er: Male

GUARDANT360

Therapy Finder Page

REPORTING	PHYSICIAN
Report Date:	
Receipt Date:	
Collection Date:	
Specimen:	
Status:	

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
CHEK2 D347N	Olaparib, Talazoparib	Yes	0.6%
ATM Loss (Single Copy Deletion)	Olaparib, Talazoparib	Yes	DETECTED
TP53 R249S	None	Yes	0.1%
TP53 c.920-6_923del (Splice Site Indel)	None	Yes	16.6%
RB1 S648fs	None	No	14.3%
CDH1 P245fs	None	No	0.5%

Variants of Uncertain Clinical Significance
PDGFRA R690S (7.5%), *PDGFRA* E485* (6.5%), *MAP2K2* P334T (0.6%), *CHEK2* K235N (0.2%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Comments

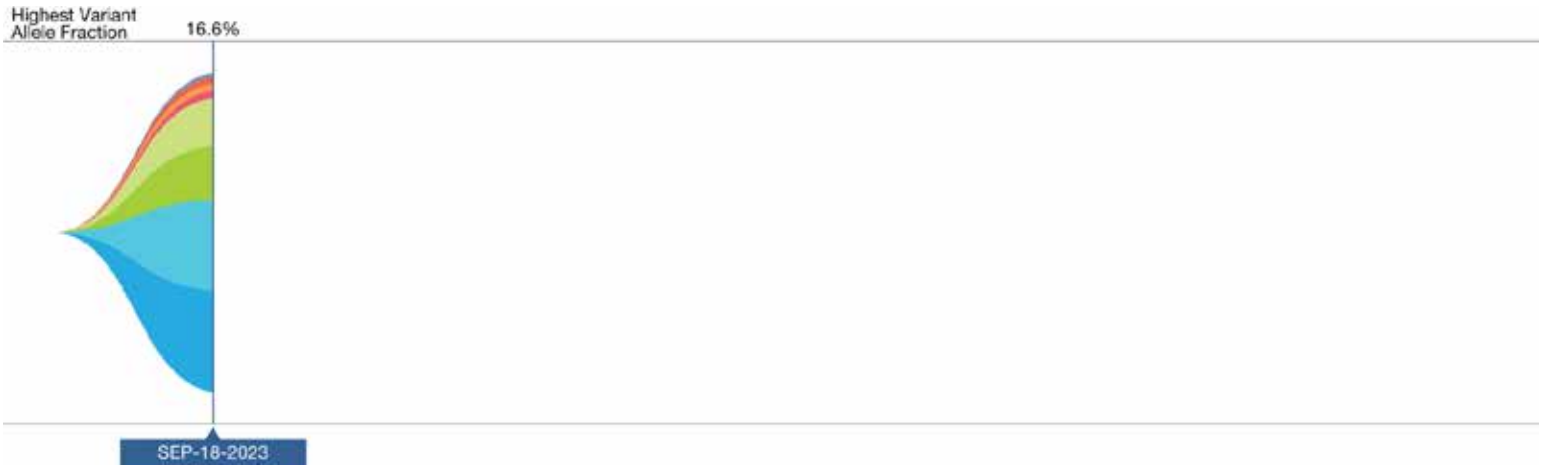
Reported by: JV4

Additional Biomarkers

Biomarker	Additional Details
Tumor Mutational Burden (TMB)	22.97 mut/Mb
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 c.920-6_923del (Splice Site Indel)	16.6%	
RB1 S648fs	14.3%	
PDGFRA R690S	7.5%	Variants of Uncertain Clinical Significance §
PDGFRA E485*	6.5%	Variants of Uncertain Clinical Significance §
CHEK2 D347N	0.6%	
MAP2K2 P334T	0.6%	Variants of Uncertain Clinical Significance §
CDH1 P245fs	0.5%	
CHEK2 K235N	0.2%	Variants of Uncertain Clinical Significance §
TP53 R249S	0.1%	
ATM Loss (Single Copy Deletion) Deletions not graphed above	DETECTED Plasma Copy Number 1.9	

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 A0855977 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
CHEK2 D347N	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
ATM Loss (Single Copy Deletion)	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 R249S	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 c.920-6_923del	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.

