Your Lab Genetics Lab
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Report Date	Jun 7, 2023	Diagnosis	Non Small Cell Lung Carcinoma	Sample Accession Number	DEMO_QIAseq_highTMB_lung
				Collection site	Lung

QIAseq Pan-cancer Multimodal Panel

The QIAseq Pan-cancer Multimodal Panel allows genomic profiling of DNA variants, RNA fusions and assessing TMB/MSI in solid tumors and heme malignancies. Developed for consolidated DNA and RNA enrichment and integrated analysis, the panel targets 1.44 Mb of the human genome to simultaneously detect DNA variants in 523 genes and RNA fusions in 56 genes.

Overall comment

The purpose of this sample report is to illustrate report components.

Analysis results: Positive

2 Biomarkers	Approved treatments	Other findings
Tumor Mutation Burden: TMB-high (17.66 Mutations/Megabase)	Pembrolizumab	Trials: 4 Phase 2 4 Phase 1/Phase 2 2 Phase 1
Microsatellite Status: MS-stable	-	Trials: 2 Phase 2 2 Phase 1/Phase 2 2 Phase 1

1 Variant of strong clinical significance, Tier 1	Approved treatments	Other findings
KRAS: p.G12C, Pathogenic	Adagrasib Sotorasib	**Resistance: afatinib, erlotinib, gefitinib, osimertinib** Trials: 1 Expanded Access 1 Phase 3 2 Phase 2/Phase 3 5 Phase 2 1 Phase 1/Phase 2

4 Variants of potential clinical significance, Tier 2	Approved treatments	Other findings
ATR: p.I774fs*5, Pathogenic	-	Trials: 1 Phase 3 4 Phase 2 5 Phase 1/Phase 2
KEAP1 †: p.R272C, Likely Pathogenic	-	Trials: 1 Phase 1
STK11: p.S283fs*3, Likely Pathogenic	-	Trials: 1 Phase 2 1 Phase 1/Phase 2
SMARCA4 †: p.W764R, Uncertain Significance	-	-

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

Interactions

None

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 3.

Report content

7 Variants of biological significance, Tier 3

31 Variants of uncertain significance, Tier 3

CHD2: p.K1245fs*4, Likely Pathogenic

EPHA3: p.G766E, Likely Pathogenic

KMT2C: p.K2797fs*26, Pathogenic

LRP1B †: p.E3468*, Likely Pathogenic

LRP1B †: p.G1801*, Likely Pathogenic

TGFBR2: p.K128fs*35, Pathogenic

TP53 †: p.E62*, Pathogenic

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

GUIDELINES

The NCCN Guidelines for Non-Small Cell Lung Carcinoma (v.3.2023) note that KRAS mutation in NSCLC is prognostic of poor survival compared with NSCLC patients lacking KRAS mutation. The Guidelines also note that the presence of a KRAS mutation identifies patients who are unlikely to benefit from further molecular testing due to the low probability of overlapping targetable alterations. The NCCN Guidelines for Non-Small Cell Lung Carcinoma (v. 3.2023) list sotorasib or adagrasib as a subsequent therapy options for patients with KRAS G12C-positive tumors after at least one line of therapy. The Guidelines note that adagrasib and sotorasib have a similar mechanism of action and it is not recommended to switch between these agents at the time of progression.

TREATMENT OPTIONS

Therapies with potential clinical benefit (3)

PEMBROLIZUMAB

Pembrolizumab, a programmed death receptor-1 (PD-1)-blocking antibody, is FDA- and EMA-approved for treating patients with unresectable or metastatic melanoma; for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB, IIC, or III melanoma following complete resection; in combination with pemetrexed and platinum chemotherapy for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations; in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, for the first-line treatment of patients with metastatic squamous NSCLC; as a single agent for treating patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy (patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab); in combination with chemotherapy, with or without bevacizumab, for treating patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test; in combination with axitinib, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC); in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC; for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions; and as a single agent for treating patients with advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; pembrolizumab is also FDA-approved as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic; as a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for treating adult patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC; in combination with platinum and fluorouracil (FU) for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell cancer (HNSCC); as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test; as a single agent for treating patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy; for treating adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL); for treating pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy; for treating adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy; for treating patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy, or who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; for treating patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy; in combination with enfortumab vedotin, for treating adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy; for treating adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options; for treating patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC), as determined by an FDA-approved test; in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; for treating patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either: in combination with platinum- and fluoropyrimidine-based chemotherapy, or as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test; as a single agent for treating patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test; for treating patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; for treating adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC); in combination with lenvatinib, for treating patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; for treating adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options; for treating patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation; for treating patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery; and, in combination with chemotherapy, for treating patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test; pembrolizumab is also EMA-approved for the first-line treatment of adult patients with metastatic non-small cell lung carcinoma (NSCLC) whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations; for treating adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option; for treating adult patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy; for treating adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for

Therapies with potential clinical benefit (3)

cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10; as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 with a CPS ≥ 1; as monotherapy for treating adult patients with recurrent or metastatic HNSCC whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy; for the first-line treatment of adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer; for treating adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer after previous fluoropyrimidine-based combination therapy; unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy; in combination with platinum and fluoropyrimidine based chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 10; in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for treating adult patients with locally advanced, or early-stage triple-negative breast cancer (TNBC) at high risk of recurrence; in combination with chemotherapy, for treating adult patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease; and, in combination with lenvatinib, for treating adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

Sensitive
Biomarker: Tumor Mutation Burden: TMB-high, Tier 1A

ADAGRASIB

Adagrasib, an inhibitor of the RAS GTPase family, is FDA-approved for treating adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA approved test, who have received at least one prior systemic therapy.

Sensitive

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

SOTORASIB

Sotorasib, an inhibitor of the RAS GTPase family, is FDA-approved for treating adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

Sensitive

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

Therapies associated with resistance (4)

AFATINIB

Afatinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test, as first-line treatment; metastatic, squamous NSCLC progressing after platinum-based chemotherapy; afatinib is EMA-approved for treating adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) who are EGFR TKI-naïve; and locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum based chemotherapy.

Resistance

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

ERLOTINIB

Erlotinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen; and for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine; erlotinib is EMA-approved for treating patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations for the first-line treatment; locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease for switch maintenance treatment after first-line chemotherapy; locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (in patients with tumours without EGFR activating mutations, erlotinib is indicated when other treatment options are not considered suitable); and metastatic pancreatic cancer, in combination with gemcitabine.

Resistance

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

Therapies associated with resistance (4)

GEFITINIB

Gefitinib, a tyrosine kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Resistance

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

OSIMERTINIB

Osimertinib, a kinase inhibitor, is FDA- and EMA-approved for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test; osimertinib is FDA-approved for treating adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, as adjuvant therapy after tumor resection; and metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy; osimertinib is EMA-approved for treating adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as adjuvant treatment after complete tumour resection; and locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Resistance

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

AVAILABLE CLINICAL TRIALS

Expanded Access clinical trials (1)

SOTORASIB

A Multicenter, Open-label, Single-arm, Expanded Access Protocol of Sotorasib for the Treatment of Subjects With Previously Treated Locally Advanced Unresectable/Metastatic NSCLC With KRAS p.G12C Mutation
NCT04667234

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

Contact

United States: AK, AL, AZ, CO, FL, IA, IL, KY, LA, MA, MD, ME, MI, MO, NC, NE, NJ, OH, PA, TN, WV
Amgen Call Center; medinfo@amgen.com;
866-572-6436;

Phase 3 clinical trials (2)

DOCETAXEL, ADAGRASIB

A Randomized Phase 3 Study of MRTX849 Versus Docetaxel in Patients With Previously Treated Non-Small Cell Lung Cancer With KRAS G12C Mutation
NCT04685135

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

Contact

United States: CA, CO, FL, GA, IL, IN, KS, LA, MD, ME, MT, NJ, NY, OH, OR, RI, TX
Mirati Therapeutics Study Locator Services;
miratistudylocator@emergingmed.com;
1-844-893-5530;

DURVALUMAB, CERALASERTIB

A Phase III, Open-label, Randomised, Multicentre Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer Without Actionable Genomic Alterations, and Whose Disease Has Progressed On or After Prior Anti-PD-(L)1 Therapy and Platinum-based Chemotherapy: LATIFY
NCT05450692

Qualifying variant

Gene	Classification	Variant
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA

Contact

United States: AZ, CA, GA, OH, PA, TX
AstraZeneca Clinical Study Information Center; information.center@astrazeneca.com;
1-877-240-9479;

Phase 2/Phase 3 clinical trials (2)

DOCETAXEL, GDC-6036

A Phase II/III Multicenter Study Evaluating the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring Actionable Somatic Mutations Detected in Blood (B-FAST: Blood-First Assay Screening Trial)
NCT03178552

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

Contact
United States: CA, MI, NH, NY, OR, TN
Reference Study ID Number: BO29554 https://forpatients.roche.com/;
global-roche-genentech-trials@gene.com;
888-662-6728 (U.S. and Canada);

PEMBROLIZUMAB, CARBOPLATIN/PEMBROLIZUMAB/PEMETREXED, CISPLATIN/PEMBROLIZUMAB/PEMETREXED, ADAGRASIB

A Phase 2 Trial of MRTX849 Monotherapy and in Combination With Pembrolizumab and a Phase 3 Trial of Adagrasib in Combination With Pembrolizumab Versus Pembrolizumab Plus Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer With KRAS G12C Mutation
NCT04613596

Qualifying variant

Gene	Classification	Variant
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T

Contact
United States: AR, AZ, CA, CO, CT, FL, GA, IL, IN, KS, KY, LA, MA, MD, MN, MS, NC, NE, NJ, NV, NY, OH, OR, SD, TN, TX, VA
Mirati Therapeutics Study Locator Services;
miratistudylocator@emergingmed.com;
18448935530;

Phase 2 clinical trials (13)

ATEZOLIZUMAB

Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial
NCT04589845

Qualifying variant

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase

Contact
United States: AL, AZ, CA, DE, FL, GA, ID, IL, MD, MI, MN, MT, NH, NJ, NM, NY, OH, OR, PA, TN, TX, VA, WA, WI
Reference Study ID Number: BO41932 https://forpatients.roche.com/;
Global-Roche-Genentech-Trials@gene.com;
888-662-6728 (U.S. and Canada);

