REPORTING

Report Date:	APR-16-2024
Receipt Date:	APR-11-2024
Collection Date:	APR-10-2024
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 3

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 5)	% cfDNA or Amplification
EGFR T790M	✓ Osimertinib ✗ Afatinib, Dacomitinib, Erlotinib, Erlotinib+ramucirumab, Gefitinib, Neratinib	Yes	0.4%
EGFR L858R	✓ Osimertinib	Yes	34.1%
BRCA2 S270*	~ Niraparib, Olaparib, Rucaparib, Talazoparib	Yes	29.4%
PIK3CA E545K	~ Alpelisib, Capivasertib	Yes	2.5%
PIK3CA E542K	~ Alpelisib, Capivasertib	Yes	0.4%
PIK3CA H1047L	~ Alpelisib, Capivasertib	Yes	0.06%
PIK3CA H1047R	~ Alpelisib, Capivasertib	Yes	0.06%
PTEN I224fs	~ Capivasertib	Yes	24.0%
TP53 R213*	None	Yes	25.2%
RB1 Q395*	None	No	1.6%

Variants of Uncertain Clinical Significance
MET E410K (0.1%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
NOTCH1 L2176L (0.2%)
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

The BRCA2 S270* (c.809C>G) alteration was detected in this patient's sample at an allele fraction suspicious for germline origin. This variant may lead to the loss of functional protein, and similar variants have been associated with hereditary predisposition to cancer. As Guardant360 is neither intended nor validated for the reporting or interpretation of germline variants, we cannot confirm the germline vs. somatic origin of this finding and recommend verification with an assay validated for germline testing if this potential incidental finding is of clinical interest.
Reported by: AC27

Additional Biomarkers

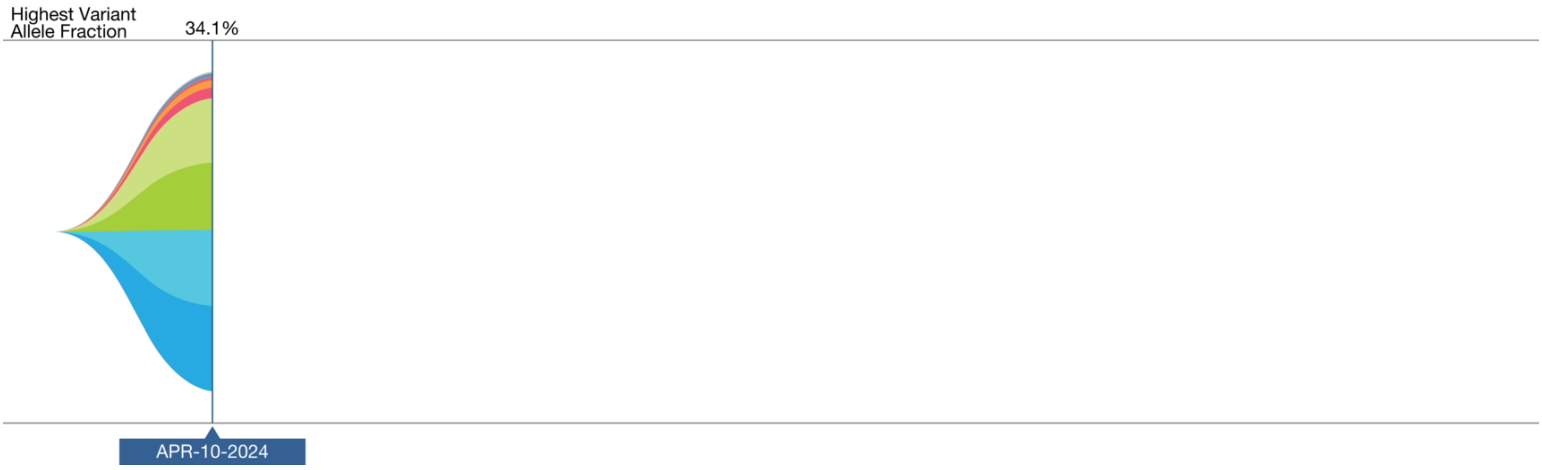
Biomarker	Additional Details
MSI-High	NOT DETECTED

We evaluated this sample for 74 genes, including the following guideline-recommended genes for NSCLC

EGFR(T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2*(HER2)	*RET*	*NTRK*	*KRAS*

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	
EGFR L858R	34.1%	
BRCA2 S270*	29.4%	
TP53 R213*	25.2%	
PTEN I224fs	24.0%	
PIK3CA E545K	2.5%	
RB1 Q395*	1.6%	
PIK3CA E542K	0.4%	
EGFR T790M	0.4%	
NOTCH1 L2176L	0.2%	Synonymous Alteration §
MET E410K	0.1%	Variants of Uncertain Clinical Significance §

Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp
PIK3CA H1047L	0.06%
PIK3CA H1047R	0.06%

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 A1015072 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
EGFR T790M	NCT04077463 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	A Study of Lazertinib as Monotherapy or in Combination With Amivantamab in Participants With Advanced Non-small Cell Lung Cancer	Phase 1	Kaohsiung, Taiwan Taipei City, Taiwan Tainan, Taiwan Taichung, Taiwan
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Taipei City, Taiwan Tainan, Taiwan Taoyuan, Taiwan Taipei, Taiwan (3) Additional trial sites available
	NCT05526755 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study of 5 Years of Adjuvant Osimertinib in Completely Resected Epidermal Growth Factor Receptor Mutation (EGFRm) Non-small Cell Lung Carcinoma (NSCLC)	Phase 2	Kaohsiung City, Taiwan Kaohsiung, Taiwan Hualien, Taiwan Taipei, Taiwan (2) Additional trial sites available
	NCT05647122 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	First in Human Study of AZD9592 in Solid Tumors	Phase 1	Taipei City, Taiwan Taipei, Taiwan Taoyuan, Taiwan Taichung, Taiwan
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Yunlin, Taiwan Taipei City, Taiwan Kaohsiung, Taiwan (2) Taipei, Taiwan (2) Additional trial sites available
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
EGFR L858R	NCT04077463 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	A Study of Lazertinib as Monotherapy or in Combination With Amivantamab in Participants With Advanced Non-small Cell Lung Cancer	Phase 1	Kaohsiung, Taiwan Taipei City, Taiwan Tainan, Taiwan Taichung, Taiwan
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Taipei City, Taiwan Tainan, Taiwan Taoyuan, Taiwan Taipei, Taiwan (3) Additional trial sites available
	NCT05663866 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Premedication to Reduce Amivantamab Associated Infusion Related Reactions	Phase 2	ChangHua, Taiwan Kaohsiung, Taiwan Taipei City, Taiwan Tainan City, Taiwan Additional trial sites available
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Yunlin, Taiwan Taipei City, Taiwan Kaohsiung, Taiwan (2) Taipei, Taiwan (2) Additional trial sites available
	NCT06120140 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib	Phase 2	Taipei, Taiwan Taoyuan City, Taiwan Hsin Chu, Taiwan
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			

Alteration	Trial ID / Contact	Title	Phase	Site(s)
BRCA2 S270*	NCT04434482 Min Song,min.song@impacttherapeutics.com,021 68411121	IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer	Phase 1 /Phase 2	Taipei, Taiwan Taoyuan, Taiwan Taichung, Taiwan Tainan, Taiwan (2)
	NCT05269316 Xiangna Chen,xiangna.chen@impacttherapeutics.com,+86-021-68411121	Study to Evaluate IMP9064 as a Monotherapy or in Combination in Patients With Advanced Solid Tumors	Phase 1	Taipei, Taiwan
	NCT05797168 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Phase I/IIa Study for AZD5335 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Solid Tumors	Phase 1 /Phase 2	Tainan City, Taiwan Taichung, Taiwan Taipei, Taiwan (2)
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
PIK3CA E545K	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Taipei City, Taiwan
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
PIK3CA E542K	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Taipei City, Taiwan
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
PIK3CA H1047L	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Taipei City, Taiwan
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
PIK3CA H1047R	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Taipei City, Taiwan
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
PTEN I224fs	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Taipei City, Taiwan
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 R213*	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			

More clinical trial options available at portal.guardanthealth.com

Definitions

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

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

Deletion (Del): The following alteration was detected in this patient: *PTEN* I224fs. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

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

Interpretation

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

Method and Limitations

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

Table 1: Genes on the Guardant360 Panel

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

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

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

Guardant360 reports fusion events involving this gene.

