REPORTING

Report Date:	MAR-05-2024
Receipt Date:	FEB-27-2024
Collection Date:	FEB-26-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Chih-Hsueh Chen
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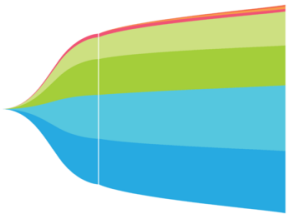
Address: F15., No 207-5 Sec 3, Beixin Rd, Xindian Dist, New Taipei City, 23143, Taiwan
Ph: +886 963 820 633 | Fax: N/A
Additional Recipient: N/A



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
KIF5B-ALK Fusion	✓ Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib	Yes	5.1%
TSC1 N532fs	None	Yes	11.6%
CDK4 Amplification	None	Yes	Medium (++)
EGFR Amplification	None	Yes	Low (+)
TP53 R280T	None	No	10.8%
TERT Promoter SNV	None	No	6.2%

Variants of Uncertain Clinical Significance
TP53 T170M (0.2%), *ATM* N3003S (0.1%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
EGFR T430T (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

Reported by: VL

Additional Biomarkers

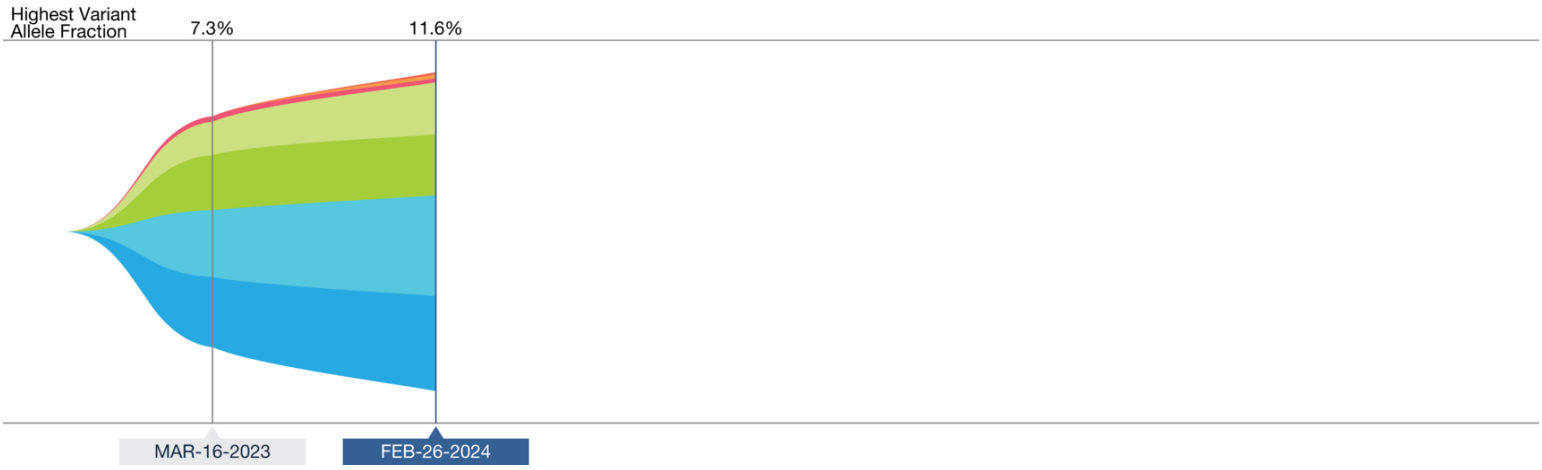
Biomarker	Additional Details
MSI-High	NOT DETECTED

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

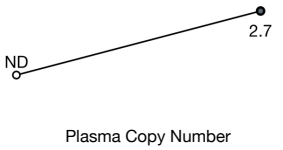
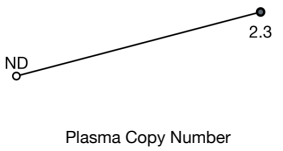
EGFR(T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2*(HER2)	*RET*	*NTRK*	*KRAS*