PEMBROLIZUMAB, IPILIMUMAB, NIVOLUMAB

Targeted Agent and Profiling Utilization Registry (TAPUR) Study
NCT02693535

Qualifying variants

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase

Gene	Classification	Variant
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA

Contact
United States: AL, AZ, CA, CT, FL, GA, HI, IL, IN, ME, MI, NC, ND, NE, NH, NM, NY, OH, OR, PA, SC, SD, TN, TX, UT, VA, WA, WI
Pam Mangat, MS; tapur@asco.org;

DURVALUMAB, TREMELIMUMAB

Phase 2 Investigation of MEDI4736 (Durvalumab) and Tremelimumab Combination in Somatically Hypermutated Recurrent Solid Tumors
NCT03911557

Qualifying variants

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase
MS-stable	Tier 3 Uncertain Significance	-

Contact
United States: KY
Heather Heath; heather.flynn@uky.edu;
859-323-6720;

PEMBROLIZUMAB

A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)
NCT02628067

Qualifying variants

Contact

Phase 2 clinical trials (13)

Biomarker	Classification	Score	United States: CA, MA, NJ
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase	Toll Free Number;
MS-stable	Tier 3 Uncertain Significance	-	1-888-577-8839;

SOTORASIB, PANITUMUMAB

Molecular Analysis for Combination Therapy Choice (ComboMATCH)
NCT05564377

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T	United States: DE, IA, ID, IL, MO, MT, NJ, NV, NY, OH, OR James M Ford;

SOTORASIB

Neoadjuvant Sotorasib in KRAS G12C Mutated, Resectable, Stage Ib-IIIA Non-Small Cell Lung Cancer (NSCLC)
NCT05400577

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T	United States: PA Hossein Borghaei, DO; Hossein.Borghaei@fccc.edu; 2152144297;

TALAZOPARIB, ZEN-3694

Phase 2 Trial of the Combination of the BET Inhibitor, ZEN003694 (ZEN-3694), and the PARP Inhibitor Talazoparib, in Patients With Molecularly-Selected Solid Tumors (ComBET)
NCT05327010

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T	United States: GA, IL, NC, TX Timothy A Yap;

SOTORASIB

A Phase II Study of AMG 510 in Participants With Previously Treated Stage IV or Recurrent KRAS G12C Mutated Non-Squamous Non-Small Cell Lung Cancer (ECOG-ACRIN LUNG-MAP SUB-STUDY)
NCT04625647

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T	United States: AK, AR, CA, CO, CT, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, ME, MI, MN, MO, MS, MT, NC, ND, NH, NJ, NM, NV, NY, OH, OK, OR, PA, SC, SD, TN, TX, VA, VT, WA, WI, WV Sukhmani K Padda;

PEMBROLIZUMAB, ADAGRASIB

A Phase 2 Trial of Combination Therapies With Adagrasib in Patients With Advanced Non-Small Cell Lung Cancer With KRAS G12C Mutation
NCT05609578

Qualifying variant

Gene	Classification	Variant	Contact
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T	United States: CA, NY, OH, WA Mirati Therapeutics Study Locator Services; miratistudylocator@emergingmed.com; 18448935530;

DURVALUMAB, CERALASERTIB

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients With Non-Small Cell Lung Cancer, Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON).
NCT03334617

Qualifying variant

Gene	Classification	Variant	Contact
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	United States: CA, DC, IL, MA, MD, PA, TN, TX, VA AstraZeneca Clinical Study Information Center; information. center@astrazeneca.com; 1-877-240-9479;

Phase 2 clinical trials (13)

TALAZOPARIB

A Pharmacodynamics-Driven Trial of Talazoparib, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Aberrations in Genes Involved in DNA Damage Response
NCT04550494

Qualifying variant			Contact
Gene	Classification	Variant	United States: FL, MD, OK
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	A P Chen;

CERALASERTIB

A Modular Phase 2a Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)
NCT04564027

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, FL, LA, MD, MI, MN, NV, NY, PA, SC
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	AstraZeneca Clinical Study Information Center; information. center@astrazeneca.com; 1-877-240-9479;

TEMSIROLIMUS

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial
NCT03297606

Qualifying variant			Contact
Gene	Classification	Variant	Janet Dancey; jdancey@ctg.queensu.ca;
STK11	Tier 2C Likely Pathogenic	p.S283fs*3 c.843_846delCCCG	613-533-6430;

Phase 1/Phase 2 clinical trials (12)

23ME-00610

A Phase 1/2a, Multicenter, Open-Label, Dose-Escalation and Expansion Study of Intravenously Administered 23ME-00610 in Patients With Advanced Solid Malignancies
NCT05199272

Qualifying variant			Contact
Biomarker	Classification	Score	United States: OR, TX, VA
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase	Study Inquiry; studyinquiry@23andme.com; (650) 963-8997;

ST-067

A Phase 1a Open-Label, Dose-Escalation, and a Phase 2 Study to Investigate the Safety, PK, PD, and Clinical Activity of ST-067 Administered Subcutaneously as Monotherapy in Patients With Relapsed or Refractory Solid Tumors
NCT04787042

Qualifying variant			Contact
Biomarker	Classification	Score	United States: AZ, CO, CT, MA, NY, OR
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase	Beatrice McQueen, Ph.D.; beatrice@simchatherapeutics.com; 805-300-3912;

PEMBROLIZUMAB, NEO-201

Phase 1/2 With Expansion Cohorts in a Study of NEO-201 in Adults With Chemo-Resistant Solid Tumors
NCT03476681

Qualifying variant			Contact
Biomarker	Classification	Score	United States: MD
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase	Ann McCoy, RN; ann.mccoy@nih.gov; 240-760-6021;

PEMBROLIZUMAB

A Phase I/II Study of Pembrolizumab (MK-3475) in Children With Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumor or Lymphoma (KEYNOTE-051)

Phase 1/Phase 2 clinical trials (12)

NCT02332668

Qualifying variant			Contact
Biomarker	Classification	Score	United States: CO, IN, MA, MO, NY, TN, TX, UT, WA
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase	Toll Free Number; 1-888-577-8839;

PEMBROLIZUMAB

A Phase 1b/2, Open-Label, Safety, Tolerability and Efficacy Study of NC410 Plus Pembrolizumab for Participants With Advanced Unresectable and/or Metastatic Immune Checkpoint Inhibitor (ICI) Refractory Solid Tumors or ICI Naïve MSS/MSI-Low Solid Tumors
NCT05572684

Qualifying variant			Contact
Biomarker	Classification	Score	United States: AZ, CO, KY, MD, NJ, OH, TX, VA, WA
MS-stable	Tier 3 Uncertain Significance	-	Associate Director Clinical Operations at NextCure, Inc.; NCClin@nextcure.com; 859-468-8632;

BINIMETINIB, LXS196

A Phase 1/2 Study of IDE196 in Patients With Solid Tumors Harboring GNAQ/11 Mutations or PRKC Fusions
NCT03947385

Qualifying variant			Contact
Biomarker	Classification	Score	United States: AZ, CA, FL, MO, NC, NY, OH, PA, TN, TX
MS-stable	Tier 3 Uncertain Significance	-	IDEAYA Clinical Trials; IDEAYAClinicalTrials@ideayabio.com; +1 650 534 3616;

AFATINIB, PEMBROLIZUMAB, CETUXIMAB, ADAGRASIB

A Phase 1/2 Multiple Expansion Cohort Trial of MRTX849 in Patients With Advanced Solid Tumors With KRAS G12C Mutation KRYSTAL-1
NCT03785249

Qualifying variants			Contact
Gene	Classification	Variant	United States: AK, AZ, CA, CO, CT, DE, FL, GA, IA, IL, KS, KY, LA, MA, MD, ME, MI, MN, MO, MT, NC, NE, NV, NY, OH, OK, OR, PA, SC, TN, TX, VA, WA, WI
KRAS	Tier 1A Pathogenic	p.G12C c.34G>T	
STK11	Tier 2C Likely Pathogenic	p.S283fs*3 c.843_846delCCCG	Mirati Therapeutics Study Locator Services; miratistudylocator@emergingmed.com; 1-844-893-5530;

LURBINECTEDIN, BERZOSERTIB

A Phase I/II Trial of Lurbinectedin With Berzosertib, an ATR Kinase Inhibitor in Small Cell Cancers and High Grade Neuroendocrine Cancers
NCT04802174

Qualifying variant			Contact
Gene	Classification	Variant	United States: MD
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	Rasa Vilimas, R.N.; vilimasrj@mail.nih.gov; (240) 858-3158;

ART0380, GEMCITABINE

A Phase I/IIa, Open-label, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of the ATR Kinase Inhibitor ART0380 Administered Orally as Monotherapy and in Combination to Patients With Advanced or Metastatic Solid Tumors
NCT04657068

Qualifying variant			Contact
Gene	Classification	Variant	United States: CO, FL, OK, PA, TN, TX
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	Sarah Cannon Development Innovations; CANN. InnovationsMedical@sarahcannon.com; 844-710-6157;

CARBOPLATIN, PEMBROLIZUMAB, BERZOSERTIB, GEMCITABINE

A Phase IB and Randomized Open-Label Phase II Study of Berzosertib (M6620, VX-970) in Combination With Carboplatin/Gemcitabine /Pembrolizumab in Patients With Chemotherapy-Naïve Advanced Non-Small Cell Lung Cancer of Squamous Cell Histology
NCT04216316

Qualifying variant	Contact

Phase 1/Phase 2 clinical trials (12)

Gene	Classification	Variant	
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	United States: CA, FL, NC, NH, NY, PA Liza C Villaruz;

CARBOPLATIN, DURVALUMAB, AZD5305, OLAPARIB, CERALASERTIB

A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ceralasertib in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies.
NCT02264678

Qualifying variant

Gene	Classification	Variant	Contact
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	United States: CA, MA, NY AstraZeneca Clinical Study Information Center; information. center@astrazeneca.com; 1-877-240-9479;

TALAZOPARIB, RP-3500, GEMCITABINE

Phase 1/2a Study of the Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Clinical Activity of RP-3500 Alone or in Combination With Talazoparib or Gemcitabine in Advanced Solid Tumors With ATR Inhibitor Sensitizing Mutations (TRESR Study)
NCT04497116