Deletion (Del): The following alteration was detected in this patient: *CDH1* P245fs; *RB1* S648fs. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

Splice Site: Splice site variants disrupt the donor and/or acceptor splice site(s), leading to abnormal mRNA splicing and altered protein levels and/or function.

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

Single Copy Deletion: Occurs when a single copy of a gene is lost due to a whole gene deletion.

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.

Checkpoint inhibition has been FDA-approved for patients who have no satisfactory alternative treatment option with a tissue TMB score of 10 mut/Mb or higher. In a large clinical study of blood TMB in patients with newly diagnosed non-small cell lung cancer (NSCLC) using Guardant360, Guardant360 TMB score of 16 mut/Mb, 76th percentile, correlates with a tissue TMB score of 10 mut/Mb (Rizvi, N.A., et al. JAMA Oncology, 2020). The distribution of tissue TMB scores has been shown to differ across tumor types (Samstein, R.M, et al. Nature Genetics, 2019). Similarly, in a landscape analysis of Guardant360 TMB, 80th percentile corresponds to the following TMB scores: NSCLC - 20.2 mut/Mb; colorectal cancer - 20.1 mut/Mb; breast cancer- 15.3 mut/Mb; prostate cancer - 13.4 mut/Mb; pancreatic cancer - 11.4 mut/Mb; head and neck squamous cell cancer (HNSCC)- 17.4 mut/Mb; cholangiocarcinoma - 10.5 mut/Mb.

Method and Limitations

Guardant360 sequences 83 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 (SNVs), gene amplifications, fusions, short insertions/deletions (indels, 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. Tumor mutational burden (TMB) score is calculated for all cancer types from somatic SNVs and indels in exons of ~ 500 genes detected in cfDNA, followed by adjusting for tumor shedding levels and the size of the panel. A "Not Evaluable" result is an inconclusive result in samples where the evidence of tumor shedding is insufficient and it does not preclude TMB-High status in tissue. 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 83 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*
CHEK2 *	*CTNNB1*	*DDR2*	*EGFR* † #	*ERBB2* †	*ESR1* †	*EZH2*	*FANCA*	*FBXW7*
FGFR1 † #	*FGFR2* †	*FGFR3* #	*GATA3*	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*
IDH1	*IDH2*	*JAK2*	*JAK3*	*KEAP1*	*KIT* †	*KRAS* †	*MAP2K1*	*MAP2K2*
MAPK1	*MAPK3*	*MET* † #	*MLH1*	*MPL*	*MSH2*	*MSH6*	*MTOR*	*MYC* †
NF1	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*	*NTRK1* #	*NTRK2* #	*NTRK3* #	*PALB2* *
PDGFRA †	*PIK3CA* †	*PMS2*	*PTEN*	*PTPN11*	*RAD51D* *	*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.