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	Alteration Trend	
TSC1 N532fs	11.6%	6.9% → 11.6%	
TP53 R280T	10.8%	7.3% → 10.8%	
TERT Promoter SNV	6.2%	5.4% → 6.2%	
KIF5B-ALK Fusion	5.1%	2.9% → 5.1%	
TP53 T170M	0.2%	0.3% → 0.2%	Variants of Uncertain Clinical Significance §
EGFR T430T	0.2%	ND → 0.2%	Synonymous Alteration §

Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend	
ATM N3003S	0.1%		Variants of Uncertain Clinical Significance §
CDK4 Amplification Amplifications not graphed above	Medium (++)		
EGFR Amplification Amplifications not graphed above	Low (+)		

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 A0975860 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
KIF5B-ALK Fusion	NCT03093116 BMS Study Connect Contact Center www.BMSStudyConnect.com,Clinical.Trials@bms.com,855-907-3286	A Study of Repotrectinib (TPX-0005) in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements	Phase 1 /Phase 2	Taipei, Taiwan Tainan, Taiwan Taiepi, Taiwan
	NCT05144997 Pfizer CT.gov Call Center,ClinicalTrials.gov_Inquiries@pfizer.com,1-800-718-1021	Lorlatinib Continuation Study	Phase 4	Taipei, Taiwan
	NCT05160922 Pfizer CT.gov Call Center,ClinicalTrials.gov_Inquiries@pfizer.com,1-800-718-1021	Crizotinib Continuation Clinical Study	Phase 4	Taipei, Taiwan
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
EGFR Amplification	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
	NCT05099172 Bayer Clinical Trials Contact,clinical-trials-contact@bayer.com,(+)1-888-84 22937	First in Human Study of BAY2927088 in Participants Who Have Advanced Non-small Cell Lung Cancer (NSCLC) With Mutations in the Genes of Epidermal Growth Factor Receptor (EGFR) and/or Human Epidermal Growth Factor Receptor 2 (HER2)	Phase 1 /Phase 2	Taipei, Taiwan Tainan, Taiwan Taoyuan, Taiwan Taichung, Taiwan
	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
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TSC1 N532fs	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
CDK4 Amplification	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			

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

Definitions

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

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

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

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

Fusion: Fusion events are gene rearrangements that fuse two previously distinct genes into a single genetic unit. Guardant360 detects fusions in the genes listed in Table 1.

Insertion (Ins): The following alteration was detected in this patient: *TSC1* N532fs. Guardant360 detects short insertions in exons of certain genes (see Table 1).

Promoter: Promoter variants occur in the region upstream of the transcriptional start site and may increase or decrease transcription of the downstream gene, leading to increased or decreased protein levels.

Interpretation

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

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

Method and Limitations

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

Table 1: Genes on the Guardant360 Panel

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

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

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

† Guardant360 reports amplifications of this gene.

Guardant360 reports fusion events involving this gene.