† Guardant360 reports amplifications of 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 A1015072 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)
EGFR T790M	NCT04077463 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	A Study of Lazertinib as Monotherapy or in Combination With Amivantamab in Participants With Advanced Non-small Cell Lung Cancer	Phase 1	Seattle, WA; Detroit, MI; Saint Louis, MO; Philadelphia, PA; Portland, OR; Salt Lake City, UT; Tampa, FL; Fairfax, VA; Boston, MA (3); New York, NY (2); CA (5); Puerto Rico; Japan (7); China (13); Taiwan (4); Korea, Republic of (4); Italy (5); France (7); Germany (8); Spain (8)
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Louisville, KY; Fort Belvoir, VA; Newark, DE; Chicago, IL; Orange, CA; Morristown, NJ; San Francisco, CA; Los Angeles, CA; Houston, TX; Frederick, MD; Atlanta, GA; Grand Junction, CO; Lexington, KY; Anchorage, AK; NY (6); Argentina (8); Singapore (2); Romania (5); United Kingdom (7); Malaysia (4); Spain (5); Canada (3); Vietnam (3); Turkey (5); China (23); Taiwan (8); Poland (4); Brazil (7); Italy (10); Germany (7)
	NCT05401110 Clinical Trial Recruitment Navigator, cancer.trial.info@cshs.org,310-423-2133	Study of Osimertinib With Carotuximab in Advanced, EGFR-mutated Non-Small Cell Lung Cancer	Phase 1	CA (5)
	NCT05507606 See https://clinicaltrials.gov/ct2/show/NCT05507606	Study of Osimertinib+Bevacizumab+Chemotherapy for EGFR+ Advanced Non-Small Cell Lung Cancer With Concurrent Mutations	Phase 2	China
	NCT05526755 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study of 5 Years of Adjuvant Osimertinib in Completely Resected Epidermal Growth Factor Receptor Mutation (EGFRm) Non-small Cell Lung Carcinoma (NSCLC)	Phase 2	Yuma, AZ; Rockville, MD; Las Vegas, NV; Santa Rosa, CA; White Plains, NY; Singapore; Hong Kong (2); Philippines (4); Taiwan (6); Korea, Republic of (15); United Kingdom (3); Italy (13); Malaysia (4); Thailand (2); Spain (8)
	NCT05647122 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	First in Human Study of AZD9592 in Solid Tumors	Phase 1	Providence, RI; Houston, TX; Duarte, CA; Mineola, NY; Milford, MA; Philadelphia, PA; Irvine, CA; Baltimore, MD; Fairfax, VA; North Haven, CT; New York, NY (3); Malaysia; Canada (2); Japan (2); China (4); Taiwan (4); Korea, Republic of (4); Italy (4); France (2); Australia (2); Spain (3)
	NCT05686434 chen chen,chen_checn@tmu.edu.cn, 13920761627	Osimertinib Therapy After Resection in High-risk Stage I EGFRm NSCLC (OSTAR)	Phase 2	China
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Canada (3); Singapore (3); Hong Kong (3); Taiwan (9); Korea, Republic of (7); Malaysia (6); Thailand (5)
	NCT05826483 Zhou Chengzhi, MD,doctorzcz@163.com, 13560351186	Almonertinib in the First-line Treatment of Patients of NSCLC With Poor Performance Status	Phase 1	China
	NCT06043973 Degan Lu, Professor,deganlu@126.com,	Almonertinib Combined With Anlotinib as First-line Treatment for Advanced Non-small Cell	Phase 3	China

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	18753157623	Lung Cance		
EGFR L858R	NCT04077463 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	A Study of Lazertinib as Monotherapy or in Combination With Amivantamab in Participants With Advanced Non-small Cell Lung Cancer	Phase 1	Seattle, WA; Detroit, MI; Saint Louis, MO; Philadelphia, PA; Portland, OR; Salt Lake City, UT; Tampa, FL; Fairfax, VA; Boston, MA (3); New York, NY (2); CA (5); Puerto Rico; Japan (7); China (13); Taiwan (4); Korea, Republic of (4); Italy (5); France (7); Germany (8); Spain (8)
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Louisville, KY; Fort Belvoir, VA; Newark, DE; Chicago, IL; Orange, CA; Morristown, NJ; San Francisco, CA; Los Angeles, CA; Houston, TX; Frederick, MD; Atlanta, GA; Grand Junction, CO; Lexington, KY; Anchorage, AK; NY (6); Argentina (8); Singapore (2); Romania (5); United Kingdom (7); Malaysia (4); Spain (5); Canada (3); Vietnam (3); Turkey (5); China (23); Taiwan (8); Poland (4); Brazil (7); Italy (10); Germany (7)
	NCT05326425 Jin Hyoung Kang,oncologykang@naver.com,82-2-2258-6043	Lazertinib in Patients With NSCLC With Asymptomatic or Mild Symptomatic Brain Metastases After Failure of EGFR TKI.	Phase 2	Korea, Republic of (6)
	NCT05465343 Junling Li, Professor,lijunling@cicams.ac.cn,010-87788495	Efficacy and Safety of Furmonertinib in Patients With EGFR Mutations in Advanced NSCLC With Brain Metastases: A Single-center, Open-label, Phase II Trial#iFORCE#	Phase 2	China
	NCT05469022 In Ae Kim, MD. PhD.,20180618@kuh.ac.kr,+821035438353	Neoadjuvant Lazertinib Therapy in EGFR-Mutation Positive Lung Adenocarcinoma Detected by BALF Liquid Biopsy	Phase 2	Korea, Republic of
	NCT05663866 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Premedication to Reduce Amivantamab Associated Infusion Related Reactions	Phase 2	Renton, WA; Fountain Valley, CA; Fairfax, VA; Taiwan (7); Korea, Republic of (6); France (6); Spain (14)
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Canada (3); Singapore (3); Hong Kong (3); Taiwan (9); Korea, Republic of (7); Malaysia (6); Thailand (5)
	NCT05826483 Zhou Chengzhi, MD,doctorzcz@163.com,13560351186	Almonertinib in the First-line Treatment of Patients of NSCLC With Poor Performance Status	Phase 1	China
	NCT06120140 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib	Phase 2	Hinsdale, IL; Westbury, NY; W. Salem, WI; Reno, NV; Flemington, NJ; CA (5); Argentina; Turkey; China (3); Taiwan (3); Korea, Republic of (2); Malaysia (4); Spain (2)
	NCT06339242 fang S Cun,fang1984@aliyun.com,83728558	A Study of Furmonertinib Combined With Chemotherapy in the Treatment of NSCLC With Leptomeningeal Metastasis	Phase 2	China
BRCA2 S270*	NCT03742895 Toll Free Number,Trialsites@merck.com,1-888-577-8839	Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)	Phase 2	Harrison, NY; Seattle, WA; New York, NY; Baltimore, MD; Middletown, NJ; Colombia; Argentina; United Kingdom; Switzerland; Ireland; Denmark; Israel; Australia; Spain (2); Canada (2); Turkey (7); Korea, Republic of (2);