Qualifying variant

Gene	Classification	Variant	Contact
ATR	Tier 2C Pathogenic	p.I774fs*5 c.2320delA	United States: IL, MA, NC, NY, RI, TN, TX Gabriela Gomez, MD, MBA; ggomez@reparerx.com; 857-340-5415;

Phase 1 clinical trials (5)

PEMBROLIZUMAB, ATRC-101

A Phase 1b Dose Escalation and Expansion Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Biological Activity of ATRC-101 as Monotherapy and in Combination With Other Anticancer Agents in Adults With Advanced Solid Malignancies
NCT04244552

Qualifying variant

Biomarker	Classification	Score	Contact
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase	United States: AZ, CA, DC, FL, MA, MN, NC, NE, NY, OH, OK, TN, TX Nick Higgins; nhiggins@atreca.com; 650-453-5279;

INBRX 105, PEMBROLIZUMAB

An Open-Label, Multicenter, First-in-Human, Dose-Escalation, Phase 1 - 2 Study of INBRX-105 and INBRX-105 in Combination With Pembrolizumab in Patients With Locally Advanced or Metastatic Solid Tumors
NCT03809624

Qualifying variant

Biomarker	Classification	Score	Contact
TMB-high	Tier 1A Pathogenic	17.66 Mutations/Megabase	United States: AZ, CA, GA, KY, MA, MI, NE, OR, PA, TX, UT, VA Amanda Sweeney; clinicaltrials@inhibrx.com; 858-500-7833;

MK-4830, PEMBROLIZUMAB

A Phase 1 Open Label, Multi-Arm, Multicenter Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab for Participants With Advanced Solid Tumors
NCT03564691

Qualifying variant

Biomarker	Classification	Score	Contact
MS-stable	Tier 3 Uncertain Significance	-	United States: MO, NJ, TX, UT, WA Toll Free Number; Trialsites@merck.com; 1-888-577-8839;

PEMBROLIZUMAB, ETC-1922159

A Phase 1A/B Study to Evaluate the Safety and Tolerability of ETC-1922159 as a Single Agent and in Combination With Pembrolizumab in Advanced Solid Tumours
NCT02521844

Qualifying variant | Contact

Phase 1 clinical trials (5)

Biomarker	Classification	Score	United States: CO, NC, TX Venkateshan Srirangam Prativadibhayankara, MD; Venkateshan_Srirangam@eddc.a-star.edu.sg; +65 6407 4213;
MS-stable	Tier 3 Uncertain Significance	-	

SAPANISERTIB, TELAGLENASTAT

A Phase 1 Trial of MLN0128 (Sapanisertib) and CB-839 HCl (Telaglenastat) in Advanced NSCLC Patients
NCT04250545

Qualifying variant

Gene	Classification	Variant
KEAP1	Tier 2C Likely Pathogenic	p.R272C c.814C>T

Contact
United States: CA, NY
Jonathan W Riess;

VARIANT DETAILS

Biomarkers (2)

Tumor Mutation Burden: TMB-high (17.66 Mutations/Megabase)

Biomarker: TMB-high
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
1 Sensitive
10 Trials

Biomarker summary: Tumor Mutational Burden-high has been detected in this case.

Clinical relevance: Deregulation of multiple cellular processes is capable of introducing DNA alterations during tumorigenesis. Genetic mutations in tumor cells have been reported to result in the production of neoantigens, which are immunogenic peptides recognized by tumor-infiltrating lymphocytes (TILs) [369, 8, 571, 198]. Studies have shown high tumor mutational burden or high levels of neoantigens to be associated with high expression of cytotoxic T-cell markers; thus, immunotherapies may be relevant in tumors with high tumor mutational burden [246, 198, 68, 547]. Indeed, high tumor mutational burden has been associated with increased clinical benefit of several immune checkpoint inhibitors, including pembrolizumab, nivolumab, nivolumab plus ipilimumab, and atezolizumab in studies of NSCLC, urothelial carcinoma, and other solid tumors [541, 74, 178, 537, 166, 231, 710, 548, 276, 205, 560]. Pembrolizumab has been FDA-approved for the treatment of pediatric and adult solid tumors with high tumor mutational burden (TMB-H), defined as ten or more mutations per megabase as determined by an approved test [409].

Disease summary: High clonal neoantigen burden has been associated with increased expression of immune-related genes in one analysis of 106 lung adenocarcinoma cases [425]. High TMB has been significantly associated with smoking history in lung adenocarcinoma studies [451, 105, 684, 626]. High tumor mutational burden has been associated with increased clinical benefit of several immune checkpoint inhibitors, including pembrolizumab, nivolumab, nivolumab plus ipilimumab, and atezolizumab in studies of NSCLC patients [541, 74, 178, 537, 166, 231].

Molecular function: A test result demonstrating high tumor mutational burden has been reported in this sample.

Incidence: One analysis of 11205 NSCLC cases has reported an average tumor mutational burden of 10.7 mutations per megabase (Mb); increased tumor mutational burden was reported in NSCLC samples with MET amplification as compared with the absence of MET amplification (6.8 mutations per Mb versus 4.4 mutations per Mb, respectively) [569]. Another study has reported an average tumor mutational burden of 6.3 mutations per Mb in 11855 lung adenocarcinoma and 9.0 mutations per Mb in 2102 lung squamous cell carcinoma cases [85].

Role in disease: Multiple mechanisms, including oncogene-induced replication stress and deregulation of DNA replication, have been reported to introduce DNA alterations during tumorigenesis, resulting in variable frequencies of somatic mutations in different cancer subtypes [369, 8]. Genetic mutations in tumor cells can result in the production of neoantigens, which are presented in context of MHC molecules on cancer cells to tumor-infiltrating lymphocytes (TILs) [198, 571, 547]. High clonal neoantigen burden has been associated with increased expression of immune-related genes in one analysis of 106 lung adenocarcinoma cases [425]. High TMB has been significantly associated with smoking history in lung adenocarcinoma studies [451, 105, 684, 626].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Biomarkers (2)

Drug sensitivity: Studies have shown high tumor mutational burden or high levels of neoantigens to be associated with high expression of cytotoxic T-cell markers; thus, immunotherapies may be relevant in tumors with high tumor mutational burden [246, 198, 68, 547]. A large study of advanced cancer patients reported that higher tumor mutation burden (TMB, defined as the highest 20% in each histology) was associated with significantly increased survival in patients treated with a variety of immune checkpoint inhibitors, although the numeric cutoff for TMB in each histology was highly variable. Tumor types with the most significant improvement were bladder, colorectal, head and neck, melanoma, and NSCLC. Breast cancer and glioma with high TMB were not associated with increased survival [560]. Pembrolizumab has been FDA-approved for the treatment of pediatric and adult solid tumors with high tumor mutational burden (TMB-H), defined as ten or more mutations per megabase as determined by an approved test. Pembrolizumab has multiple FDA-approved indications in NSCLC, including as a first-line therapy for inoperable stage 3 or metastatic NSCLC patients lacking ALK and EGFR mutations but harboring PD-L1 expression in at least 1% of tumor cells, for metastatic NSCLC following disease progression on platinum-based chemotherapy with PD-L1 expression in at least 1% of tumor cells, as a first-line treatment in combination with pemetrexed and carboplatin in non-squamous NSCLC and in combination with carboplatin and either paclitaxel or nab-paclitaxel in squamous cell NSCLC, irrespective of PD-L1 status, and as an adjuvant treatment following resection and platinum-based chemotherapy for patients with stage 1B, 2, or 3A NSCLC [487, 236, 185, 335, 180, 505, 441, 470]. Cemiplimab has been approved by the FDA as a monotherapy for the first-line treatment of either locally advanced NSCLC patients who are not candidates for definitive chemoradiation or metastatic NSCLC patients with tumors expressing PD-L1 in 50% or more of cells and lacking alterations in EGFR, ALK and ROS1 [574]. Additionally, cemiplimab-rwlc in combination with platinum-based chemotherapy has been FDA-approved for treatment of adult patients with advanced NSCLC lacking EGFR, ALK, and ROS1 alterations, regardless of PD-L1 status [202]. The combination of nivolumab and ipilimumab has been FDA-approved for the first-line treatment of metastatic/recurrent NSCLC patients expressing PD-L1 in 1% or more of tumor cells as determined by an approved test and lacking EGFR and ALK genomic alterations, and as a first-line therapy in combination with two cycles of platinum-doublet chemotherapy for metastatic/recurrent NSCLC patients lacking EGFR and ALK genomic alterations [233]. Atezolizumab has been FDA-approved as a front-line therapy in combination with bevacizumab, paclitaxel, and carboplatin or paclitaxel protein-bound and carboplatin for the treatment of non-squamous NSCLC patients lacking EGFR and ALK alterations [602, 601]. Durvalumab in combination with tremelimumab and platinum-based chemotherapy has been FDA-approved for adult patients with metastatic NSCLC without sensitizing EGFR mutation or ALK aberrations. Nivolumab has been FDA-approved for the treatment of metastatic NSCLC following progression on or after platinum-based chemotherapy; additionally, nivolumab plus platinum-doublet chemotherapy has been FDA-approved for adult patients with resectable NSCLC in the neoadjuvant setting [61, 57, 300]. Atezolizumab monotherapy has been approved by the FDA-approved as a first-line therapy for NSCLC patients lacking EGFR and ALK alterations and with PD-L1 expression in 50% or more of tumor cells or in 10% or more of tumor-infiltrating immune cells, as adjuvant treatment following complete resection and platinum-based chemotherapy for adult NSCLC patients lacking EGFR and ALK alterations and with PD-L1 expression on 1% or more of tumor, and for the treatment of metastatic NSCLC following progression on or after platinum-based chemotherapy and an approved targeted therapy for those patients harboring an EGFR or ALK alteration [278, 155]. Durvalumab has been FDA-approved as a consolidation therapy in patients with unresectable stage 3 NSCLC who have not progressed following chemoradiation [17].

Drug resistance: None.

Approved Drugs: Pembrolizumab.