About the Test

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

Testing Performed at: Guardant Health

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

Additional information is available

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

Visit **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A0975860 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)
KIF5B-ALK Fusion	NCT02201992 See https://clinicaltrials.gov/ct2/show/NCT02201992	Crizotinib in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer That Has Been Removed by Surgery and ALK Fusion Mutations (An ALCHEMIST Treatment Trial)	Phase 3	Berlin, VT; Providence, RI; Cody, WY; Jonesboro, AR; Sheridan, WY; Cheyenne, WY; Fort Smith, AR; Sioux Falls, SD (3); Burlington, VT (2); Washington, DC (4); HI (21); DE (8); TX (20); MA (14); MD (15); ME (13); IA (31); ID (13); MI (83); MN (48); MO (33); IL (70); IN (23); MS (9); MT (8); AK (9); VA (17); NC (26); ND (7); NE (15); AZ (9); NH (6); NJ (28); NM (7); FL (19); NV (44); WA (42); NY (26); SC (22); WI (64); OH (72); GA (16); OK (5); CA (113); WV (7); OR (14); KS (30); CO (43); KY (14); PA (84); CT (18); LA (22); TN (10); Guam; Puerto Rico (3)
	NCT03093116 BMS Study Connect Contact Center www.BMSStudyConnect.com,Clinical.Trials@bms.com,855-907-3286	A Study of Repotrectinib (TPX-0005) in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements	Phase 1 /Phase 2	Appleton, WI; Saint Louis, MO; Baltimore, MD; Memphis, TN; Peoria, IL; Aurora, CO; Bolivar, MO; Fairfax, VA; Ann Arbor, MI; Goldsboro, NC; Philadelphia, PA; Chicago, IL; Columbus, OH; New Brunswick, NJ; Columbus, GA; Saint Paul, MN; Seattle, WA; Kingwood, TX; Cleveland, OH; Athens, GA; Hollywood, FL; Cincinnati, OH; Canton, OH; Dallas, TX; Tampa, FL; Houston, TX (2); Detroit, MI (2); Boston, MA (2); Washington, DC (2); New York, NY (2); CA (6); Korea, Democratic People's Republic of; Denmark; Singapore (2); Hungary (2); Hong Kong (2); Japan (9); United Kingdom (5); Spain (8); Canada (5); Netherlands (2); Belgium (2); China (30); Taiwan (3); Poland (5); Korea, Republic of (7); Italy (6); France (8); Australia (3); Germany (4)
	NCT04302025 Reference Study ID Number: ML41591 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728	A Study of Multiple Therapies in Biomarker-Selected Patients With Resectable Stages IB-III Non-Small Cell Lung Cancer	Phase 2	Saint Louis, MO; New Haven, CT; Chicago, IL; Columbus, OH; Kingwood, TX; Pittsburgh, PA; Washington, DC; Aurora, CO; Tampa, FL; Fairfax, VA; Columbia, MO; Lebanon, NH; Ann Arbor, MI; New York, NY (3); Houston, TX (2); Boston, MA (2); CA (5)
	NCT04772235 A responsible person designated by the sponsor,investigacion@mfar.net,0034934344412	Phase I Study of Repotrectinib and Osimertinib in NSCLC Patients	Phase 1	Spain (4)