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Guatemala (4); Mexico (3); France (2); Peru (5)
	NCT03891615 Zofia Piotrowska, MD, MPH,zofia.piotrowska@mgh.harvard.edu,617-643-9707	Niraparib in Combination With Osimertinib in EGFR-Mutated Advanced Lung Cancer	Phase 1	Boston, MA (3)
	NCT04434482 Min Song,min.song@impacttherapeutics.com,021 68411121	IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer	Phase 1 /Phase 2	Evergreen Park, IL; Canton, OH; Columbus, OH; Tennessee, TN; China (4); Taiwan (5); Korea, Republic of (4); Australia (4)
	NCT05269316 Xiangna Chen,xiangna.chen@impacttherapeutics.com,+86-021-68411121	Study to Evaluate IMP9064 as a Monotherapy or in Combination in Patients With Advanced Solid Tumors	Phase 1	Greenville, SC; New York, NY; Dallas, TX; Hackensack, NJ; China; Taiwan; Australia (2)
	NCT05327010 See https://clinicaltrials.gov/ct2/show/NCT05327010	Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial	Phase 2	Houston, TX; Chapel Hill, NC; Atlanta, GA; Pittsburgh, PA; Chicago, IL; Aurora, CO; Gainesville, FL; Galveston, TX; Lexington, KY; Charlottesville, VA; Bethesda, MD (2); CA (8)
	NCT05338346 Edwin Hoe,edwin.hoe@antengene.com,+61 497 390477	A Study of ATG-018 (ATR Inhibitor) Treatment in Patients With Advanced Solid Tumors and Hematological Malignancies	Phase 1	Australia (5)
	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
	NCT05797168 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Phase I/IIa Study for AZD5335 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Solid Tumors	Phase 1 /Phase 2	Houston, TX; Duarte, CA; Louisville, KY; Boston, MA; Columbus, OH; Irvine, CA; Portland, OR; Aurora, CO; Providence, RI (2); Canada (5); Japan (2); China (5); Taiwan (4); United Kingdom (4); Israel (2); Australia (2); Spain (4)
PIK3CA E545K	NCT03065062 Geoffrey Shapiro, MD, Geoffrey_Shapiro@dfci.harvard.edu,617-632-4942	Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors	Phase 1	Boston, MA (3)
	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Cleveland, OH; Newark, DE; Taiwan; Australia; Korea, Republic of (2); United Kingdom (3); Israel (3); France (6); Spain (7)
	NCT04551521 Richard Schlenk, Prof. Dr.,richard.schlenk@nct-heidelberg.de,+49622156 x6228	CRAFT: The NCT-PMO-1602 Phase II Trial	Phase 2	Germany (8)
	NCT05216432 Relay Therapeutics Inc, ClinicalTrials@relaytx.com,617-322-0731	First-in-Human Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, as a Single Agent in Advanced Solid Tumor Patients and in Combination With Fulvestrant in Patients With Advanced Breast Cancer	Phase 1	Denver, CO; Tucson, AZ; Orlando, FL; Houston, TX; Madison, WI; Plantation, FL; Chicago, IL; Nashville, TN; Fairfax, VA; Ann Arbor, MI; Boston, MA (2); New York, NY (2); Italy; France; Spain (5)
	NCT05683418	A Study to Evaluate the Safety and Tolerability	Phase 1	Los Angeles, CA; Duarte, CA;

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	Clinical Trials, clinicaltrials@totusmedicines.com,Please e-mail	of TOS-358 in Adults With Select Solid Tumors		Detroit, MI; Oklahoma City, OK; Philadelphia, PA; Cleveland, OH; West Valley City, UT; Cincinnati, OH; Chicago, IL; New Haven, CT; Baltimore, MD; Fairfax, VA
PIK3CA E542K	NCT03065062 Geoffrey Shapiro, MD, Geoffrey_Shapiro@dfci.harvard.edu,617-632-4942	Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors	Phase 1	Boston, MA (3)
	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Cleveland, OH; Newark, DE; Taiwan; Australia; Korea, Republic of (2); United Kingdom (3); Israel (3); France (6); Spain (7)
	NCT04551521 Richard Schlenk, Prof. Dr.,richard.schlenk@nct-heidelberg.de,+49622156 x6228	CRAFT: The NCT-PMO-1602 Phase II Trial	Phase 2	Germany (8)
	NCT05216432 Relay Therapeutics Inc, ClinicalTrials@relaytx.com,617-322-0731	First-in-Human Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, as a Single Agent in Advanced Solid Tumor Patients and in Combination With Fulvestrant in Patients With Advanced Breast Cancer	Phase 1	Denver, CO; Tucson, AZ; Orlando, FL; Houston, TX; Madison, WI; Plantation, FL; Chicago, IL; Nashville, TN; Fairfax, VA; Ann Arbor, MI; Boston, MA (2); New York, NY (2); Italy; France; Spain (5)
	NCT05683418 Clinical Trials, clinicaltrials@totusmedicines.com,Please e-mail	A Study to Evaluate the Safety and Tolerability of TOS-358 in Adults With Select Solid Tumors	Phase 1	Los Angeles, CA; Duarte, CA; Detroit, MI; Oklahoma City, OK; Philadelphia, PA; Cleveland, OH; West Valley City, UT; Cincinnati, OH; Chicago, IL; New Haven, CT; Baltimore, MD; Fairfax, VA
PIK3CA H1047L	NCT03065062 Geoffrey Shapiro, MD, Geoffrey_Shapiro@dfci.harvard.edu,617-632-4942	Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors	Phase 1	Boston, MA (3)
	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Cleveland, OH; Newark, DE; Taiwan; Australia; Korea, Republic of (2); United Kingdom (3); Israel (3); France (6); Spain (7)
	NCT04551521 Richard Schlenk, Prof. Dr.,richard.schlenk@nct-heidelberg.de,+49622156 x6228	CRAFT: The NCT-PMO-1602 Phase II Trial	Phase 2	Germany (8)
	NCT05216432 Relay Therapeutics Inc, ClinicalTrials@relaytx.com,617-322-0731	First-in-Human Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, as a Single Agent in Advanced Solid Tumor Patients and in Combination With Fulvestrant in Patients With Advanced Breast Cancer	Phase 1	Denver, CO; Tucson, AZ; Orlando, FL; Houston, TX; Madison, WI; Plantation, FL; Chicago, IL; Nashville, TN; Fairfax, VA; Ann Arbor, MI; Boston, MA (2); New York, NY (2); Italy; France; Spain (5)
	NCT05683418 Clinical Trials, clinicaltrials@totusmedicines.com,Please e-mail	A Study to Evaluate the Safety and Tolerability of TOS-358 in Adults With Select Solid Tumors	Phase 1	Los Angeles, CA; Duarte, CA; Detroit, MI; Oklahoma City, OK; Philadelphia, PA; Cleveland, OH;