* Guardant360 reports losses in 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 A0855977 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)
CHEK2 D347N	NCT03209401 See https://clinicaltrials.gov/ct2/show/NCT03209401	Niraparib Plus Carboplatin in Patients With Homologous Recombination Deficient Advanced Solid Tumor Malignancies	Phase 1	Charlotte, NC; Hackensack, NJ; Washington, DC (2)
	NCT03842228 See https://clinicaltrials.gov/ct2/show/NCT03842228	Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations	Phase 1	Houston, TX; Madison, WI; Pittsburgh, PA; Austin, TX; Chicago, IL; Columbus, OH; Aurora, CO; Galveston, TX; Boston, MA (3); CA (6)
	NCT04826341 Rasa Vilimas, R.N.,vilimasrj@mail.nih.gov, (240) 858-3158	A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer, Extra-Pulmonary Small Cell Neuroendocrine Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors	Phase 1 /Phase 2	Bethesda, MD
	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)
	NCT05700721 Timothy Yap, MBBS,PHD, tyap@mdanderson.org,(713) 563-1784	Phase II Trial of the PARP Inhibitor Niraparib and PD-1 Inhibitor Dostarlimab in Patients With Advanced Cancers With Active Progressing Brain Metastases (STARLET)	Phase 2	Houston, TX
ATM Loss (Single Copy Deletion)	NCT03209401 See https://clinicaltrials.gov/ct2/show/NCT03209401	Niraparib Plus Carboplatin in Patients With Homologous Recombination Deficient Advanced Solid Tumor Malignancies	Phase 1	Charlotte, NC; Hackensack, NJ; Washington, DC (2)
	NCT03842228 See https://clinicaltrials.gov/ct2/show/NCT03842228	Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations	Phase 1	Houston, TX; Madison, WI; Pittsburgh, PA; Austin, TX; Chicago, IL; Columbus, OH; Aurora, CO; Galveston, TX; Boston, MA (3); CA (6)
	NCT04826341 Rasa Vilimas, R.N.,vilimasrj@mail.nih.gov, (240) 858-3158	A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer, Extra-Pulmonary Small Cell Neuroendocrine Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors	Phase 1 /Phase 2	Bethesda, MD
	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)
	NCT05700721 Timothy Yap, MBBS,PHD, tyap@mdanderson.org,(713) 563-1784	Phase II Trial of the PARP Inhibitor Niraparib and PD-1 Inhibitor Dostarlimab in Patients With Advanced Cancers With Active Progressing Brain Metastases (STARLET)	Phase 2	Houston, TX
TP53 R249S	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)
	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 (2)
	NCT05253053	To Evaluate Efficacy and Safety of TT-00420 as	Phase 1	China (3)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	Caixia Sun, Ph.D., clinicaltrial@transtherabio.com,025-58216298	Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors	/Phase 2	
	NCT05815160 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	Debio 0123 in Combination With Carboplatin and Etoposide in Adult Participants With Small Cell Lung Cancer That Recurred or Progressed After Previous Standard Platinum-Based Therapy	Phase 1	Spain (6)
TP53 c.920-6_923del	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)
	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 (2)
	NCT05253053 Caixia Sun, Ph.D., clinicaltrial@transtherabio.com,025-58216298	To Evaluate Efficacy and Safety of TT-00420 as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors	Phase 1 /Phase 2	China (3)
	NCT05815160 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	Debio 0123 in Combination With Carboplatin and Etoposide in Adult Participants With Small Cell Lung Cancer That Recurred or Progressed After Previous Standard Platinum-Based Therapy	Phase 1	Spain (6)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
ATM Loss (Single Copy Deletion)	ART0380		Atr inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	ATG-018		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Marginal zone lymphoma (MZL), Diffuse large B-cell lymphoma (DLBCL))
	ATRN-119		Atr inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	AZD5305		PARP inhibitor.	Phase 2 (Solid Tumor)
	AZD9574		PARP1 inhibitor (brain penetrant).	Phase 2 (Glioma, Pancreatic carcinoma, Prostate carcinoma, Ovarian carcinoma, Breast carcinoma)
	Berzosertib		Atr inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 2 (Gastric carcinoma, Neuroendocrine carcinoma, Small cell carcinoma, Osteosarcoma, Non-small cell lung carcinoma (NSCLC), Prostate carcinoma, Ovarian carcinoma, Gastroesophageal junction carcinoma, Urothelial carcinoma, Bladder carcinoma, Leiomyosarcoma, Renal pelvis carcinoma, Lung cancer)
	Ceralasertib		Atr inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Non-small cell lung carcinoma (NSCLC), Lung cancer)
	Elimusertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Head and neck squamous cell carcinoma (HNSCC))
	Fluzoparib		PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Pancreatic carcinoma, Ovarian carcinoma, Breast carcinoma)
	IDX-1197		PARP inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	IMP9064		Atr inhibitor.	Phase 1 (Solid Tumor)
	Ipilimumab	Yervoy	Anti-CTLA-4 monoclonal antibody.	Phase 3 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Melanoma, Head and neck squamous cell carcinoma (HNSCC), CRC with MSI-H or dMMR)
	Niraparib	Zejula	PARP inhibitor.	Phase 3 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma with BRCA1/2 mutation)
	Nivolumab	Opdivo	Anti-PD-1 monoclonal antibody.	Phase 3 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Gastric carcinoma, Hodgkin lymphoma (HL), Melanoma, Non-small cell lung carcinoma (NSCLC), Renal cell carcinoma, Head and neck squamous cell carcinoma (HNSCC), Gastroesophageal junction carcinoma, Urothelial carcinoma, Bladder carcinoma, Esophageal carcinoma, CRC with MSI-H or dMMR)
	Olaparib	Lynparza	PARP inhibitor.	Phase 3 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Pancreatic adenocarcinoma with germline BRCA1/2 mutation, Prostate cancer with HRR gene