	NCT05015010 See https://clinicaltrials.gov/ct2/show/NCT05015010	Alectinib in Neo-adjuvant Treatment of Stage III NSCLC	Phase 2	Italy (20)
	NCT05144997 Pfizer CT.gov Call Center,ClinicalTrials.gov_Inquiries@pfizer.com,1-800-718-1021	Lorlatinib Continuation Study	Phase 4	Orange, CA; Japan; Taiwan; Singapore (2); France (2); Spain (2)
	NCT05160922 Pfizer CT.gov Call Center,ClinicalTrials.gov_Inquiries@pfizer.com,1-800-718-	Crizotinib Continuation Clinical Study	Phase 4	Russian Federation; Taiwan; Italy; China (11)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	1021			
	NCT05380024 See https://clinicaltrials.gov/ct2/show/NCT05380024	A Study of Ensartinib as Neoadjuvant Therapy for Patients With ALK Positive Resectable Non-Small Cell Lung Cancer	Phase 2	China (2)
EGFR Amplification	NCT03574402 Yi-Long Wu, Professor,syylwu@live.cn, 862083827812	Phase II Umbrella Study Directed by Next Generation Sequencing	Phase 2	China
	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)
	NCT04606381 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	A Study of Amivantamab Subcutaneous (SC) Administration for the Treatment of Advanced Solid Malignancies	Phase 1	West Hollywood, CA; Indianapolis, IN; New York, NY; Portland, OR; Nashville, TN; Canada; United Kingdom; Korea, Republic of (4)
	NCT05099172 Bayer Clinical Trials Contact,clinical-trials-contact@bayer.com,(+)1-888-84 22937	First in Human Study of BAY2927088 in Participants Who Have Advanced Non-small Cell Lung Cancer (NSCLC) With Mutations in the Genes of Epidermal Growth Factor Receptor (EGFR) and/or Human Epidermal Growth Factor Receptor 2 (HER2)	Phase 1 /Phase 2	Houston, TX; Detroit, MI; Bethesda, MD; Boston, MA; Atlanta, GA; Nashville, TN; Fairfax, VA; Gilbert, AZ; Duarte, CA (2); Singapore (2); Hong Kong (2); Japan (8); Portugal (2); Spain (6); Netherlands (2); Belgium (2); China (12); Taiwan (4); Poland (2); Korea, Republic of (6); Brazil (3); Italy (8); Israel (2); France (5)
	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)
	NCT05845671 Stephanie Biller,stephanie.biller@cuanschutz.edi,17208480729	Amivantamab With Tyrosine Kinase Inhibitors (TKI) for Advanced NSCLC With ALK, ROS1, or RET Alterations	Phase 1 /Phase 2	Aurora, CO (3)
TSC1 N532fs	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)
	NCT03297606 Janet Dancey,jdancey@ctg.queensu.ca, 613-533-6430	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)	Phase 2	Canada (9)
	NCT03994796 Priscilla Brastianos, MD, pbrastianos@partners.org,617-724-1074	Genetic Testing in Guiding Treatment for Patients With Brain Metastases	Phase 2	Deerfield Beach, FL; Minneapolis, MN; Midlothian, VA; Worcester, MA; Colorado Springs, CO; Berlin, VT; Neptune, NJ; Vancouver, WA; Boston, MA; Richmond, VA; Summit, NJ; Oklahoma City, OK; Edina, MN; Bremerton, WA; Jacksonville, FL; Kennewick, WA; Pennington, NJ;