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				West Valley City, UT; Cincinnati, OH; Chicago, IL; New Haven, CT; Baltimore, MD; Fairfax, VA
PIK3CA H1047R	NCT03065062 Geoffrey Shapiro, MD, Geoffrey_Shapiro@dfci.harvard.edu,617-632-4942	Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors	Phase 1	Boston, MA (3)
	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Cleveland, OH; Newark, DE; Taiwan; Australia; Korea, Republic of (2); United Kingdom (3); Israel (3); France (6); Spain (7)
	NCT04551521 Richard Schlenk, Prof. Dr.,richard.schlenk@nct-heidelberg.de,+49622156 x6228	CRAFT: The NCT-PMO-1602 Phase II Trial	Phase 2	Germany (8)
	NCT05216432 Relay Therapeutics Inc, ClinicalTrials@relaytx.com,617-322-0731	First-in-Human Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, as a Single Agent in Advanced Solid Tumor Patients and in Combination With Fulvestrant in Patients With Advanced Breast Cancer	Phase 1	Denver, CO; Tucson, AZ; Orlando, FL; Houston, TX; Madison, WI; Plantation, FL; Chicago, IL; Nashville, TN; Fairfax, VA; Ann Arbor, MI; Boston, MA (2); New York, NY (2); Italy; France; Spain (5)
	NCT05307705 Patient Advocacy, clinicaltrials@loxooncology.com;,855-569-6305	A Study of LOXO-783 in Patients With Breast Cancer/Other Solid Tumors	Phase 1	Saint Louis, MO; Rochester, NY; New York, NY; Jacksonville, FL; San Francisco, CA; Santa Monica, CA; Houston, TX; Rochester, MN; Atlanta, GA; Scottsdale, AZ; Palo Alto, CA; San Antonio, TX; Nashville, TN; Boston, MA (2); Dallas, TX (2); Singapore; Italy; Canada (2); Belgium (2); Japan (4); China (4); Korea, Republic of (2); United Kingdom (2); France (6); Australia (3); Germany (3); Spain (8)
	NCT05683418 Clinical Trials, clinicaltrials@totusmedicines.com,Please e-mail	A Study to Evaluate the Safety and Tolerability of TOS-358 in Adults With Select Solid Tumors	Phase 1	Los Angeles, CA; Duarte, CA; Detroit, MI; Oklahoma City, OK; Philadelphia, PA; Cleveland, OH; West Valley City, UT; Cincinnati, OH; Chicago, IL; New Haven, CT; Baltimore, MD; Fairfax, VA
PTEN I224fs	NCT03065062 Geoffrey Shapiro, MD, Geoffrey_Shapiro@dfci.harvard.edu,617-632-4942	Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors	Phase 1	Boston, MA (3)
	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Cleveland, OH; Newark, DE; Taiwan; Australia; Korea, Republic of (2); United Kingdom (3); Israel (3); France (6); Spain (7)
	NCT03891615 Zofia Piotrowska, MD, MPH,zofia.piotrowska@mgh.harvard.edu,617-643-9707	Niraparib in Combination With Osimertinib in EGFR-Mutated Advanced Lung Cancer	Phase 1	Boston, MA (3)
	NCT04551521	CRAFT: The NCT-PMO-1602 Phase II Trial	Phase 2	Germany (8)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	Richard Schlenk, Prof. Dr.,richard.schlenk@nct-heidelberg.de,+49622156 x6228			
	NCT05683418 Clinical Trials, clinicaltrials@totusmedicines.com,Please e-mail	A Study to Evaluate the Safety and Tolerability of TOS-358 in Adults With Select Solid Tumors	Phase 1	Los Angeles, CA; Duarte, CA; Detroit, MI; Oklahoma City, OK; Philadelphia, PA; Cleveland, OH; West Valley City, UT; Cincinnati, OH; Chicago, IL; New Haven, CT; Baltimore, MD; Fairfax, VA
	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 R213*	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)
	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)
	NCT05489731 li zhang, professor,zhangli6@mail.sysu.edu.cn,13902282893	VIC-1911 Combined With Osimertinib for EGFR -Mutant Non-small Cell Lung Cancer	Phase 1	China

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
PTEN I224fs	ABTL0812		Inhibitor of mTORC1/mTORC2 /Dhfr.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Endometrial carcinoma)
	Alpelisib	Piqray	p110-alpha inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HR+, HER2-) with a PIK3CA mutation, as determined by a validated test)
	Archexin	Archexin	Akt1 antisense oligonucleotide.	Phase 1 (Solid Tumor) Phase 2 (Pancreatic carcinoma, Renal cell carcinoma)
	ARQ 751		Akt inhibitor.	Phase 1 (Solid Tumor)
	AZD8186		p110-beta and p110-delta small molecule inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Breast carcinoma (triple negative), Lung squamous cell carcinoma)
	Bimiralisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma (triple negative), Primary central nervous system lymphoma (PCNSL))
	Buparlisib		PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Head and neck squamous cell carcinoma (HNSCC), Breast carcinoma)
	Capivasertib	Truqap	Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HR+, HER2-) with a PIK3CA/AKT1 /PTEN mutation)
	CC-115		DNA-PK/dual mTORC1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma)
	Copanlisib	Aliqopa	PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Non-Hodgkin lymphoma (NHL))
	CYH33		p110-alpha-specific small molecule inhibitor.	Phase 1 (Solid Tumor)
	Everolimus	Afinitor	mTOR inhibitor, immunosuppressant.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (TSC associated renal angiomyolipoma and subependymal giant cell astrocytoma, Renal cell carcinoma, Gastrointestinal neuroendocrine carcinoma, Lung carcinoid, Breast carcinoma (hormone receptor +, HER2-), Subependymal giant cell astrocytoma)
	Gedatolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	GSK2636771		p110-beta small molecule inhibitor.	Phase 2 (Solid Tumor) Phase 1 (Prostate carcinoma)
	HS-10352		p110-alpha-specific small molecule inhibitor.	Phase 1 (Breast carcinoma)
	Inavolisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Breast carcinoma)
	Ipatasertib		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Prostate carcinoma, Breast carcinoma)
	ME-344		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Small cell lung carcinoma (SCLC))
	MEN1611		PI3K inhibitor.	Phase 2 (Metaplastic breast carcinoma,