Phase 3: The Phase 3 Checkmate 026 study of nivolumab vs chemotherapy in 541 squamous or non-squamous stage IV or recurrent NSCLC patients having PD-L1 expression of 1% or more has reported a higher response rate to nivolumab and longer progression-free survival in the group of patients with a high tumor mutational burden (47% and 9.7 months) than in those with a low tumor mutational burden (28% and 5.8 months); patients with both high mutational burden and high PD-L1 expression had a higher response rate than those with either factor alone, although the study was not powered for this analysis [77]. Results from a portion of the Phase 3 CheckMate 227 trial testing nivolumab plus ipilimumab to chemotherapy in NSCLC patients harboring a high tumor mutational burden, defined as at least 10 mutations per Mb, has reported a significantly higher progression-free survival of 7.2 months with nivolumab plus ipilimumab as compared with 5.5 months with chemotherapy. The clinical benefit of nivolumab plus ipilimumab over chemotherapy was also reported to be independent of PD-L1 expression levels [231]. A double-blind randomized Phase 3 study (KEYNOTE-407) of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in 559 untreated, metastatic, squamous cell NSCLC patients has reported median overall and progression-free survival of 15.9 and 6.4 months with pembrolizumab and 11.3 and 4.8 months with placebo, respectively; PD-L1 expression level did not impact survival benefit and grade 3 or higher adverse events were reported in 69.8% and 68.2% of pembrolizumab- and placebo-treated patients [505]. Phase 3 studies of pembrolizumab alone (KEYNOTE-042) or in combination with pemetrexed and a platinum-based drug (KEYNOTE-189) compared with chemotherapy as a first-line therapy in NSCLC patients lacking sensitizing EGFR and ALK mutations have reported a longer overall survival (OS) in patients treated with pembrolizumab than in those treated with chemotherapy, with one study reporting OS in patients with a PD-L1 tumor proportion score of 1%

Biomarkers (2)

or greater, 50% or greater, and 20% or greater of 20.0 vs 12.2, 17.7 vs 13.0, and 16.7 vs 12.1 months in those treated with pembrolizumab vs chemotherapy [180, 441]. A Phase 2/3 study of pembrolizumab versus docetaxel in 1034 previously treated PD-L1-positive NSCLC patients (KEYNOTE-010) has reported significantly longer overall survival with pembrolizumab, as well as significantly increased progression-free survival in patients with at least 50% of tumor cells expressing PD-L1; in addition, fewer grade 3-5 treatment-related adverse events were seen with pembrolizumab [236]. Interim analysis of a Phase 3 trial (PEARLS /KEYNOTE-091) of pembrolizumab vs placebo as adjuvant treatment in 1177 patients with completely resected NSCLC reported median disease-free survival (DFS) of 53.6 and 42.0 months in the pembrolizumab and placebo arms, respectively; median DFS was not reached in either arm for patients with a PD-L1 TPS score of 50% or higher. Grade 3 or higher adverse events were reported in 34% (198/580) and 26% (150/581) of patients in the pembrolizumab and placebo arms [470]. The randomized double-blind Phase 3 KEYNOTE-671 study of perioperative pembrolizumab or placebo in combination with cisplatin-based chemotherapy followed by adjuvant pembrolizumab or placebo in 797 early-stage NSCLC patients has reported 24-month event-free survival rate of 62.4% and 40.6%, 24-month overall survival rate of 80.9% and 77.6%, major pathological response rate of 30.2% and 11.0%, and pathological complete response rate of 18.1% and 4.0% in the pembrolizumab and placebo arms, respectively [661]. The Phase 3 EMPOWER-Lung 1 study of cemiplimab compared with platinum-doublet chemotherapy in NSCLC patients expressing PD-L1 in 50% or more of tumor cells has reported a median progression-free survival rate of 8.2 months with cemiplimab and 5.7 months with chemotherapy; median overall survival was not reached in the cemiplimab group and was 14.2 months in the chemotherapy group [574]. Preliminary results from the Phase 3 EMPOWER-Lung 3 study of first-line chemotherapy with either cemiplimab or placebo in 466 patients with NSCLC lacking actionable mutations reported overall response rates of 43.3% and 22.7%, as well as median overall survival of 21.9 and 13.0 months and median progression-free survival of 8.2 and 5.0 in the cemiplimab and placebo arms, respectively. Grade 3 or higher adverse events were reported in 43.6% and 31.4% of patients in the cemiplimab and placebo arms. A Phase 3 trial of cemiplimab combined with chemotherapy versus chemotherapy alone in 466 patients with advanced NSCLC lacking EGFR, ALK and ROS1 alterations has reported a median overall survival of 21.9 months in the cemiplimab plus chemotherapy arm compared with 13.0 months in the placebo plus chemotherapy arm. Grade 3 or higher adverse events were reported in 43.6% (136/312) and 31.4% (48/153) of evaluable patients in the cemiplimab plus chemotherapy and placebo plus chemotherapy arms, respectively [202]. A Phase 3 randomized trial (CheckMate 227) of nivolumab plus ipilimumab as a first-line treatment for patients with stage 4 or recurrent NSCLC, has reported a median overall survival of 17.1 months with nivolumab plus ipilimumab and 14.9 months with chemotherapy, and two-year overall survival rates of 40.0% and 32.8%, respectively, for patients with PD-L1 positivity of at least 1%. The study also reported a benefit with the combination treatment for patients with less than 1% of PD-L1 expression, with a median overall survival of 17.2 months with nivolumab plus ipilimumab and 12.2 months with chemotherapy. Grade 3 or 4 treatment-related adverse events were reported in 32.8% of patients receiving nivolumab plus ipilimumab and in 36.0% of patients receiving chemotherapy [233]. The Phase 3 Lung-MAP S1400I study of nivolumab plus ipilimumab vs nivolumab in 252 advanced immunotherapy-naïve lung squamous cell carcinoma patients was closed for futility at interim analysis; median overall survival and investigator-assessed progression-free survival were not significantly different between groups (10 months and 3.8 months for ipilimumab/nivolumab, and 11 months and 2.9 months for nivolumab, respectively). Response rates were 18% for ipilimumab/nivolumab, and 17% for nivolumab. Treatment discontinuation due to toxicities occurred in 25% of patients treated with ipilimumab/nivolumab and 15% of patients treated with nivolumab alone [194]. The Phase 3 CheckMate 9LA study of nivolumab plus ipilimumab in combination with two cycles of platinum-doublet chemotherapy as compared with four cycles of chemotherapy alone in 719 patients with advanced NSCLC without EGFR/ALK alterations has reported significantly improved median overall survival in the combination arm (15.6 versus 10.9 months) across PD-L1 expression and histology subgroups as well as grade 3/4 treatment-related adverse events in 47% and 38% and treatment-related deaths in seven and six patients in the combination and chemotherapy arms, respectively [504]. A Phase 3 study (IMpower150) of atezolizumab with bevacizumab, carboplatin, and paclitaxel (ABCP) as compared with BCP alone in patients with nonsquamous NSCLC either harboring or lacking EGFR or ALK alterations has reported significantly improved median progression-free and overall survival in all atezolizumab-treated groups, including those lacking EGFR and ALK alterations [601, 602]. The Phase 3 MYSTIC trial of durvalumab with or without tremelimumab versus platinum-based doublet chemotherapy in 1118 immunotherapy- or chemotherapy-naïve NSCLC patients without EGFR sensitizing mutation or ALK rearrangement has reported that for 488 patients with tumor cell PD-L1 expression of at least 25%, the median overall survival was 16.3 months in the durvalumab alone arm compared with 11.9 months for the durvalumab plus tremelimumab arm and 12.9 months for the chemotherapy arm. Median progression-free survival was 3.9 and 5.4 months following durvalumab plus tremelimumab or chemotherapy, respectively. Grade 3-4 adverse events were reported in 14.9%, 22.9% and 33.8% of patients treated with durvalumab alone, durvalumab plus tremelimumab, or chemotherapy, respectively [540]. The Phase 3 POSEIDON study of first-line durvalumab in combination with tremelimumab and chemotherapy (arm 1) as compared with durvalumab plus chemotherapy (arm 2) or chemotherapy alone (arm 3) in 973 metastatic NSCLC patients without EGFR/ALK alterations has reported significant improvements in 24-month overall survival rates in arm 1 as compared with arm 3, regardless of KRAS, STK11 and KEAP1 mutation status. The Phase 3 CheckMate 017 study comparing nivolumab with docetaxel in previously treated metastatic lung SCC patients has reported superior overall survival with nivolumab (9.2 months) compared with docetaxel (6.0 months) [61]. The Phase 3 CheckMate 057 trial of

Biomarkers (2)