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Kearney, NE; Jackson, MS; Rochester, MN; Atlanta, GA; Burlington, VT; Longmont, CO; Salt Lake City, UT; Lexington, KY; Coral Gables, FL; Shreveport, LA (2); NY (5); WI (19); IA (11); OH (17); ID (6); MI (46); CA (7); OR (5); IL (19); MT (7); PA (8); NC (8)
	NCT04341181 Ulrik Lassen, Prof.,ulrik.lassen@regionh.dk,+45 3545 8923	ProTarget - A Danish Nationwide Clinical Trial on Targeted Cancer Treatment Based on Genomic Profiling	Phase 2	Denmark (7)
	NCT04803318 Zhenfeng Zhang, MD, PhD, zhangzhf@gzhmu.edu.cn, +862039195966	Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors	Phase 2	China
CDK4 Amplification	NCT02693535 Pam Mangat, MS,tapur@asco.org,www.tapur.org	TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer	Phase 2	Phoenix, AZ; Manchester, NH; Charlotte, NC; Portland, OR; Fargo, ND; Concord, NH; Houston, TX; Chapel Hill, NC; Cedar City, UT; Omaha, NE; Birmingham, AL; Portsmouth, NH; Hilton Head Island, SC; Nashville, TN; Fairfax, VA; Kettering, OH; Sioux Falls, SD; Saint George, UT; Chicago, IL; Seattle, WA; Indianapolis, IN; Cincinnati, OH; Salt Lake City, UT; West Chester, OH; Bismarck, ND; Bluffton, SC (3); FL (37); NY (5); WI (16); ME (19); GA (6); MI (11); CA (21); PA (5); CT (7); NM (5)
	NCT02896335 Priscilla Brastianos, MD, PBRASTIANOS@mgh.harvard.edu,617-724-8770	Palbociclib In Progressive Brain Metastases	Phase 2	Boston, MA (2)
	NCT03297606 Janet Dancey,jdancey@ctg.queensu.ca, 613-533-6430	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)	Phase 2	Canada (9)
	NCT04693468 Timothy A. Yap,tyap@mdanderson.org, 713-563-1784	Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial	Phase 1	Houston, TX
	NCT05159245 Tanja Juslin,tanja.juslin@hus.fi, +358405597415	The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs	Phase 2	Finland (4)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
EGFR Amplification	ABBV-221		Anti-Egfr antibody drug conjugate.	Phase 1 (Solid Tumor)
	ABBV-321		Anti-Egfr antibody conjugated to monomethyl auristatin F.	Phase 1 (Solid Tumor) Phase 1 (Glioblastoma, Head and neck squamous cell carcinoma (HNSCC), Brain and Central Nervous System Tumors, Lung squamous cell carcinoma)
	ABT806		Anti-Egfr and EGFRvIII antibody.	Phase 1 (Solid Tumor) Phase 2 (Gastroesophageal junction carcinoma)
	Afatinib	Gilotrif	Irreversible pan-ErbB kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Lung squamous cell carcinoma, EGFR-mutant NSCLC)
	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)
	ASP-1929		An antibody-dye conjugate comprised of cetuximab and IRDye700DX acting as photoimmunotherapy.	Phase 3 (Head and neck carcinoma)
	AVID100		Anti-Egfr antibody-drug conjugate with DM1.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Breast carcinoma (triple negative))
	AZD9592		Bispecific anti-Met/Egfr antibody drug conjugate.	Phase 1 (Solid Tumor)
	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)
	BCA101		Anti-Egfr antibody fused to the extracellular domain of human TGF-beta receptor II.	Phase 1 (Solid Tumor) Phase 1 (Head and neck squamous cell carcinoma (HNSCC), Brain and Central Nervous System Tumors, Anal squamous cell carcinoma)
	BDTX-189		Irreversible Egfr/Her2 inhibitor.	Phase 2 (Solid Tumor)
	BL-B01D1		an EGFR x ERBB3 bispecific antibody-drug conjugate.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	CMAB009		Anti-Egfr monoclonal antibody.	Phase 3 (Colorectal carcinoma (CRC))
	CPGJ602		Recombinant human-mouse chimeric anti-Egfr monoclonal antibody.	Phase 2 (Colorectal carcinoma (CRC))
	D2C7-IT		Immunotoxin targeting both wild-type Egfr and Egfr-vIII.	Phase 1 (Glioblastoma)
	EGFR(V)-EDV-Dox		Doxorubicin-loaded EGFR-targeting nanocells.	Phase 1 (Glioblastoma)
	ERAS-601		Shp-2 inhibitor.	Phase 2 (Solid Tumor)
	Furmonertinib		Third generation mutation-specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	GC1118		Anti-Egfr monoclonal antibody.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, Glioblastoma, Gastroesophageal junction carcinoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	HBI-2376		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	KL-140		Anti-Egfr monoclonal antibody.	Phase 3 (Colorectal carcinoma (CRC))
	Lifirafenib		Dual Braf/Egfr inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	MM-151		Anti-Egfr monoclonal antibody mixture.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Modotuximab		Anti-EGFR antibody.	Phase 1 (Gastric carcinoma, Colorectal carcinoma (CRC))
	Neratinib	Nerlynx	Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HER2+))
	Nimotuzumab	Theraloc	Anti-Egfr monoclonal antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Gastric carcinoma, Glioblastoma, Glioma, Pancreatic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Esophageal carcinoma, Cervical carcinoma)