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				Colorectal carcinoma (CRC))
	Miransertib		Akt inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	MK-2206		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Gallbladder carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Hodgkin lymphoma (HL), Lymphoma, Melanoma, Carcinoid tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Adenoid cystic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Gastrointestinal neuroendocrine carcinoma, Mucinous colon adenocarcinoma, Breast carcinoma, Chronic lymphocytic leukemia (CLL), Acute myeloid leukemia (AML), Cholangiocarcinoma, Thymic neoplasm, Peritoneal papillary serous carcinoma, Lung cancer, Colorectal carcinoma (CRC), Diffuse large B-cell lymphoma (DLBCL))
	MSC2363318A		Akt1, Akt3, and p70S6K inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma)
	Niraparib	Zejula	PARP inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma with BRCA1/2 mutation)
	Olaparib	Lynparza	PARP inhibitor.	Phase 2 (Lung adenocarcinoma) FDA Approved in other indications (Pancreatic adenocarcinoma with germline BRCA1/2 mutation, Prostate cancer with HRR gene mutation, Ovarian carcinoma with BRCA1/2 mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Onatasertib		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor, Bladder neuroendocrine carcinoma, Multiple myeloma (MM), Diffuse large B-cell lymphoma (DLBCL))
	Paxalisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Glioblastoma, Breast carcinoma)
	Perifosine		Akt inhibitor, induces apoptosis; mechanism of action is context specific.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Multiple myeloma (MM), Colorectal carcinoma (CRC))
	Pilaralisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Endometrial carcinoma, Breast carcinoma)
	Ridaforolimus		mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Sarcoma)
	RLY-2608		p110-alpha-specific small molecule inhibitor.	Phase 1 (Solid Tumor)
	RLY-5836		p110-alpha-specific small molecule inhibitor.	Phase 1 (Solid Tumor)
	RMC-5552		mTORC1-specific inhibitor.	Phase 1 (Solid Tumor)
	Samotolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Prostate carcinoma)
	Sapanisertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				Phase 2 (Uterine carcinosarcoma, Hepatocellular carcinoma (HCC), Lymphoma, Merkel cell carcinoma, Anaplastic thyroid carcinoma, Pancreatic neuroendocrine tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Urothelial carcinoma, Bladder carcinoma, Breast carcinoma, Multiple myeloma (MM), Non-Hodgkin lymphoma (NHL), Lung cancer, Sarcoma, Acute lymphoblastic leukemia (ALL))
	Serabelisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Endometrial carcinoma, Renal cell carcinoma, Breast carcinoma (triple negative))
	SF1126		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC))
	Talazoparib	Talzenna	PARP inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Prostate cancer with HRR gene mutation, Breast carcinoma with germline BRCA1/2 mutation)
	TAS-117		Akt inhibitor.	Phase 2 (Solid Tumor)
	TAS0612		Akt/p70S6K/p90RSK1 multikinase inhibitor.	Phase 1 (Solid Tumor)
	Temsirolimus	Torisel	mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Renal cell carcinoma)
	TOS-358		p110-alpha-specific small molecule inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Gastric carcinoma, Endometrial carcinoma, Head and neck squamous cell carcinoma (HNSCC), Ovarian carcinoma, Urothelial carcinoma, Breast carcinoma, Cervical carcinoma, Colorectal carcinoma (CRC))
	Triciribine		DNA synthesis and Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Breast carcinoma)
	Uprosertib		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Uveal melanoma, Breast carcinoma, Cervical carcinoma, Acute myeloid leukemia (AML), Multiple myeloma (MM))
	Vistusertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Meningioma, Small cell lung carcinoma (SCLC), Solid Tumor, Diffuse large B-cell lymphoma (DLBCL))
	WGI-0301		Nanoliposomal Archexin, an Akt1 antisense oligonucleotide.	Phase 1 (Solid Tumor)
EGFR T790M L858R	ABT-101		Egfr/Her2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Head and neck squamous cell carcinoma (HNSCC))
	Amivantamab	Rybrevant	Bispecific anti-Met/Egfr antibody.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (NSCLC with EGFR exon 20 insertion)
	Aumolertinib		Egfr T790M inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC))
	Avitinib		Irreversible mutation-specific Egfr kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Non-Hodgkin lymphoma (NHL))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	AZD3759		Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BAY2927088		Egfr/Her2 kinase inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	BBP-398		Shp-2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Befotertinib		Third generation mutation-specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC))
	BLU-451		Egfr inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	BLU-945		Fourth generation Egfr inhibitor targeting T790M and T790M /C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BPI-361175		Fourth generation Egfr inhibitor targeting T790M and T790M /C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BPI-7711		Egfr T790M inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	CLN-081		Covalent mutation-specific (L858R, T790M, exon 19 deletion, exon 20 insertion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	CM93		Third generation mutation-specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 1 (Glioblastoma)
	ERAS-601		Shp-2 inhibitor.	Phase 2 (Solid Tumor)
	ET0038		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	Furmonertinib		Third generation mutation-specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	FWD1509		Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	H002		Fourth generation Egfr inhibitor targeting exon 19del/L858R, T790M, and C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	HBI-2376		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	Hemay022		Egfr tyrosine kinase inhibitor.	Phase 1 (Breast carcinoma (HER2+))
	JIN-A02		Fourth generation Egfr inhibitor targeting T790M and T790M /C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	Lazertinib		Third generation mutation-specific Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	Lifirafenib		Dual Braf/Egfr inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	MCLA-129		Anti-EGFR/c-Met bispecific antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Head and neck squamous cell carcinoma (HNSCC), Esophageal squamous cell carcinoma)
	Mobocertinib	Exkivity	Mutation-specific Egfr/Her2	Phase 3 (Non-small cell lung carcinoma (NSCLC))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
			inhibitor.	Phase 3 (NSCLC with EGFR exon 20 insertion, Lung cancer)
	Modotuximab		Anti-EGFR antibody.	Phase 1 (Gastric carcinoma, Colorectal carcinoma (CRC))
	Nazartinib		Third generation EGFR mutant-specific (T790M, L858R, exon 19 deletion) tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	NX-019		Egfr inhibitor.	Phase 1 (Solid Tumor)
	Olafertinib		Third generation mutation-specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Olmutinib		Egfr inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	Osimertinib	Tagrisso	Egfr T790M inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (EGFR-mutant lung carcinoid, EGFR-mutant lung large cell neuroendocrine carcinoma, EGFR-mutant NSCLC)
	Pirotinib		ErbB family inhibitor.	Phase 1 (Solid Tumor)
	Poziotinib		Egfr/Her2/ErbB4 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Head and neck squamous cell carcinoma (HNSCC), Breast carcinoma, Esophageal squamous cell carcinoma, Colorectal carcinoma (CRC))
	Pyrotinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	SKLB1028		Egfr/Flt3/c-Abl inhibitor.	Phase 2 (Acute myeloid leukemia (AML))
	Sunvozertinib		Bispecific anti-Egfr/Her2 monoclonal antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Non-Hodgkin lymphoma (NHL))
	TAS2940		Egfr/Her2 kinase inhibitor.	Phase 1 (Solid Tumor)
	TAS3351		Fourth generation Egfr inhibitor targeting T790M and T790M /C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	TAVO412		Anti-c-Met/anti-EGFR/anti-VEGF trispecific antibody.	Phase 1 (Solid Tumor)
	Varlitinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Cholangiocarcinoma)
	ZN-e4		Egfr T790M inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
PIK3CA H1047L E542K H1047R E545K	ABTL0812		Inhibitor of mTORC1/mTORC2 /Dhfr.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Endometrial carcinoma)
	Alpelisib	Piqray	p110-alpha inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HR+, HER2-) with a PIK3CA mutation, as determined by a validated test)
	Archexin	Archexin	Akt1 antisense oligonucleotide.	Phase 1 (Solid Tumor) Phase 2 (Pancreatic carcinoma, Renal cell carcinoma)
	ARQ 751		Akt inhibitor.	Phase 1 (Solid Tumor)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Bimiralisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma (triple negative), Primary central nervous system lymphoma (PCNSL))
	Buparlisib		PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Head and neck squamous cell carcinoma (HNSCC), Breast carcinoma)
	Capivasertib	Truqap	Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HR+, HER2-) with a PIK3CA/AKT1 /PTEN mutation)
	CC-115		DNA-PK/dual mTORC1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma)
	Copanlisib	Aliqopa	PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Non-Hodgkin lymphoma (NHL))
	CYH33		p110-alpha-specific small molecule inhibitor.	Phase 1 (Solid Tumor)
	Fimepinostat		PI3K/HDAC inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Thyroid carcinoma, Diffuse large B-cell lymphoma (DLBCL))
	Gedatolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	HS-10352		p110-alpha-specific small molecule inhibitor.	Phase 1 (Breast carcinoma)
	Inavolisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Breast carcinoma)
	Ipatasertib		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Prostate carcinoma, Breast carcinoma)
	ME-344		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Small cell lung carcinoma (SCLC))
	MEN1611		PI3K inhibitor.	Phase 2 (Metaplastic breast carcinoma, Colorectal carcinoma (CRC))
	Miransertib		Akt inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	MK-2206		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Gallbladder carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Hodgkin lymphoma (HL), Lymphoma, Melanoma, Carcinoid tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Adenoid cystic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Gastrointestinal neuroendocrine carcinoma, Mucinous colon adenocarcinoma, Breast carcinoma, Chronic lymphocytic leukemia (CLL), Acute myeloid leukemia (AML), Cholangiocarcinoma, Thymic neoplasm, Peritoneal papillary serous carcinoma, Lung cancer, Colorectal carcinoma (CRC), Diffuse large B-cell lymphoma (DLBCL))
	MSC2363318A		Akt1, Akt3, and p70S6K inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Onatasertib		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor, Bladder neuroendocrine carcinoma, Multiple myeloma (MM), Diffuse large B-cell lymphoma (DLBCL))
	Paxalisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Glioblastoma, Breast carcinoma)
	Perifosine		Akt inhibitor, induces apoptosis; mechanism of action is context specific.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Multiple myeloma (MM), Colorectal carcinoma (CRC))
	Pilaralisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Endometrial carcinoma, Breast carcinoma)
	RLY-2608		p110-alpha-specific small molecule inhibitor.	Phase 1 (Solid Tumor)
	RLY-5836		p110-alpha-specific small molecule inhibitor.	Phase 1 (Solid Tumor)
	RMC-5552		mTORC1-specific inhibitor.	Phase 1 (Solid Tumor)
	Samotolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Prostate carcinoma)
	Sapanisertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Uterine carcinosarcoma, Hepatocellular carcinoma (HCC), Lymphoma, Merkel cell carcinoma, Anaplastic thyroid carcinoma, Pancreatic neuroendocrine tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Urothelial carcinoma, Bladder carcinoma, Breast carcinoma, Multiple myeloma (MM), Non-Hodgkin lymphoma (NHL), Lung cancer, Sarcoma, Acute lymphoblastic leukemia (ALL))
	Serabelisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Endometrial carcinoma, Renal cell carcinoma, Breast carcinoma (triple negative))
	SF1126		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC))
	TAS-117		Akt inhibitor.	Phase 2 (Solid Tumor)
	TAS0612		Akt/p70S6K/p90RSK1 multikinase inhibitor.	Phase 1 (Solid Tumor)
	TOS-358		p110-alpha-specific small molecule inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Gastric carcinoma, Endometrial carcinoma, Head and neck squamous cell carcinoma (HNSCC), Ovarian carcinoma, Urothelial carcinoma, Breast carcinoma, Cervical carcinoma, Colorectal carcinoma (CRC))
	Triciribine		DNA synthesis and Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Breast carcinoma)
	Uprosertib		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Uveal melanoma, Breast carcinoma, Cervical carcinoma, Acute myeloid leukemia (AML), Multiple myeloma (MM))
	Vistusertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Meningioma, Small cell lung carcinoma