nivolumab versus docetaxel in advanced non-squamous cell NSCLC patients has reported a superior median overall survival of 12.2 months with nivolumab, as compared with 9.4 months with docetaxel; at 12 months and 18 months, the overall survival rates with nivolumab were 51% and 39%, respectively, as compared with 39% and 23% with docetaxel, respectively [57]. An analysis of the Phase 3 CheckMate 017 and 057 trials of nivolumab versus docetaxel in NSCLC has reported a five-year pooled overall survival rate of 13.4% and 2.6% and a five-year progression-free survival rate of 8.0% and 0% in patients treated with nivolumab or docetaxel, respectively; at follow-up between 3-5 years, treatment-related adverse events were reported in 25.8% (8/31) of patients treated with nivolumab [56]. The Phase 3 CheckMate 816 study of nivolumab plus platinum-doublet chemotherapy as compared with chemotherapy alone in 358 patients with resectable NSCLC without EGFR /ALK alterations has reported pathological complete response in 24.0% and 2.2%, median event-free survival of 31.6 and 20.8 months, and grade 3/4 treatment-related adverse events in 33.5% and 36.9% of patients in the nivolumab plus chemotherapy and chemotherapy alone arms, respectively [167]. Two studies (OAK and POPLAR) comparing atezolizumab with docetaxel in locally advanced or metastatic NSCLC patients following failure on platinum therapy have, combined, examined 1137 NSCLC patients and report a median overall survival of 13.3 months in the OAK study and 12.6 months in POPLAR with atezolizumab compared with 9.8 and 9.7 months with docetaxel, respectively; while both studies report a greater benefit in patients expressing PD-L1, response was also seen in those lacking PD-L1 expression [421, 179, 155, 679]. The Phase 3 IMpower131 study of atezolizumab plus carboplatin and paclitaxel (Arm A), atezolizumab plus carboplatin and nab-paclitaxel (Arm B), or carboplatin plus nab-paclitaxel (Arm C) as first-line therapy in 1021 advanced squamous NSCLC patients has reported a median overall survival of 14.2 months and 13.5 months in Arms B and C respectively, with treatment-related grade 3/4 adverse events observed in 68.0% and 57.5%, and treatment-related serious adverse events in 21.0% and 10.5% of these patients [278]. The Phase 3 IMpower110 study of first-line atezolizumab versus chemotherapy in 572 patients with ALK and EGFR wild-type NSCLC reported significantly improved median overall survival in the atezolizumab arm as compared with chemotherapy in 205 patients with PD-L1 expression on 50% or greater of tumor cells or on 10% or greater of tumor-infiltrating immune cells. Grade 3 or higher adverse events were reported in 30.1% and 52.5% of patients, respectively [237]. The Phase 3 IMpower010 study of adjuvant atezolizumab as compared with best supportive care after adjuvant chemotherapy in 990 patients with stage 1b-3a resected NSCLC has reported significantly increased median disease-free survival in the atezolizumab arm in the subset of patients with PD-L1 expression in more than 1% of tumor cells and in the subset of all randomized stage 2-3a stage patients. Grade 3-4 and grade 5 adverse events were reported in 11% (53/495) and 1% (4/495) of atezolizumab-treated patients [157]. The Phase 3 IMpower132 study of atezolizumab in combination with carboplatin or cisplatin and pemetrexed as compared with chemotherapy alone, followed by maintenance therapy with atezolizumab plus pemetrexed or pemetrexed alone, respectively, in 578 chemotherapy-naive stage 4 non-squamous NSCLC patients without EGFR/ALK alterations has reported significantly higher median progression-free survival (7.6 versus 5.2 months), but not median overall survival (18.1 versus 13.6 months) in the atezolizumab arm. Grade 3/4 treatment-related adverse events (TRAE) were observed in 54.6% and 40.1% and grade 5 TRAE in 3.8% and 2.9% of patients in the atezolizumab and chemotherapy arms, respectively [468]. Updated analyses of the Phase 3 PACIFIC study of durvalumab or placebo following chemoradiotherapy in 709 patients with stage 3 NSCLC has reported five-year overall survival rates of 42.9% and 33.4%, and five-year progression-free survival rates of 33.1% and 19%, following durvalumab or placebo, respectively. An earlier update noted that median time to distant metastasis or death was significantly longer following durvalumab as compared with placebo (28.3 vs 16.2 months). Grade 3-4 adverse events were reported in 30.5% and 26.1% of patients, and treatment discontinuation due to adverse events was reported in 15.4% and 9.8%, respectively [17, 16, 208, 151, 614]. A randomized Phase 3 study (JAVELIN Lung 200) of avelumab versus docetaxel in 792 patients with advanced NSCLC progressing after platinum-based chemotherapy has reported no significant difference in the median overall survival in PD-L1-positive patients receiving avelumab compared with docetaxel (11.4 vs 10.3 months). Treatment-related adverse events were reported in 64% (251/393) of avelumab-treated patients as compared with 86% (313/365) of docetaxel-treated patients [34]. However, increased two-year overall survival rates were observed in the avelumab arm in patients with PD-L1 expression in more than 50% of cells (36.4% versus 17.7%) and PD-L1 expression in more than 80% of cells (40.2% versus 20.3%) [496].

Biomarkers (2)

Phase 2: The Phase 2 KEYNOTE-158 study of pembrolizumab in advanced solid tumor patients has reported an overall objective response in 29% (30/102) of patients with high tumor mutational burden (TMB-H), defined as ten or more mutations per megabase [409]. The Phase 2 CheckMate 568 study of nivolumab plus ipilimumab as a first-line therapy in advanced/metastatic NSCLC patients has reported an overall response rate (ORR) of 30%, and 41% in those with PD-L1 expression in 1% or more of tumor cells; ORR was also greater in patients with increasing TMB score, plateauing at 10 mutations/Mb. Progression-free survival was additionally reported to be longer in patients with a TMB of 10 mutations/Mb or higher than in those with fewer than 10 mutations/Mb [529]. A Phase 2 nonrandomized controlled study (TELMA) of atezolizumab plus bevacizumab as first-line treatment in 38 advanced nonsquamous NSCLC patients with high tumor mutation burden (TMB) and no EGFR, ALK, STK11, MDM2, or ROS1 alterations has reported median progression-free survival (PFS) of 13 months, median overall survival (OS) of not reached, and an objective response rate (ORR) of 42.1%, with partial response in 16 patients and stable disease in 14 patients. Most treatment-related adverse events were grade 1 or 2. No association between PD-L1 levels and ORR, PFS, or OS was observed [516]. A Phase 2 nonrandomized trial (GFPC 06-2018) in 149 previously treated, non-squamous advanced NSCLC patients, with tumors harboring EGFR mutation or ALK/ROS1 fusion, has reported objective response rates of 58.2% and 46.5% in the atezolizumab, platinum, pemetrexed, bevacizumab (APPB) arm and the atezolizumab, platinum, pemetrexed (APP) arm, respectively. Median progression-free survival of 7.3 and 7.2 months, and overall survival of 17.2 and 16.8 months were reported in the APPB arm and the APP arm, respectively. Grade 3-4 adverse events were reported in 69.1% of patients in the APPB arm and 51.4% of patients in the APP arm [71]. The Phase 2 PERLA trial of dostarlimab plus chemotherapy (n=121) versus pembrolizumab plus chemotherapy (n=122) in patients with first-line metastatic non-squamous NSCLC with known PD-L1 status and without EGFR, ALK, or other actionable alterations reported that the overall response rate was 46% for dostarlimab plus chemotherapy, with complete and partial responses reported in two and 52 patients, respectively, compared with 37% for patients treated with pembrolizumab plus chemotherapy, with complete and partial responses reported in three and 42 patients, respectively. A Phase 1/2 study of avelumab in combination with pepinemab in advanced NSCLC patients following progression on prior systemic therapy and/or immunotherapies has reported partial response rate of 24% and disease control rate of 81% in 21 immuno-naive patients and partial response rate of 7% and disease control rate of 59% in 29 patients with progression following immunotherapies [576].

Phase 1: A retrospective analysis of 25 NSCLC patients with EGFR mutation treated with nivolumab has reported a significantly higher tumor mutational burden in responders than in non-responders [222]. A safety and efficacy analysis of the Phase 1 GARNET trial of dostarlimab in 67 patients with advanced/recurrent NSCLC (cohort E) reported a confirmed immune-related objective response rate of 27% (18/67), including two complete and 16 partial responses. Median duration of response was 11.6 months, and responses were reported in 2/24 patients with PD-L1 tumor proportion score (TPS) <1%, 4/20 patients with PD-L1 TPS 1-49%, and in 2/5 patients with PD-L1 TPS ≥50%. Grade 3 or higher treatment-related adverse events (TRAE) were reported in 12% (8/67) of patients (with fatigue being the most common), while immune-related TRAE of any grade were reported in 28% (19/67) of patients [442].

Preclinical: N/A: Preclinical data are not presented when higher level data are available.

Biomarkers (2)

Microsatellite Status: MS-stable

Biomarker: MS-stable
Classification: Tier 3
Assessment: Uncertain Significance

Treatment options
6 Trials

Biomarker summary: MSI stable or low instability has been detected in this case.

Clinical relevance: Tumors exhibiting microsatellite instability (MSI) have a higher mutational burden than microsatellite stable (MSS) tumors and express higher levels of immune checkpoint receptors [306, 7, 246, 646, 385]. Thus, checkpoint inhibitors, several of which have received agency approval for certain indications, may be clinically relevant for tumors exhibiting MSI [434, 647, 494, 639, 338, 667]. In fact, pembrolizumab has been FDA-approved as a second or later line of therapy for the treatment of pediatric and adult solid tumors with high microsatellite instability (MSI-H) or that are deficient in mismatch repair (dMMR), as a front-line therapy for colorectal carcinoma patients with MSI-H or dMMR, and endometrial carcinoma patients with MSI-H or dMMR, who are not eligible for curative surgery or radiation, following progression on systemic therapy [346, 338]. In addition, nivolumab and the combination of nivolumab and ipilimumab have been FDA-approved for the treatment of MSI-H or dMMR colorectal carcinoma [483, 484]. In contrast, the combination of lenvatinib and pembrolizumab has been FDA-approved for the treatment of advanced endometrial cancer patients with unresectable tumors lacking markers for MSI-H and dMMR following disease progression on systemic therapy [401].

Disease summary: MSI has been reported in less than 1% of non-small cell lung carcinoma (NSCLC) samples analyzed in scientific studies [606, 573, 124, 674, 475, 634]. MSI has been associated with squamous cell histology and loss of Mlh1 protein expression in studies of non-small cell lung carcinoma (NSCLC) [320, 87].

Molecular function: Low microsatellite instability (MSI-L) is defined as having alterations in the length of nucleotide repeats in one or fewer out of five microsatellites tested (or in less than 30% of tested loci if a larger panel is tested). Microsatellite stable (MSS) tumors are defined as having no alterations in the length of nucleotide repeats in any of five microsatellites tested. MSI-L tumors have been reported to be similar to MSS tumors [230, 52, 347].

Incidence: MSI has been reported in less than 1% of non-small cell lung carcinoma (NSCLC) samples analyzed in scientific studies [606, 573, 124, 674, 475, 634].

Role in disease: MSI is associated with the loss or dysfunction of DNA mismatch repair (MMR) proteins that are required for correcting errors that occur during DNA replication or recombination; germline mutations in genes encoding MMR proteins are associated with Lynch syndrome, a hereditary cancer-predisposition syndrome also known as hereditary nonpolyposis colorectal cancer (HNPCC) [393, 110, 230]. Tumors exhibiting MSI have been reported to have increased numbers of tumor-infiltrating lymphocytes (TILs) and a significantly higher mutational burden than microsatellite stable (MSS) tumors [306, 7, 246, 646]. MSI has been associated with squamous cell histology, tobacco consumption, and loss of Mlh1 protein expression in studies of non-small cell lung carcinoma (NSCLC) [320, 87, 674, 80, 79, 688].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: MSI has been reported to correlate with high levels of immune checkpoint gene expression in some types of cancer, including colorectal and endometrial carcinoma, and with clinical response to checkpoint inhibition in colorectal carcinoma; thus, immunotherapies may be relevant in tumors exhibiting MSI [385, 338, 246]. Checkpoint inhibitors are currently in clinical development, several of which have received agency approval for certain indications [434, 667]. The combination of lenvatinib and pembrolizumab has been FDA-approved for the treatment of advanced endometrial cancer patients with unresectable tumors lacking markers for MSI-H and dMMR following disease progression on systemic therapy [401].