	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)
	REGN7075		anti-EGFR/CD28 bispecific antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Cutaneous squamous cell carcinoma, Breast carcinoma (triple negative), Colorectal carcinoma (CRC))
	SI-B001		Anti-Egfr/ErbB3 bispecific antibody.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Esophageal 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))
	Sym004		Anti-Egfr antibody mixture.	Phase 2 (Glioma, Head and neck squamous cell carcinoma (HNSCC), Colorectal carcinoma (CRC))
	SYN004		Anti-Egfr monoclonal antibody.	Phase 1 (Solid Tumor) Phase 1 (Lung squamous cell carcinoma)
	TAK-186		A Conditional Bispecific Redirected Activation (COBRA) Protein targeting Egfr and CD3.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Colorectal carcinoma (CRC))
	TAS2940		Egfr/Her2 kinase inhibitor.	Phase 1 (Solid Tumor)
	Varlitinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Cholangiocarcinoma)
	WSD0922-FU		Blood-brain barrier penetrable	Phase 1 (Non-small cell lung carcinoma (NSCLC))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
			EGFR/EGFRvIII inhibitor.	Phase 1 (Glioblastoma, Anaplastic astrocytoma)
TSC1 N532fs	ABTL0812		Inhibitor of mTORC1/mTORC2 /Dhfr.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Endometrial carcinoma)
	Apitolisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Breast carcinoma)
	Bimiralisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma (triple negative), Primary central nervous system lymphoma (PCNSL))
	CC-115		DNA-PK/dual mTORC1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma)
	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)
	ME-344		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Small cell lung carcinoma (SCLC))
	MSC2363318A		Akt1, Akt3, and p70S6K inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma)
	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)
	Ridaforolimus		mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Sarcoma)
	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))
	SF1126		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC))
	Temsirolimus	Torisel	mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				FDA Approved in other indications (Renal cell carcinoma)
	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))
KIF5B-ALK Fusion	Alectinib	Alecensa	Alk and Ret inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (ALK-rearranged NSCLC)
	Alkotinib		Dual Alk/Ros1 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	Brigatinib	Alunbrig	Dual Alk/Egfr kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (ALK-rearranged NSCLC)
	Ceritinib	Zykadia	Alk/Ros1 kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (ALK-rearranged NSCLC)
	Crizotinib	Xalkori	Alk/Met/Ros1 kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (ALK-positive inflammatory myofibroblastic tumor, ALK- and ROS1-rearranged NSCLC, Anaplastic large cell lymphoma, ALK positive)
	Ensartinib		Alk small molecule kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Lung cancer)
	Entrectinib	Rozlytrek	Pan-Trk, Ros1, and Alk kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Solid tumor with NTRK fusion, ROS1-rearranged NSCLC)
	Iruplinalkib		Alk inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (ALK-rearranged NSCLC)
	Lorlatinib	Lorbrena	Alk/Ros1 inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (ALK-rearranged NSCLC)
	NVL-520		Alk/Ros1 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor)
	NVL-655		Alk inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor)
	PLB1003		Alk inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	Repotrectinib	Augtyro	Alk/Ros1/Src/Trk/FAK kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (ROS1-rearranged NSCLC)
	SY-3505		Alk inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	TGRX-326		Alk/Ros1 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	TPX-0131		Alk inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	Unecritinib		Alk/Met/Ros1 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor, Anaplastic large cell lymphoma (ALCL))
CDK4 Amplification	Abemaciclib	Verzenio	Cdk4/6/9 inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (hormone receptor +, HER2-))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Alvocidib		Cdk inhibitor targeting several Cdks, including Cdk1, Cdk2, Cdk4, Cdk5, Cdk6, Cdk7, and Cdk9.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Melanoma, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Germ cell tumor, Esophageal carcinoma, Breast carcinoma, Chronic lymphocytic leukemia (CLL), Acute myeloid leukemia (AML), Multiple myeloma (MM), B-cell lymphoma, Testicular cancer, Lung cancer, Sarcoma, Colorectal carcinoma (CRC), Acute lymphoblastic leukemia (ALL), Myelodysplastic Syndrome (MDS))