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				(SCLC), Solid Tumor, Diffuse large B-cell lymphoma (DLBCL))
	WGI-0301		Nanoliposomal Archexin, an Akt1 antisense oligonucleotide.	Phase 1 (Solid Tumor)
BRCA2 S270*	AMXI-5001		Dual PARP1/2 and microtubule polymerization inhibitor.	Phase 2 (Solid Tumor)
	ATG-018		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Marginal zone lymphoma (MZL), Diffuse large B-cell lymphoma (DLBCL))
	AZD9574		PARP1 inhibitor (brain penetrant).	Phase 2 (Glioma, Pancreatic carcinoma, Prostate carcinoma, Ovarian carcinoma, Breast carcinoma)
	Camonsertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Fluzoparib		PARP inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Pancreatic carcinoma, Ovarian carcinoma, Breast carcinoma)
	IDX-1197		PARP inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	Niraparib	Zejula	PARP inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma with BRCA1/2 mutation)
	Nivolumab+ipilimumab	Opdivo+Yervoy	Anti-PD-1 monoclonal antibody + anti-CTLA-4 monoclonal antibody combination.	FDA Approved in this indication (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (NSCLC with high PD-L1 expression, Hepatocellular carcinoma (HCC), Melanoma, Renal cell carcinoma, Esophageal squamous cell carcinoma, CRC with MSI-H or dMMR, Mesothelioma)
	NMS-03305293		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma)
	Olaparib	Lynparza	PARP inhibitor.	Phase 2 (Lung adenocarcinoma) FDA Approved in other indications (Pancreatic adenocarcinoma with germline BRCA1/2 mutation, Prostate cancer with HRR gene mutation, Ovarian carcinoma with BRCA1/2 mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Pamiparib		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Gastric carcinoma, Gastroesophageal junction carcinoma)
	RP12146		PARP inhibitor.	Phase 1 (Gastric carcinoma, Pancreatic carcinoma, Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Breast carcinoma, Cholangiocarcinoma, Colorectal carcinoma (CRC))
	Rucaparib	Rubraca	PARP inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				mutation, Ovarian carcinoma)
	Saruparib		PARP1 inhibitor.	Phase 2 (Solid Tumor)
	Senaparib		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Small cell lung carcinoma (SCLC))
	Stenoparib		PARP inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Pancreatic carcinoma, Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma, Colorectal carcinoma (CRC))
	Talazoparib	Talzenna	PARP inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Prostate cancer with HRR gene mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Veliparib		PARP inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Glioblastoma, Ovarian carcinoma, Ovarian carcinosarcoma, Breast carcinoma, Lung cancer)
TP53 R213*	Adavosertib		Wee1 tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Lymphoma, Embryonal tumor with multi-layered rosettes (ETMR), Medulloblastoma, Small cell lung carcinoma (SCLC), 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))
	AL8326		Aurora kinase B/VEGFRs/Fgfr multi-kinase inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Small cell lung carcinoma (SCLC))
	Alisertib		Aurora kinase A inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	ATO	Trisenox	PML-RARA inhibitor. Inhibits multiple signaling pathways, including the Hedgehog pathway.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) 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)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	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))
EGFR L858R	BDTX-1535		Irreversible brain-penetrant fourth generation Egfr inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Glioma)
	Icotinib	Conmana	Egfr inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Esophageal carcinoma)
	WSD0922-FU		Blood-brain barrier penetrable EGFR/EGFRvIII inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Glioblastoma, Anaplastic astrocytoma)
PIK3CA H1047R	LOXO-783		p110-alpha H1047R inhibitor.	