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

Variant of strong clinical significance (1)

KRAS G12C

Gene: KRAS
Exon: 2
Nucleotide:
NM_004985.5:
g.25245351C>A
c.34G>T
Amino Acid: p.G12C
Allelic Fraction: 40.0% (of 500 reads)
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
2 Sensitive
4 Resistance
10 Trials

Biomarker summary: KRAS-G12C (NM_004985) is an activating mutation.

Clinical relevance: KRAS encodes the signaling protein K-Ras, a member of the Ras family; activating KRAS alterations may result in activation of downstream signaling pathways, including the Raf/MEK/ERK pathway [519, 458]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant [281, 2, 405, 256, 373, 240, 51, 734]. Other clinical approaches are also under investigation in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors [192, 400, 551, 318, 638, 99]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically [367, 261, 480, 501]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy [1, 280]. In addition, the combination of adagrasib with cetuximab has been reported to provide clinical benefit in colorectal carcinoma patients with KRAS G12C mutation and has been granted “breakthrough” designation by the FDA for accelerated review [701].

Disease summary: KRAS mutation, particularly G12C, has been associated with smoking in NSCLC patients; additionally, KRAS mutations have also been associated with adenocarcinoma histology and are generally mutually exclusive with EGFR mutations and ALK rearrangements [113, 351, 382, 381, 117, 176, 339, 92, 488, 588, 104, 728]. While some studies have suggested that KRAS mutation status may predict lack of response to the Egfr inhibitors erlotinib and gefitinib in NSCLC patients, a retrospective study suggests that there is no significant difference in response to Egfr tyrosine kinase inhibitors among NSCLC patients with KRAS wild-type and KRAS mutation, when EGFR mutation status is included in the analysis [408, 389, 625, 491, 552]. In addition, case studies of NSCLC patients harboring ALK mutations or EML4-ALK fusions have reported the emergence of KRAS activating alterations upon acquired resistance to crizotinib, demonstrating a role for KRAS in crizotinib resistance in NSCLC [26, 135, 550, 78, 55].

Molecular function: The KRAS G12C mutation lies within the first "G box" domain of the K-Ras protein, one of several conserved regions responsible for GTP binding and hydrolysis; disruption of this region creates a protein that is defective for GTP hydrolysis and is therefore constitutively active [423, 444, 111]. KRAS G12C has been reported as the most common KRAS mutation in non-small cell lung carcinoma (NSCLC), and has been shown to have transforming ability and lead to activation of MEK and ERK signaling; in contrast to KRAS G12D, the G12C mutation has been reported not to result in activation of Akt [183, 160, 254, 628].

Incidence: KRAS mutations have been reported in 17% (7590/43749) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). KRAS mutations have been reported in 19-36% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). KRAS mutations have been reported in 10-30% of NSCLC samples analyzed in scientific studies, with mutations reported more frequently in adenocarcinoma as compared with squamous cell carcinoma samples [381, 587, 572, 176, 33, 279, 248].

Role in disease: The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers [153, 156, 218]. KRAS mutation, particularly G12C, has been associated with smoking in NSCLC patients; additionally, KRAS mutations have also been associated with adenocarcinoma histology and are generally mutually exclusive with EGFR mutations and ALK rearrangements [113, 351, 382, 381, 117, 279, 176, 339, 92, 488, 588, 104, 728]. Studies analyzing KRAS mutation association with PD-L1 expression in NSCLC patients have reported mixed results; while two older large meta-analyses have reported no association or negative association, smaller studies and one newer large meta-analysis have reported a positive association [273, 279, 586, 336, 303, 307, 116, 511, 333, 6, 728, 707, 721, 352, 11, 565, 406].

Diagnostic significance: Unknown.

Prognostic significance: Numerous studies have reported KRAS mutations to be associated with poor survival in NSCLC patients [283, 724, 599, 650, 438, 174, 163].

Drug sensitivity: Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf/MEK/ERK and PI3K/Akt/mTOR [711, 65]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant [281, 518, 114, 2, 405, 256, 373, 240, 51, 734]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors [192, 400, 551, 318, 638, 99]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically [261, 480, 501, 454]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test,

following treatment with at least one prior systemic therapy [1, 280]. Studies analyzing KRAS mutation association with clinical benefit of PD-1/PD-L1 inhibitors to NSCLC patients have reported mixed results, with some studies reporting no significant association while other studies have reported that KRAS mutation correlated with improved clinical outcome of NSCLC patients treated with PD-1/PD-L1 inhibitors [334, 292, 697, 264, 336].

Drug resistance: In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies [154, 145, 365, 526, 75, 125, 142, 653, 356]. While some studies have suggested that KRAS mutation status may predict lack of response to the Egfr inhibitors erlotinib and gefitinib in NSCLC patients, a retrospective study suggests that there is no significant difference in response to Egfr tyrosine kinase inhibitors among NSCLC patients with KRAS wild-type and KRAS mutation, when EGFR mutation status is included in the analysis [408, 389, 625, 491, 552]. Case studies of NSCLC patients harboring ALK mutations or EML4-ALK fusions have reported the emergence of KRAS alterations upon acquired resistance to crizotinib, demonstrating a role for KRAS in crizotinib resistance in NSCLC [26, 135, 550, 78, 55].

Approved Drugs: Sotorasib Adagrasib.

Phase 3: A Phase 3 trial (SELECT-1) of second-line selumetinib plus docetaxel or placebo plus docetaxel in patients with KRAS-mutant NSCLC reported progression-free survival of 3.9 and 2.8 months, and median overall survival of 8.7 and 7.9 months, respectively, with lack of significant differences; grade 3 or higher adverse events were reported in 67% and 45% of patients in the selumetinib and placebo arms, respectively [281]. The Phase 3 CodeBreak 200 trial of sotorasib versus docetaxel in 345 KRAS G12C-mutated NSCLC patients who had progressed following treatment with platinum-based chemotherapy and checkpoint inhibitors reported greater median progression-free survival in the sotorasib arm as compared with the docetaxel arm (5.6 vs. 4.5 months). In addition, fewer serious treatment-related adverse events were observed in the sotorasib treatment arm (10.7% [18/169]) as compared with the docetaxel arm (22.5% [34/151]) [739].

Phase 2: A randomized Phase 2 trial in 129 KRAS-mutant NSCLC patients treated with either trametinib or docetaxel reported a similar response rate and progression-free survival between the two regimens. In the trametinib cohort, 12% (10/86) of patients achieved a partial response, with a 12-week median progression-free survival, and in the docetaxel cohort, 12% (5/43) of patients achieved a partial response, with a median progression-free survival of 11 weeks [51]. A Phase 2 study in 55 heavily pretreated KRAS-mutant non-small cell lung cancer patients treated with the focal adhesion kinase inhibitor defactinib has reported that 28% (15 /55) of patients met the 12-week progression-free endpoint, with partial response in one patient and a median progression-free survival of 45 days; treatment was reported to be well-tolerated, with grade 1 or 2 fatigue, gastrointestinal events, and increased bilirubin cited as the most common adverse events [192]. The Phase 2 CodeBreaK 100 study of sotorasib in 126 advanced NSCLC patients harboring KRAS G12C previously treated with standard therapies has reported a confirmed objective response rate of 37.1% in 124 evaluable patients, with complete responses and partial responses reported in 3.2% (4/124) and 33.9% (42/124) of the patients, respectively. In addition, the disease control rate was 80.6% (100/124), and median progression-free and overall survival were 6.8 months and 12.5 months, respectively. Grade 3 and 4 adverse events were reported in 19.8% (25/126) and 1/126 patients, respectively [598]. The Phase 1/2 KRYSTAL-1 study of adagrasib in KRAS G12C solid tumor patients, including 79 NSCLC patients has reported partial responses in 45% (23/51) of evaluable NSCLC patients and an overall response rate of 64% in NSCLC patients with tumors harboring KRAS G12C and STK11 mutations. The most common treatment-related adverse events included nausea, diarrhea, vomiting. A Phase 2 study of the MEK inhibitor mirdametinib (PD0325901) in previously treated NSCLC patients did not report any objective responses, but did report stable disease of up to ten months in 20.6% (7/34) of patients [225]. A randomized Phase 2 trial of the combination of selumetinib and erlotinib in 79 NSCLC patients reported no significant improvement in objective response rate or progression-free survival with combination treatment as compared with either monotherapy; in addition, KRAS mutational status had no impact on treatment outcomes [82]. A randomized Phase 2 trial of selumetinib or placebo with docetaxel in 212 NSCLC patients reported that selumetinib was not associated with significant improvement in progression-free or overall survival in the total population or in KRAS-wild-type patients; a higher objective response rate (ORR) of 33% was reported with selumetinib treatment as compared with an ORR of 14% with placebo in the total population [609]. A Phase 2 trial of platinum chemotherapy/pemetrexed with or without selumetinib in patients with NSCLC reported objective response rates of 35%, 62%, and 24% in patients receiving chemotherapy with intermittent (Arm A; n=20) or continuous (Arm B; n=21) selumetinib, or chemotherapy alone (Arm C; n=21), respectively. Progression-free survival was 7.5, 6.7, and 4.0 months, respectively. Addition of selumetinib resulted in increased gastrointestinal or skin-related adverse events [429].

Phase 1: A Phase 1b study of binimetinib combined with buparlisib in patients with solid tumors reported partial responses in 1/13 EGFR-mutant and 0/11 KRAS-mutant NSCLC cases. Continuous dosing was associated with significant toxicities in the wider trial, with 36.0% (32/89) of patients discontinuing treatment due to adverse events [32]. A Phase 1 study of binimetinib combined with carboplatin plus pemetrexed chemotherapy in 12 evaluable patients with KRAS/NRAS/EGFR mutation-positive non-squamous NSCLC reported an investigator-assessed objective response rate (ORR) of 50% and a disease control rate of 83.3%.