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				mutation, Ovarian carcinoma, Ovarian carcinoma with BRCA1/2 mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Pamiparib		PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Gastric carcinoma, Gastroesophageal junction carcinoma)
	RP-3500		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	RP12146		PARP inhibitor.	Phase 1 (Small cell lung carcinoma (SCLC)) Phase 1 (Gastric carcinoma, Pancreatic carcinoma, Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma, Cholangiocarcinoma, Colorectal carcinoma (CRC))
	Rucaparib	Rubraca	PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma)
	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 2 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Prostate cancer with HRR gene mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Tuvusertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Merkel cell carcinoma, Non-small cell lung carcinoma (NSCLC), Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Colorectal carcinoma (CRC))
	Veliparib		PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Glioblastoma, Non-small cell lung carcinoma (NSCLC), Ovarian carcinoma, Ovarian carcinosarcoma, Breast carcinoma, Lung cancer)
	VX-803		Atr inhibitor.	Phase 1 (Solid Tumor)
CHEK2 D347N	ART0380		Atr inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	ATG-018		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Marginal zone lymphoma (MZL), Diffuse large B-cell lymphoma (DLBCL))
	ATRN-119		Atr inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	AZD5305		PARP inhibitor.	Phase 2 (Solid Tumor)
	AZD9574		PARP1 inhibitor (brain penetrant).	Phase 2 (Glioma, Pancreatic carcinoma, Prostate carcinoma, Ovarian carcinoma, Breast carcinoma)
	Berzosertib		Atr inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 2 (Gastric carcinoma, Neuroendocrine carcinoma, Small cell carcinoma, Osteosarcoma, Non-small cell lung carcinoma (NSCLC), Prostate carcinoma, Ovarian carcinoma, Gastroesophageal junction carcinoma, Urothelial carcinoma, Bladder carcinoma, Leiomyosarcoma, Renal pelvis carcinoma, Lung cancer)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Ceralasertib		Atr inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Non-small cell lung carcinoma (NSCLC), Lung cancer)
	Elimusertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Head and neck squamous cell carcinoma (HNSCC))
	Fluzoparib		PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Pancreatic carcinoma, Ovarian carcinoma, Breast carcinoma)
	IDX-1197		PARP inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	IMP9064		Atr inhibitor.	Phase 1 (Solid Tumor)
	Niraparib	Zejula	PARP inhibitor.	Phase 3 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma with BRCA1/2 mutation)
	Olaparib	Lynparza	PARP inhibitor.	Phase 3 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Pancreatic adenocarcinoma with germline BRCA1/2 mutation, Prostate cancer with HRR gene mutation, Ovarian carcinoma, Ovarian carcinoma with BRCA1/2 mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Pamiparib		PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Gastric carcinoma, Gastroesophageal junction carcinoma)
	RP-3500		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	RP12146		PARP inhibitor.	Phase 1 (Small cell lung carcinoma (SCLC)) Phase 1 (Gastric carcinoma, Pancreatic carcinoma, Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma, Cholangiocarcinoma, Colorectal carcinoma (CRC))
	Rucaparib	Rubraca	PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma)
	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 2 (Small cell lung carcinoma (SCLC)) FDA Approved in other indications (Prostate cancer with HRR gene mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Tuvusertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Merkel cell carcinoma, Non-small cell lung carcinoma (NSCLC), Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Colorectal carcinoma (CRC))
	Veliparib		PARP inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Glioblastoma, Non-small cell lung carcinoma (NSCLC), Ovarian carcinoma, Ovarian carcinosarcoma, Breast carcinoma, Lung cancer)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	VX-803		Atr inhibitor.	Phase 1 (Solid Tumor)
