yoshimi N, Suzui M, Yamauchi A, Tarao M, Mori H "Different expression patterns of cyclins A, D1 and E in human colorectal cancer." Journal of cancer research and clinical oncology(1996): 122-6
78. Salon C, Merdzhanova G, Brambilla C, Brambilla E, Gazzeri S, Eymin B "E2F-1, Skp2 and cyclin E oncoproteins are upregulated and directly correlated in high-grade neuroendocrine lung tumors." Oncogene(2007): 6927-36
79. Bruyère C, Meijer L "Targeting cyclin-dependent kinases in anti-neoplastic therapy." Current opinion in cell biology(2013): 772-9

References

80. Scaltriti M, Eichhorn P, Cortés J, Prudkin L, Aura C, Jiménez J, Chandarlapaty S, Serra V, Prat A, Ibrahim Y, Guzmán M, Gili M, Rodríguez O, Rodríguez S, Pérez J, Green S, Mai S, Rosen N, Hudis C, Baselga J "Cyclin E amplification/overexpression is a mechanism of trastuzumab resistance in HER2+ breast cancer patients." Proceedings of the National Academy of Sciences of the United States of America(2011): 3761-6

81. Yang L, Fang D, Chen H, Lu Y, Dong Z, Ding H, Jing Q, Su S, Huang S "Cyclin-dependent kinase 2 is an ideal target for ovary tumors with elevated cyclin E1 expression." Oncotarget(2015): 20801-12

82. Au-Yeung G, Lang F, Azar W, Mitchell C, Jarman K, Lackovic K, Aziz D, Cullinane C, Pearson R, Mileshkin L, Rischin D, Karst A, Drapkin R, Etemadmoghadam D, Bowtell D "Selective Targeting of Cyclin E1-Amplified High-Grade Serous Ovarian Cancer by Cyclin-Dependent Kinase 2 and AKT Inhibition." Clinical cancer research : an official journal of the American Association for Cancer Research(2017): 1862-1874

83. Cocco E, Lopez S, Black J, Bellone S, Bonazzoli E, Predolini F, Ferrari F, Schwab C, Menderes G, Zammataro L, Buza N, Hui P, Wong S, Zhao S, Bai Y, Rimm D, Ratner E, Litkouhi B, Silasi D, Azodi M, Schwartz P, Santin A "Dual CCNE1/PIK3CA targeting is synergistic in CCNE1-amplified/PIK3CA-mutated uterine serous carcinomas in vitro and in vivo." British journal of cancer(2016): 303-11

84. Moore KN, Chambers SK, Hamilton EP, et al. "Adavosertib with chemotherapy (CT) in patients (pts) with platinum-resistant ovarian cancer (PPROC): An open label, four-arm, phase II study" J Clin Oncol(2019): Abstract 5513

85. Herrera-Abreu M, Palafox M, Asghar U, Rivas M, Cutts R, Garcia-Murillas I, Pearson A, Guzman M, Rodriguez O, Grueso J, Bellet M, Cortés J, Elliott R, Pancholi S, Baselga J, Dowsett M, Martin L, Turner N, Serra V "Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer." Cancer research(2016): 2301-13

86. Taylor-Harding B, Aspuria P, Agadjanian H, Cheon D, Mizuno T, Greenberg D, Allen J, Spurka L, Funari V, Spiteri E, Wang Q, Orsulic S, Walsh C, Karlan B, Wiedemeyer W "Cyclin E1 and RTK/RAS signaling drive CDK inhibitor resistance via activation of E2F and ETS." Oncotarget(2015): 696-714