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
EGFR T790M	The presence of an EGFR abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Egfr protein, which can lead to excessive proliferation. [1]. The EGFR T790M mutation has typically been reported as a secondary resistance mutation to the Egfr inhibitors erlotinib, gefitinib and afatinib, but has also been reported as a rare germline variant in de novo non-small cell lung cancer, particularly in lung adenocarcinoma. [2,3]. Several studies have reported the presence of the T790M mutation in the germline in 0-1% of NSCLC cases, although one study did detect this mutation in 50% (5/10) of cases; in addition, T790M was associated with a 31% risk of lung cancer in never smokers in one study. [4-7].	The presence of a sensitizing EGFR mutation in a tumor is the strongest biological predictor of sensitivity to an Egfr tyrosine kinase inhibitor (TKI). Compared with conventional chemotherapy, Egfr TKIs have been shown to improve progression-free survival in non-small cell lung cancer patients whose tumors harbor EGFR mutations. [8-11]. The EGFR T790M mutation reported here has been described as a "gatekeeper" mutation that confers resistance to the tyrosine kinase inhibitors erlotinib and gefitinib. [12,13]. Studies have also reported the emergence of EGFR T790M upon resistance to afatinib monotherapy. [3,15]. Third generation irreversible Egfr TKIs that target the EGFR T790M mutation have shown efficacy in T790M-mutant NSCLC and are under clinical investigation. Osimertinib has received approval by the FDA, EMA, and PMDA for the treatment of EGFR T790M-mutant metastatic NSCLC as well as EGFR-mutated NSCLC that has not been exposed to previous TKI treatment. [16-21]. However, this EGFR mutation has been associated with resistance to erlotinib; thus, the relevance of ramucirumab plus erlotinib is uncertain.	A Phase 2 study has reported no clinical responses in 12 non-small cell lung cancer (NSCLC) patients who harbored EGFR T790M and were treated with neratinib. [22]. In addition, Phase 2 studies have reported limited clinical activity with dacomitinib in NSCLC patients who harbored EGFR T790M, with 2/32 patients having shown a partial response. [23-25]. Some patients with EGFR-mutant NSCLC exhibit resistance to Egfr inhibition; resistance has been associated with insertions in EGFR exon 20, the T790M mutation in EGFR, and amplification of the gene MET. [26-28]. Several studies have reported that resistance to Egfr TKIs in NSCLC is mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features. [29-32].
EGFR L858R	The presence of an EGFR abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Egfr protein, which can lead to excessive proliferation. [1].	The presence of a sensitizing EGFR mutation in a tumor is the strongest biological predictor of sensitivity to an Egfr tyrosine kinase inhibitor (TKI). Compared with conventional chemotherapy, Egfr TKIs have been shown to improve progression-free survival in non-small cell lung cancer patients whose tumors harbor EGFR mutations. [8-11]. The Egfr TKIs erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib have been approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR mutations; osimertinib has additionally been approved for the treatment of NSCLC with EGFR T790M. [8,11,16,33-37]. Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations. [3]. The combination of erlotinib and ramucirumab as well as osimertinib plus platinum-based chemotherapy have been FDA-approved for the treatment of metastatic NSCLC patients with	Some patients with EGFR-mutant NSCLC exhibit resistance to Egfr inhibition; resistance has been associated with insertions in EGFR exon 20, the T790M mutation in EGFR, and amplification of either MET or ERBB2. [26-28,49]. Third generation irreversible Egfr TKIs that target the EGFR T790M mutation have shown efficacy in T790M-mutant NSCLC, including osimertinib, which has received approval by the FDA, EMA, and PMDA for the treatment of EGFR T790M-mutant metastatic NSCLC. [17-21]. Several studies have reported that resistance to Egfr TKIs in NSCLC is mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features. [29-32]. Preclinical studies have reported increased Smo expression in NSCLC cell lines resistant to first, second, and third generation Egfr inhibitors as compared with sensitive ones; treatment with Smo inhibitors was observed to restore sensitivity in the resistant cell lines. [50-52].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		tumors harboring an EGFR exon 19 deletion or the exon 21 L858R mutation. [38-40]. Amivantamab has been approved by the FDA for NSCLC patients with EGFR exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy and as frontline therapy in combination with carboplatin and pemetrexed. The accelerated FDA approval of mobocertinib for NSCLC patients with EGFR exon 20 insertions has been withdrawn due to lack of progression-free survival benefit in the confirmatory Phase 3 trial. [41-44]. Studies have reported non-squamous NSCLC patients with metastatic disease and tumors harboring an EGFR exon 19 deletion or L858R mutation to be sensitive to osimertinib, erlotinib, afatinib, gefitinib, dacomitinib, and the combination of erlotinib plus ramucirumab. [8,11,16,33,38,45]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors. [46]. However, one of the EGFR mutations in the report has been associated with resistance to erlotinib; thus, the relevance of ramucirumab plus erlotinib is uncertain. However, EGFR T790M, also detected in this tumor, has been associated with resistance to the Egfr tyrosine kinase inhibitors erlotinib, gefitinib, afatinib, and dacomitinib. [3,12,15,15-25,27,47].	
BRCA2 S270*	Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis. [53,54]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers. [55-63]. The risk of developing breast or ovarian carcinoma in BRCA2 mutation carriers has been reported to be 45-69% and 11-17%, respectively. [64-66]. In a study in BRCA1 and BRCA2 germline mutation carriers examining the risk of developing cancers other than breast or ovarian, the risk of lung cancer was determined to be only slightly elevated. [67]. Loss of heterozygosity at the BRCA2 locus has been reported frequently in NSCLC, cited in 44% (38 /87) and 70% (30/43) of cases in two separate studies, and loss of Brca2	Inactivating BRCA2 alterations have been reported to predict sensitivity to platinum-based chemotherapy and PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, which are FDA-approved in specific indications. [70-74]. The PARP inhibitor olaparib has been approved by the FDA for use in advanced ovarian cancer, metastatic Her2 negative breast cancer, and pancreatic adenocarcinoma patients with germline BRCA1/2 mutations as well as for castration-resistant adult prostate cancer patients with tumors harboring germline or somatic alteration in one or more homologous recombination repair genes, including BRCA1/2 mutations; rucaparib has been approved by the FDA for advanced ovarian cancer and castration-resistant prostate cancer patients with either germline or somatic BRCA1/2 mutations. [73,73-81]. Olaparib in combination with abiraterone and	

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	expression has been associated with lung adenocarcinoma cases, as compared with lung squamous cell carcinoma cases. [68,69].	prednisone or prednisolone has been approved by the FDA for the treatment of adult patients with metastatic castration-resistant prostate cancer with deleterious BRCA mutation as determined by an FDA-approved companion diagnostic test. [82]. In addition, talazoparib in combination with enzalutamide has been FDA-approved for the treatment of metastatic castration-resistant prostate cancer patients with tumors harboring germline or somatic alteration in one or more homologous recombination repair genes, including BRCA2 mutation. [83-85]. Furthermore, niraparib in combination with abiraterone acetate plus prednisone has been approved by the FDA for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) harboring deleterious or suspected deleterious BRCA1/2 mutations. [86,87]. Loss of Brca2 expression has been reported to enhance sensitivity to cisplatin in preclinical studies of NSCLC. [88,89].	
PIK3CA E545K	PIK3CA mutations are not mutually exclusive with EGFR or KRAS or BRAF mutations, and are associated with increased PI3K signaling and increased activation of Akt. [90,91]. PIK3CA mutations have been associated with activation of PI3K/Akt signaling and colony formation in NSCLC cell lines, and the PIK3CA H1047R activating mutation has been shown to drive tumorigenesis in combination with BRAF V600E in a mouse model of NSCLC. [90,92].	Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which have been approved in specific cancer indications, including the PI3K inhibitors alpelisib and copanlisib, the Akt inhibitor capivasertib, and the mTOR inhibitors everolimus and temsirolimus. [93-95]. While PIK3CA activating alterations have been suggested to predict sensitivity to the mTOR inhibitors everolimus and temsirolimus, results from clinical studies have been mixed, with several reporting no associations between PIK3CA mutational status and response to therapy. [94,96-99]. Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development. [100-102]. The p110-alpha inhibitor alpelisib has been approved for the treatment of men and postmenopausal women with PIK3CA-mutated, hormone receptor positive, Her2 negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy. [103]. The Akt inhibitor capivasertib has been approved by the FDA in combination with fulvestrant for the treatment of	PIK3CA mutations have been reported in EGFR-mutant NSCLC patients following emergence of resistance to osimertinib and have been associated with osimertinib resistance in preclinical NSCLC models. Combined treatment with osimertinib and a PI3K inhibitor reversed the resistance. [105-108].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		adult patients with hormone receptor positive, Her2 negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. [104].	
PIK3CA E542K	PIK3CA mutations are not mutually exclusive with EGFR or KRAS or BRAF mutations, and are associated with increased PI3K signaling and increased activation of Akt. [90,91]. PIK3CA mutations have been associated with activation of PI3K/Akt signaling and colony formation in NSCLC cell lines, and the PIK3CA H1047R activating mutation has been shown to drive tumorigenesis in combination with BRAF V600E in a mouse model of NSCLC. [90,92].	Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which have been approved in specific cancer indications, including the PI3K inhibitors alpelisib and copanlisib, the Akt inhibitor capivasertib, and the mTOR inhibitors everolimus and temsirolimus. [93-95]. While PIK3CA activating alterations have been suggested to predict sensitivity to the mTOR inhibitors everolimus and temsirolimus, results from clinical studies have been mixed, with several reporting no associations between PIK3CA mutational status and response to therapy. [94,96-99]. Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development. [100-102]. The p110-alpha inhibitor alpelisib has been approved for the treatment of men and postmenopausal women with PIK3CA-mutated, hormone receptor positive, Her2 negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy. [103]. The Akt inhibitor capivasertib has been approved by the FDA in combination with fulvestrant for the treatment of adult patients with hormone receptor positive, Her2 negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. [104].	PIK3CA E542K has been reported in a fulvestrant-resistant ER positive breast cancer case; E542K was reported to decrease fulvestrant sensitivity in a breast cancer cell model. [109]. PIK3CA mutations have been reported in EGFR-mutant NSCLC patients following emergence of resistance to osimertinib and have been associated with osimertinib resistance in preclinical NSCLC models. Combined treatment with osimertinib and a PI3K inhibitor reversed the resistance. [105-108].
PIK3CA H1047L	PIK3CA mutations are not mutually exclusive with EGFR or KRAS or BRAF mutations, and are associated with increased PI3K signaling and increased activation of Akt. [90,91]. PIK3CA mutations have been associated with	Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which have been approved in specific cancer indications, including the PI3K inhibitors alpelisib and copanlisib, the	PIK3CA mutations have been reported in EGFR-mutant NSCLC patients following emergence of resistance to osimertinib and have been associated with osimertinib resistance in preclinical NSCLC models. Combined