TP53 R249S c.920-6_923del (Splice Site Indel)	Adavosertib		Wee1 tyrosine kinase inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 2 (Embryonal tumor with multi-layered rosettes (ETMR), Medulloblastoma, Solid Tumor, Primary myelofibrosis (PMF), Ovarian carcinosarcoma, Acute myeloid leukemia (AML), MDS/MPN, unclassifiable, Chronic myelomonocytic leukemia (CMML), Peritoneal papillary serous carcinoma, Myelodysplastic Syndrome (MDS))
	Alisertib		Aurora A kinase inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	AMG 900		Aurora A/B/C kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	AT9283		Aurora A, B, Jak2, Jak3, Bcr-Abl kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Acute myeloid leukemia (AML), Multiple myeloma (MM), Acute lymphoblastic leukemia (ALL))
	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))
	Debio 0123		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	ENMD-2076		Aurora A kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Fibrolamellar hepatocellular carcinoma, Ovarian carcinoma, Breast carcinoma, Fallopian tube adenocarcinoma, Sarcoma)
	IMP7068		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	Kevetrin		Blocks Mdm2-p53 interaction, restoring transcriptional activity of p53.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma)
	LY3295668		Aurora A kinase inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), 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)
	SNS-314		Aurora A/B kinase inhibitor.	Phase 1 (Solid Tumor)
	SY-4835		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	TAS-119		Aurora A kinase inhibitor.	Phase 1 (Solid Tumor)
	TT-00420		Aurora A/B kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Breast carcinoma (triple negative))
TP53 R249S	COTI-2		Reactivates mutant p53.	Phase 1 (Endometrial carcinoma, Head and neck squamous cell carcinoma (HNSCC), Ovarian carcinoma, Cervical carcinoma)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
CHEK2 D347N	CHEK2 encodes the protein checkpoint kinase 2 (Chk2), a serine /threonine kinase which plays an important role in the DNA damage response; it is a putative tumor suppressor. [1-3]. Germline CHEK2 mutations are associated with Li-Fraumeni syndrome 2 and confer increased susceptibility to breast, colorectal, and prostate cancer. [2,4-7]. One study analyzing 131 pancreatic neuroendocrine neoplasm samples reported that low Chk2 expression was significantly associated with tumor recurrence, perineural invasion, and nodal involvement. [8].	Depletion of CHEK2 has been reported to increase sensitivity to PARP inhibitors in preclinical models and PARP inhibitors are in clinical trials in cancers with DNA repair deficiencies, including CHEK2 alterations. [9-13]. 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 or BRCA2 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 CHEK2 mutation; rucaparib has been approved by the FDA for advanced ovarian cancer and castration-resistant prostate cancer patients with either germline or somatic BRCA1 or BRCA2 mutations. [14-22]. 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 CHEK2. [23-25]. In addition, preclinical studies have indicated that Atr inhibitors are effective in cancer cells with defects in homologous recombination. [26-29].	
ATM Loss (Single Copy Deletion)	ATM deficiency in cells has been reported to result in progression through the cell cycle even in the presence of DNA damage, resulting in the accumulation of DNA errors and genomic instability that can lead to cancer. [30].	Based on preclinical and clinical evidence, ATM-deficient tumors may be sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors, Atr inhibitors, and DNA-PKcs inhibitors, which are under investigation in clinical trials. [31-37]. 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 or BRCA2 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 ATM mutation; rucaparib has been approved by the FDA for advanced ovarian cancer and castration-resistant prostate cancer patients with either germline or somatic BRCA1 or BRCA2 mutations. [14-22]. In addition, talazoparib in combination with enzalutamide has been FDA-	