	Dalpiciclib		Cdk4/6 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	FCN-437c		Cdk4/6 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma)
	FN-1501		Multikinase inhibitor of Cdk2/4/6 and Flt3.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	Lerociclib		Cdk4/6 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Breast carcinoma)
	Narazaciclib		Ark5 and Cdk4 multi-kinase inhibitor.	Phase 1 (Solid Tumor)
	Palbociclib	Ibrance	Cdk4/6 inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (hormone receptor +, HER2-))
	PF-06873600		Cdk2/4/6 inhibitor.	Phase 2 (Ovarian carcinoma, Breast carcinoma)
	PF-07220060		Cdk4 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Liposarcoma)
	PF-07224826		CDK2/4/6 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma, Liposarcoma)
	Ribociclib	Kisqali	Cdk4/6 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (hormone receptor +, HER2-))
	SPH4336		Cdk4/6 inhibitor.	Phase 2 (Solid Tumor) Phase 3 (Breast carcinoma)
	TQB3616		Cdk4/6 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Breast carcinoma)
	Trilaciclib	Cosela	Cdk4/6 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Small cell lung carcinoma (SCLC))
	Voruciclib		Multikinase inhibitor of Cdk1/4/6/9.	Phase 1 (Solid Tumor) Phase 1 (Marginal zone lymphoma (MZL), Brain and Central Nervous System Tumors, Hematologic malignancies, Chronic lymphocytic leukemia (CLL), Acute myeloid leukemia (AML), Mantle cell lymphoma (MCL), Follicular lymphoma (FL), Diffuse large B-cell lymphoma (DLBCL), Small lymphocytic lymphoma)
TERT Promoter SNV	Tertomotide		hTERT vaccine.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Pancreatic carcinoma)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
KIF5B-ALK Fusion	ALK was originally identified in anaplastic lymphoma as a fusion partner with the gene product of NPM1; ALK has subsequently been identified as a fusion partner with numerous other genes, including EML4 in lung cancer. [1]. The ALK gene can become oncogenic by a gene rearrangement, copy number gain, or genetic mutation. [1,2]. Patients with EML4-ALK fusions generally have wild-type EGFR, KRAS, and TP53, and are resistant to Egfr inhibitors, although there have been reports of non-small cell lung carcinoma (NSCLC) tumors which harbor concomitant EGFR mutations and EML4-ALK translocations. [3,4]. ALK rearrangements have been associated with younger age, increased disease stage, nodal metastasis, invasive mucinous disease, and with epithelial-mesenchymal transition marker expression in lung adenocarcinoma. [5-10].	Tumors with ALK activation, by either mutation, fusion, or amplification, may be sensitive to Alk inhibitors. [11]. The Alk inhibitors crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib have been approved for ALK-translocation-positive non-small cell lung cancer; additional Alk inhibitors are under investigation in clinical trials. [12-17]. Crizotinib has additionally been FDA-approved for the treatment of pediatric and young adult patients with relapsed /refractory ALK-positive anaplastic large cell lymphoma or ALK-positive inflammatory myofibroblastic tumors. [18-20].	Secondary mutations in ALK can confer resistance to different Alk inhibitors, such as crizotinib, ceritinib, alectinib, or brigatinib, in ALK-rearranged NSCLC. [21-25]. Other mechanisms of resistance to crizotinib have also been reported, including activation of Egfr, K-Ras, PI3K/Akt /mTOR, and Hsp90 signaling. [26-33]. Multiple case studies have reported that failure of alectinib treatment in NSCLC harboring ALK rearrangements is associated with transformation of disease into SCLC. [34-36].
TSC1 N532fs	The Hamartin and Tuberin proteins form a heterodimer that acts as a GTPase activating protein (GAP) for Rheb. [37,38]. GTP-bound Rheb is a potent activator of the mammalian target of rapamycin (mTOR). [38]. Germline mutations in TSC1 or TSC2 are associated with the rare autosomal dominant syndrome tuberous sclerosis complex. Patients with this disorder develop nonmalignant tumors in many organs including the brain, kidney, lung, heart, and liver. [39]. TSC1/2 mutations have been associated with high PD-L1 expression and tumor mutational burden in the analysis of NSCLC patient datasets. [40].	Currently no therapies directly targeting inactivation of Hamartin are approved or are under investigation in clinical trials.Loss or inactivation of TSC1 leads to activation of mTOR and therefore may predict sensitivity to mTOR inhibitors. [38,41]. In a number of cancer types (including bladder, breast, thyroid, and PEComa), patients who have had exceptional responses to mTOR inhibitors have been found to harbor TSC1 or TSC2 inactivating alterations. [42-47]. The mTOR inhibitors everolimus and temsirolimus have been approved for some indications. Everolimus has been approved in subependymal giant cell astrocytoma associated with tuberous sclerosis (due to TSC1 or TSC2 inactivation), as well as for other indications. These agents and other mTOR inhibitors are being studied in clinical trials in multiple tumor types. [48-50]. Decreased TSC1 mRNA expression has been significantly associated with response to erlotinib in patient-derived xenograft zebrafish models. [51].	