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	activation of PI3K/Akt signaling and colony formation in NSCLC cell lines, and the PIK3CA H1047R activating mutation has been shown to drive tumorigenesis in combination with BRAF V600E in a mouse model of NSCLC. [90,92].	Akt inhibitor capivasertib, and the mTOR inhibitors everolimus and temsirolimus. [93-95]. While PIK3CA activating alterations have been suggested to predict sensitivity to the mTOR inhibitors everolimus and temsirolimus, results from clinical studies have been mixed, with several reporting no associations between PIK3CA mutational status and response to therapy. [94,96-99]. Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development. [100-102]. The p110-alpha inhibitor alpelisib has been approved for the treatment of men and postmenopausal women with PIK3CA-mutated, hormone receptor positive, Her2 negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy. [103]. The Akt inhibitor capivasertib has been approved by the FDA in combination with fulvestrant for the treatment of adult patients with hormone receptor positive, Her2 negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. [104].	treatment with osimertinib and a PI3K inhibitor reversed the resistance. [105-108].
PIK3CA H1047R	PIK3CA mutations are not mutually exclusive with EGFR or KRAS or BRAF mutations, and are associated with increased PI3K signaling and increased activation of Akt. [90,91]. PIK3CA mutations have been associated with activation of PI3K/Akt signaling and colony formation in NSCLC cell lines, and the PIK3CA H1047R activating mutation has been shown to drive tumorigenesis in combination with BRAF V600E in a mouse model of NSCLC. [90,92].	Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which have been approved in specific cancer indications, including the PI3K inhibitors alpelisib and copanlisib, the Akt inhibitor capivasertib, and the mTOR inhibitors everolimus and temsirolimus. [93-95]. While PIK3CA activating alterations have been suggested to predict sensitivity to the mTOR inhibitors everolimus and temsirolimus, results from clinical studies have been mixed, with several reporting no associations between PIK3CA mutational status and response to therapy. [94,96-99]. Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development. [100-102]. The p110-alpha inhibitor alpelisib has been approved	PIK3CA mutations have been reported in EGFR-mutant NSCLC patients following emergence of resistance to osimertinib and have been associated with osimertinib resistance in preclinical NSCLC models. Combined treatment with osimertinib and a PI3K inhibitor reversed the resistance. [105-108].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		for the treatment of men and postmenopausal women with PIK3CA-mutated, hormone receptor positive, Her2 negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy. [103]. The Akt inhibitor capivasertib has been approved by the FDA in combination with fulvestrant for the treatment of adult patients with hormone receptor positive, Her2 negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. [104].	
PTEN I224fs	Loss of PTEN (through mutation or deletion) can lead to uncontrolled cell growth and suppression of apoptosis. [110]. PTEN haploinsufficiency has been associated with tumorigenesis in some tumor types, including astrocytoma and prostate cancer. [111-114]. PTEN germline mutations are found in several cancer-predisposition syndromes, such as Cowden syndrome and Proteus syndrome. [115]. Loss of Pten protein expression has been associated with higher stage, lymph node metastases, and poorly differentiated disease in NSCLC patients. [116-121]. Deletion of PTEN has been shown to lead to the formation of lung squamous cell carcinoma tumors in preclinical studies. [122,123].	Because PTEN negatively regulates the PI3K/Akt/mTOR pathway, PTEN loss or mutation leads to activation of the PI3K pathway and may therefore predict sensitivity to inhibitors of the PI3K/Akt /mTOR pathway. [124]. The PI3K inhibitors alpelisib and copanlisib, the Akt inhibitor capivasertib, and the mTOR inhibitors everolimus and temsirolimus have been approved in specific cancer indications. These and other PI3K, Akt, and mTOR inhibitors, as well as dual PI3K/mTOR inhibitors are also currently in clinical trials, alone or in combination with other therapies. [93-95,103,125]. The Akt inhibitor capivasertib has been approved by the FDA in combination with fulvestrant for the treatment of adult patients with hormone receptor positive, Her2 negative locally advanced or metastatic breast cancer with PIK3CA /AKT1/PTEN alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. [104]. In addition, preclinical studies have shown that PTEN-deficient tumors may be sensitive to PARP inhibitors, and PARP inhibitors are in clinical trials for patients with PTEN-deficient tumors. [126-133].	Preclinical studies have associated decreased expression of Pten with gefitinib and erlotinib resistance in EGFR-mutant NSCLC cell lines. [134-136]. Mutation of PTEN has been reported to be associated with a low objective response rate (ORR) to Egfr tyrosine kinase inhibitors in lung adenocarcinomas harboring EGFR mutations, with 7.3% ORR in PTEN-mutated cases compared to 70.9% ORR in wild-type PTEN lung adenocarcinomas. [137].
TP53 R213*	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [138]. Carriers of a germline mutation in TP53 have Li-Fraumeni	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for	Mutations in TP53 may increase resistance to ionizing radiation therapy. [170,171].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias. [139-141]. 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. [142-146]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. [147]. TP53 mutation and expression of p53 have been correlated with the lung squamous cell carcinoma subtype, and p53 expression in lung squamous cell carcinoma has also been associated with disease stage and higher grade tumors. [148-151]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. [152-156]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients. [157].	TP53 and (dendritic cell-based) TP53 vaccines. [158-160]. 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. [161-163]. 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. [164-169].	
RB1 Q395*	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. [172]. 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. [173]. Inactivation of the Rb pathway has been reported to occur frequently in NSCLC and play a role in NSCLC carcinogenesis. [174-176]. The role of RB1 as a tumor suppressor has been demonstrated in a study that showed RB1 depletion resulted in increased cell proliferation and tumor growth in NSCLC cell lines and xenograft models, as compared with RB1-proficient models. [177]. RB1 loss in lung adenocarcinoma tumors harboring an EGFR activating mutation has been reported to be associated with transformation to small cell lung carcinoma. [178,179].	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. [180-183]. 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. [184,185]. Studies have reported that negative Rb expression is associated with increased sensitivity to cisplatin-based chemotherapy in NSCLC. [177,186].	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. [184,187-191]. Loss of RB1 has been associated with lack of response to Cdk4/6 inhibitors. [192-198]. 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. [29-32]. 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. [199]. RB1 mutations have been associated with lack of response to immunotherapy in one analysis of 97 NSCLC patients. [200].

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