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		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 ATM mutation. [23-25]. A preclinical study reported a significant correlation between low ATM mRNA or low Atm protein expression and significantly increased response to talazoparib in a patient-derived xenograft SCLC model. Depletion of ATM in two SCLC cell lines resulted in significantly increased sensitivity to cisplatin, olaparib, and talazoparib. [38].	
TP53 R249S	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [39]. 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. [40-42]. 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. [43-47]. TP53 is one of the most commonly mutated genes in SCLC, and alterations of TP53 have been reported to be important for SCLC carcinogenesis. [48,49]. In a study of 110 SCLC samples, nearly all tumors were found to have bialellic 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. [50]. TP53 mutation has been significantly associated with advanced stage in a study of 51 SCLC cases. [51] .	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. [52-54]. 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. [55-57]. 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. [58-63]. 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. [59].	Mutations in TP53 may increase resistance to ionizing radiation therapy. [64,65].
TP53 c.920-6_923del	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [39]. 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.	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. [52-54]. Inhibition of components of the DNA damage checkpoint, including Wee1, has been	Mutations in TP53 may increase resistance to ionizing radiation therapy. [64,65].

Relevance of Detected Alterations

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RB1 S648fs	RB1 inactivation has been shown to cause epigenetic deregulation of genes involved in several cancer pathways and is thus speculated to play a key role in cancer development. [66]. Retinoblastoma, a malignant tumor of the retina, arises from mutations in both RB1 alleles. Hereditary retinoblastoma patients carry one RB1 germline mutation, which also increases their risk of developing a second type of cancer later in life. [67]. RB1 inactivation by various mechanisms, such as mutation and deletion, has been reported as a common event in small cell lung carcinoma (SCLC), with loss of Rb protein expression considered a hallmark molecular event in SCLC. [49,69]. In a study of 110 SCLC samples, nearly all tumors were found to have bialellic 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. [50].	At this time, there are no therapeutic options to target the inactivation of Rb. Preclinical studies are actively investigating possible therapies to address Rb inactivation, exploring avenues such as Aurora kinase inhibitors, Bcl-2 family inhibitors, and Notch pathway activation. [70-73]. Loss of Rb function has been associated with increased sensitivity to cytotoxic agents in both preclinical studies and in patients with bladder or breast cancer. [74,75].	The effect of Rb expression on chemoresistance is complex, as both Rb protein expression and loss of Rb protein have been associated with resistance to chemotherapeutics. [74,76-80]. Loss of RB1 has been associated with lack of response to Cdk4/6 inhibitors. [81-87]. Several studies have reported that resistance to Egfr tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) can be mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features. [88-91]. One study reported loss of RB1 gene and Rb protein expression in all ten EGFR-mutant NSCLC cases that had transformed to SCLC at the time of acquired resistance to Egfr TKIs and in cell lines derived from resistant EGFR-mutant NSCLC cases, but not in any of 11 cases of NSCLC that developed resistance but maintained NSCLC histology. [92].
CDH1 P245fs	Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis. [93,94]. Altered localization or loss of E-cadherin expression has been reported to be associated with higher tumor	Presently, there are no targeted therapies to address loss or mutation of CDH1.A preclinical study has reported that loss of E-cadherin function resulted in increased Notch1	

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	grade, advanced stage, and lymph node metastasis in lung neuroendocrine tumor (NET) samples. [95,96]	signaling and Bcl-2 overexpression, opening the possibility for therapies targeting these pathways. [97].	

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