Variant of strong clinical significance (1)

Further, the ORR for KRAS/NRAS mutation-positive patients was 62.5% compared with 25% for patients with tumors harboring wild-type KRAS/NRAS. The median progression-free survival was 4.5 months and grade 3/4 treatment related adverse events were reported in eight patients, with dose limiting toxicities reported in two patients [173]. A Phase 1 study of binimetinib combined with cisplatin plus pemetrexed chemotherapy in 18 patients with KRAS mutation-positive advanced NSCLC reported clinical responses in 3/9 evaluable patients. In addition, the median progression-free and overall survival were 5.7 and 6.5 months, respectively [170]. A Phase 1/1b trial of binimetinib with erlotinib in NSCLC patients harboring KRAS or EGFR mutation reported partial response and stable disease in 21% (9/43) and 23% (10/43) of patients, respectively. Median progression-free and overall survival were 5.5 and 17.0 months, respectively, and adverse events were predominantly grades 1 and 2. A Phase 1 study of ulixertinib in 135 patients with advanced solid tumors, including an expansion study in 108 patients with melanoma having NRAS or BRAF mutation, colorectal and non-small cell lung cancer having BRAF mutation, or solid tumors having BRAF or MAP2K1/2 mutation, has reported partial responses in 11% (3/27) of patients in the escalation phase, in 11% (9/83) of evaluable patients in the expansion phase, and in 25% (3/12) of BRAF-mutant NSCLC cases; no drug-related deaths were reported, but 32% of 108 patients required dose reductions [623]. A Phase 1 study of mirdametinib (PD-0325901) with dacomitinib in 41 KRAS-mutant solid tumor patients (27 colorectal, 11 non-small cell lung, and three pancreatic carcinoma) has reported tumor regression in eight patients but toxicities rash (85%), diarrhea (88%) and nausea (63%), precluded long-term treatment [741]. A Phase 1 multicenter trial of refametinib in 53 patients with advanced cancer reported suppression of ERK phosphorylation and stable disease in 11 patients for four or more courses of therapy [676]. A Phase 1 study of refametinib in combination with sorafenib in 54 patients with advanced solid tumors reported, in 38 non-hepatocellular carcinoma (non-HCC) patients evaluable for response, a partial response lasting approximately one year in a colorectal carcinoma patient and stable disease in 63.2% (24/38) of patients; treatment was associated with a reduction in ERK activation in five of six non-HCC biopsied cases [3]. The Phase 1 SELECT-3 trial with first-line selumetinib and platinum-doublet chemotherapy in 55 advanced NSCLC patients has reported confirmed and unconfirmed partial responses in 20% (11/55) and 16% (9/55) of patients, respectively, and stable disease in 38% (21/55) of patients. Selumetinib with pemetrexed regimens were reported to be well-tolerated while selumetinib plus gemcitabine regimens were reported to be non-tolerated or were discontinued [209]. A Phase 1b solid tumor study of cobimetinib with atezolizumab reported confirmed responses in 17.8% (5/28) of patients with NSCLC [232]. Phase 1 studies of trametinib in combination with docetaxel, pemetrexed, or buparlisib have reported stable disease in 46%, 59%, and 53% of NSCLC patients, respectively; KRAS mutation status was not found to significantly affect these rates [39].

Preclinical: A preclinical study of cobimetinib in NSCLC xenograft models reported that tumor growth inhibition did not correlate with KRAS status; pictilisib increased the efficacy of cobimetinib in an NSCLC xenograft model harboring a KRAS mutation [241]. A preclinical study of refametinib in murine NSCLC models reported stable tumor volume as compared with significantly increased tumor volume in control-treated animals [398].

Variants of potential clinical significance (4)

ATR I774fs*5

Gene: ATR
Exon: 10
Nucleotide: NM_001184.4: g.142555898delT c.2320delA
Amino Acid: p.I774fs*5
Allelic Fraction: 14.0% (of 156 reads)
Classification: Tier 2C
Assessment: Pathogenic

Treatment options
10 Trials

Biomarker summary: ATR-I774fs*5 (NM_001184) is an inactivating mutation.

Clinical relevance: ATR encodes the protein ataxia telangiectasia and Rad3 related (Atr), which phosphorylates the tumor suppressor Brca1 and several cell cycle checkpoint proteins, including Chk1; it plays a key role in maintaining genome integrity via regulation of DNA repair and replication [214, 363]. Based on a synthetic lethal approach and preclinical evidence, Atr-deficient tumors may be sensitive to poly-ADP ribose polymerase (PARP) inhibitors [508, 506]. In addition, activation of Atr has been reported in some tumor types, perhaps as compensation for lack of Atm [495].

Disease summary: Haploinsufficiency of ATR combined with oncogenic mutations, including KRAS G12D and TP53 heterozygosity, has been reported to be associated with an increased incidence of lung adenocarcinoma in mice [199]. ATR mutations have been significantly associated with pleural invasion in a study of 98 lung adenocarcinoma patients [731].

Molecular function: This ATR frameshift alteration is expected to effectively truncate the 2644-amino acid Atr protein, resulting in the loss of a portion or all of the protein kinase domain as well as the entire FATC domain (UniProt). Due to the loss of several critical functional domains, this mutation is predicted to be inactivating.

Incidence: ATR mutations have been reported in 4.4% (197/4494) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). ATR mutations have been reported in 0.0-4.5% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). ATR mutations have been reported in 8-20% of NSCLC patients [390, 731, 377].

Variants of potential clinical significance (4)

Role in disease: Early in the progression of cancer, the Atr/Atm-regulated DNA damage response network is proposed to be activated to prevent genomic instability and malignant conversion [36]. Atr inactivation, either by mutation or decreased expression, is associated with increased microsatellite instability (MSI) and chromosome instability (CIN) in a variety of tumor types, including colorectal and endometrial cancers [263, 655, 437]. In addition, activation of Atr has been reported in some tumor types, perhaps as compensation for lack of Atm [561, 495]. Haploinsufficiency of ATR combined with oncogenic mutations, including KRAS G12D and TP53 heterozygosity, has been reported to be associated with an increased incidence of lung adenocarcinoma in mice [199]. ATR mutations have been significantly associated with pleural invasion in a study of 98 lung adenocarcinoma patients [731].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Based on a synthetic lethal approach and preclinical evidence, ATR-deficient tumors may be sensitive to PARP inhibitors, which are currently being tested in clinical trials for patients with solid tumors [508, 506, 422]. In addition, Atr inhibition has been reported to result in increased sensitivity to DNA damaging chemotherapy and ionizing radiation [675, 91, 568, 253, 583, 215].

Drug resistance: None.

Approved Drugs: None.

Phase 3: A Phase 3 study of first-line carboplatin and paclitaxel in combination with veliparib or placebo in 970 patients with advanced squamous cell lung cancer, including 57% of current smokers, has reported a similar median overall survival (OS) in smokers of 11.9 and 11.1 months with veliparib and placebo, respectively; median OS was 12.2 and 11.2 months with veliparib and placebo in the overall population, with a median progression-free survival of 5.6 months per arm [523]. A Phase 3 trial of chemotherapy with or without veliparib in 595 former or current smokers with advanced non-squamous NSCLC reported median overall survival of 11.2 and 9.2 months in the veliparib and control arms, respectively, within a cohort of patients positive for a 52-gene expression signature (LP52). The median overall survival for the overall population was 12.1 months in both arms. The primary endpoint was not met [206].

Phase 2: A Phase 2 study of talazoparib in 47 previously treated lung squamous cell carcinoma patients harboring a deleterious alteration in a homologous recombination repair gene was closed for futility, with objective response rate of 11% and disease control rate of 51% in the overall population. Median progression-free and overall survival were determined to be 2.5 months and 5.7 months, respectively [485]. The Phase 2 JASPER study of niraparib in combination with pembrolizumab in 38 patients with advanced NSCLC and no known EGFR-sensitizing mutations and/or ALK or ROS1 translocations has reported an overall response rate of 56.3% and 20%, two and zero complete responses, seven and four partial responses, a median duration of response of 19.7 and 9.4 months, a median progression-free survival of 8.4 and 4.2 months, a median overall survival of not reached and 7.7 months, and grade 3 or higher adverse events in 88.2% and 85.7% of patients with PD-L1 tumor proportion scores of at least 50% or under 50%, respectively [525]. A Phase 2 study of gefitinib with or without olaparib in 182 non-small cell lung carcinoma patients has reported that the addition of olaparib did not provide clinical benefit over gefitinib monotherapy. The median progression-free survival (PFS) was 10.9 months in the gefitinib arm compared with 12.8 months in the gefitinib plus olaparib arm [184]. A Phase 2 trial (PIN) of olaparib maintenance or placebo monotherapy with induction chemotherapy in 70 patients with advanced NSCLC reported no significant difference in progression-free survival in the olaparib arm as compared with placebo-treated patients [158]. Preliminary results from a Phase 2 trial of olaparib with durvalumab in patients with advanced NSCLC reported partial response and stable disease in 2/15 and 7/15 patients, respectively. Median progression-free survival was 3.2 months, and was significantly improved in patients with EGFR wild-type NSCLC as compared with EGFR-mutant NSCLC. Grade 3 or higher adverse events were reported in 4/15 patients. A Phase 2 study of rucaparib in 59 eligible advanced non-small cell lung cancer patients with homologous recombination deficiency, as determined based on high genomic loss of heterozygosity and/or a deleterious BRCA1/2 mutation, was closed due to futility in both the squamous and non-squamous cohorts at scheduled interim analysis. An overall response rate of 7% and a median progression-free survival of 3.2 months were reported in the full study; anemia (22%), lymphopenia (8%), fatigue (8%), and transaminitis (5%) were reported to be the most frequent grade 3 or higher adverse events.

Phase 1: A Phase 1 study of olaparib in combination with loco-regional radiotherapy with or without cisplatin in 28 non-small cell lung cancer patients with loco-regional or oligometastatic disease has reported that the treatment was intolerable due to esophageal, hematological, and severe pulmonary toxicity [738].

Variants of potential clinical significance (4)

Preclinical: A preclinical study has reported that talazoparib combined with gemcitabine synergistically inhibited NSCLC cell line growth in vitro and further inhibited tumor growth in a xenograft model in vivo, as compared with either agent alone [271]. A preclinical study reported that niraparib enhanced the sensitivity of NSCLC cell lines to radiation [64]. A preclinical study has reported niraparib treatment to activate alpha- and gamma-interferon pathways in NSCLC cells; the combination of niraparib and anti-PD1 therapy in immunocompetent cells exhibited synergistic antitumor activity in both BRCA-proficient and BRCA-deficient NSCLC tumors [672].