CDK4 Amplification	CDK4 in association with Cyclin D1, as a cyclin-dependent kinase, plays a key role in the cell cycle progression across the G1/S phase transition. [52,53] . Cdk4 expression in NSCLC has been	Cdk4 and its functional homolog, Cdk6, are the targets for several investigational cancer drugs, by virtue of their role in cell cycle progression; Cdk4/6 inhibitors lead to cell cycle	A study analyzing 65 advanced NSCLC patients, who received EGFR-tyrosine kinase inhibitors (TKIs), has reported an association of CDK4/6 amplification with de novo EGFR-TKI resistance. [59].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	associated with the presence of lymph node metastases and higher stage disease in one study. [54]. In addition, Cdk4 expression in NSCLC cell lines has been associated with cell proliferation, cell cycle progression, and decreased apoptosis in a preclinical study. [55].	arrest, which is the basis for their development as anti-cancer agents. [56-58].	Furthermore, CDK4 alterations detected in cell free DNA have been retrospectively associated with poor response to osimertinib in a cohort of 41 NSCLC cases, while alterations in CDK4 or CDK6 detected in cell free DNA have been retrospectively associated with poor response to Egfr TKIs in a cohort of 64 NSCLC cases. [60].
EGFR Amplification	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. [61].	EGFR amplification or increased copy number may result in elevated Egfr protein expression and thus predict sensitivity to Egfr targeted therapies. The Egfr tyrosine kinase inhibitors (TKIs) erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib have been approved for the treatment of non-small cell lung carcinoma (NSCLC) with specific EGFR mutations; however, only modest clinical benefit for gefitinib or erlotinib has been reported in patients harboring EGFR amplification without concurrent sensitizing mutations. [62-69]. Anti-Egfr monoclonal antibodies are also approved in some indications, including cetuximab, which is an approved therapy for head and neck and colorectal cancer, and panitumumab, which is approved in colorectal cancer. [70-72]. However, molecular analyses of tumor samples from a Phase 3 study in head and neck squamous cell carcinoma revealed that neither Egfr expression nor EGFR amplification predicted response to cetuximab. [73,74]. 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. [62,75-80]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors. [81].	EGFR amplification has been reported as an acquired alteration in 15.5% (16 /103) of EGFR exon19del or L858R-mutant NSCLC patients who were treated with Egfr TKI and in 9.7% (3 /31) of patients treated with Egfr TKI in combination with bevacizumab. [82].
TP53 R280T	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [83]. 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. [84-86]. Expression of p53 in normal cells is low; however, TP53 alterations,	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines. [103-105]. Inhibition of components of the DNA damage checkpoint, including Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical	Mutations in TP53 may increase resistance to ionizing radiation therapy. [115,116].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects. [87-91]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. [92]. 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. [93-96]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. [97-101]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients. [102].	cancer models with deficiency of p53 function. [106-108]. 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. [109-114].	
TERT Promoter SNV	TERT promoter mutations have been suggested to act as driver events in the malignant transformation of cells to melanoma and perhaps other types of cancer. [117].	Therapies targeting telomeres or telomerase components have been in development, although discoveries regarding alternative roles in normal cells, as well as consequences of shortened telomeres, may limit their use. [118-122].	

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