KEAP1 R272C

Gene: KEAP1
Exon: 3
Nucleotide:
NM_203500.2:
g.10492088G>A
c.814C>T
Amino Acid: p.R272C
Allelic Fraction: 64.0% (of 275 reads)
Classification: Tier 2C
Assessment: Likely Pathogenic

Treatment options
1 Trial

Biomarker summary: KEAP1-R272C (NM_012289) is an inactivating mutation.

Clinical relevance: KEAP1 encodes the Kelch-like ECH-associated protein 1, Keap1, an adaptor protein of the Cul3/Rbx1 E3 ubiquitin ligase complex that has been shown to target several proteins for proteasomal degradation, including the NF-E2-related factor (Nrf) family of transcription factors [619, 717, 718, 340, 204]. KEAP1/NFE2L2 alterations have been reported to increase sensitivity to the glutaminase inhibitor telaglenastat (CB-839) in lung adenocarcinoma preclinical models and this effect was enhanced by the presence of STK11 mutations. Clinical trials of telaglenastat are underway in KEAP1/NFE2L2 mutant cancers [177, 545].

Disease summary: Low Keap1 expression has been associated with lymph node metastasis in NSCLC in one study, and alterations in KEAP1, including mutation, loss of heterozygosity, and promoter methylation, have been correlated with NSCLC disease progression [103, 446]. In preclinical studies, loss or mutation of KEAP1 has been reported to result in increased Nrf2 activity and promote NSCLC cell proliferation, migration, and tumor metastasis [103, 266, 590, 545]. Studies have reported that high Nrf2 expression or NFE2L2/KEAP1 mutations in NSCLC are associated with resistance to chemotherapy or radiotherapy [49, 666, 579, 708, 201]. Some studies have also reported that mutations in NFE2L2 or KEAP1 are associated with poor response to immunotherapy in NSCLC patients; however, one retrospective study has reported that the addition of durvalumab following concurrent chemoradiation improved local regional control to a similar extent in patients with mutations in NFE2L2 or KEAP1 as compared with wild-type patients [716, 733, 579, 536, 682].

Molecular function: KEAP1 R272C is a missense alteration located in the BTB and C-terminal Kelch (BACK) domain of the Keap1 protein (UniProt). KEAP1 R272C has been reported to impair the ability of Keap1 to repress Nrf2 as compared with wild-type Keap1 in a cell model [473].

Incidence: KEAP1 mutations have been reported in 14% (703/5107) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). KEAP1 mutations have been reported in 0.0-22% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). In the scientific literature, KEAP1 mutations have been reported in 11-17% of NSCLC samples [559, 733, 660, 168].

Role in disease: KEAP1 mutation and loss of Keap1 function have been reported in numerous tumor types and correlated with activation of Nrf2 and tumorigenesis [31, 590, 585, 722, 486, 188]. Low Keap1 expression has been associated with lymph node metastasis in NSCLC in one study, and alterations in KEAP1, including mutation, loss of heterozygosity, and promoter methylation, have been correlated with NSCLC disease progression [103, 446]. In preclinical studies, loss or mutation of KEAP1 has been reported to result in increased Nrf2 activity and promote NSCLC cell proliferation, migration, and tumor metastasis [103, 266, 590, 545].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: KEAP1/NFE2L2 alterations have been reported to increase sensitivity to the glutaminase inhibitor telaglenastat (CB-839) in lung adenocarcinoma preclinical models and this effect was enhanced by the presence of STK11 mutations. Clinical trials of telaglenastat are underway in KEAP1/NFE2L2 mutant cancers [177, 545].

Drug resistance: Mutations leading to loss of Keap1 function and disruption of the Keap1-Nrf2 complex, resulting in constitutively active Nrf2, have been reported to result in resistance to chemotherapeutics [631, 683, 590, 722, 585]. Studies have reported that high Nrf2 expression or NFE2L2/KEAP1 mutations in NSCLC are associated with resistance to chemotherapy or radiotherapy [49, 666, 579, 708, 201]. Some studies have also reported that mutations in NFE2L2 or KEAP1 are associated with poor response to immunotherapy in NSCLC patients; however, one retrospective study has reported that the addition of durvalumab following concurrent chemoradiation improved local regional control to a similar extent in patients with mutations in NFE2L2 or KEAP1 as compared with wild-type patients [716, 733, 579, 536, 682].

Approved Drugs: None.

Variants of potential clinical significance (4)

Phase 3: None.

Phase 2: None.

Phase 1: A Phase 1 study of the glutaminase inhibitor telaglenastat (CB-839) in 25 evaluable patients with advanced solid tumors reported an acceptable safety profile and stable disease in 28% (7/25) of patients, including in 50% (2/4) of NSCLC patients.

Preclinical: One preclinical study has described a small molecule inhibitor of Nrf2, ML385, that selectively inhibited the growth of KEAP1-mutant NSCLC cells and acted synergistically with several chemotherapeutic compounds, including doxorubicin, taxol and platinum-based drugs [591].

STK11 S283fs*3

Gene: STK11
Exon: 6
Nucleotide: NM_000455.5: g.1221321_1221324delCCCG c.843_846delCCCG
Amino Acid: p.S283fs*3
Allelic Fraction: 20.0% (of 500 reads)
Classification: Tier 2C
Assessment: Likely Pathogenic

Treatment options
2 Trials

Biomarker summary: STK11-S283fs*3 (NM_000455) is an inactivating mutation.

Clinical relevance: STK11 encodes a serine/threonine-protein kinase also known as Lkb1 (UniProt) [293, 265]. Inactivation of Lkb1 has been reported to activate the mTOR pathway and tumors harboring STK11 alterations have been reported to be sensitive to mTOR inhibitors [580, 139, 493, 313]. Everolimus and temsirolimus have been approved by the FDA, EMA, and PMDA for use in some indications, and clinical trials of these and other mTOR inhibitors are currently underway in multiple tumor types [445, 251].

Disease summary: STK11 mutations have been significantly associated with negative PD-L1 expression in non-small cell lung carcinoma (NSCLC) cases [492, 567, 332, 597, 554, 662, 565]. STK11 loss in conjunction with activated KRAS has been demonstrated to drive lung tumorigenesis, and inhibition of downstream targets of Lkb1 has been shown to be effective in inhibiting tumor growth and prolonging survival in mouse models of Lkb1-deficient non-small cell lung carcinoma (NSCLC) [268, 411, 81, 575]. Further, one study analyzing 154 KRAS-mutated NSCLC cases reported that loss of Lkb1 expression was significantly associated with a larger number of metastatic sites at diagnosis, an increased incidence of extra-thoracic and brain metastases, and positive smoking status [73]. STK11 mutations have been significantly associated with lack of response to PD-1 /PD-L1 inhibitors in non-small cell lung carcinoma (NSCLC) patients in several studies; however, one study has reported no significant association between STK11 or KEAP1 mutation and response to pembrolizumab [299, 128, 492].

Molecular function: The alteration reported in this tumor is expected to effectively truncate the 433-amino acid Lkb1 protein within or prior to the protein kinase domain (UniProt). Loss of all or part of the protein kinase domain is expected to render Lkb1 catalytically inactive. Such a truncation would result in loss of a region of C-terminal residues, the phosphorylation of which was reported to be required for Lkb1 activity and nucleocytoplasmic export [732, 23]. In addition, this alteration is likely to elicit nonsense-mediated decay [366, 513, 455, 538]. Therefore, this alteration is predicted to lead to a loss of protein function.

Incidence: STK11 mutations have been reported in 8.7% (746/8559) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). STK11 mutations have been reported in 6.3-22% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). In addition, STK11 mutations have been detected in 9-21% of NSCLC cases in the scientific literature, with one meta-analysis reporting STK11 mutation in 9.2% (134/1463) of all cases, including in 10.4% (121/1160) of lung adenocarcinoma and 4.3% (13/303) of lung squamous cell carcinoma cases [587, 492, 126, 622, 417].

Role in disease: Because the STK11 gene encodes a tumor suppressor, deletion or inactivation of this gene results in reduced cell cycle control [580]. Inactivating germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder associated with increased susceptibility to various cancers [265, 621, 534, 742]. STK11 mutations have been significantly associated with negative PD-L1 expression in non-small cell lung carcinoma (NSCLC) cases [492, 567, 332, 597, 554, 662, 565]. STK11 loss in conjunction with activated KRAS has been demonstrated to drive lung tumorigenesis, and inhibition of downstream targets of Lkb1 has been shown to be effective in inhibiting tumor growth and prolonging survival in mouse models of Lkb1-deficient NSCLC [268, 411, 81, 575]. Further, one study analyzing 154 KRAS-mutated NSCLC cases reported that loss of Lkb1 expression was significantly associated with a larger number of metastatic sites at diagnosis, an increased incidence of extra-thoracic and brain metastases, and positive smoking status [73].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Variants of potential clinical significance (4)

Drug sensitivity: Inactivation of Lkb1 has been reported to activate the mTOR pathway and tumors harboring STK11 alterations have been reported to be sensitive to mTOR inhibitors [580, 139, 493, 313]. Everolimus and temsirolimus have been approved by the FDA, EMA, and PMDA for use in some indications, and clinical trials of these and other mTOR inhibitors are currently underway in multiple tumor types [445, 251]. Several other therapeutic strategies targeting Lkb1 inactivation are being explored in preclinical studies [81, 671, 383, 539].

Drug resistance: STK11 mutations have been significantly associated with lack of response to PD-1/PD-L1 inhibitors in non-small cell lung carcinoma (NSCLC) patients in several studies; however, one study has reported no significant association between STK11 or KEAP1 mutation and response to pembrolizumab [299, 128, 492]. STK11 mutation co-occurring with KEAP1 or KRAS mutation has also been associated with poor response to PD-1/PD-L1 inhibitors in NSCLC patients [492, 581, 597]. In addition, studies have also reported that NSCLC patients with tumors harboring triple STK11/KRAS/TP53 mutations exhibited lack of response and poor treatment outcome to PD-1/PD-L1 inhibitors [328, 502]. STK11 mutations or loss have also been significantly associated with lack of response to radiotherapy or chemotherapy in NSCLC patients, with one study reporting that combined STK11/KRAS mutations, compared with STK11/TP53 mutations, correlated with poorer response to radiotherapy [30, 595]. However, case studies have reported clinical responses in NSCLC patients with tumors harboring STK11 mutation alone or in combination with KRAS or TP53 mutation to PD-1 /PD-L1 inhibitors or in combination with NFE2L2 mutation to chemotherapy, with one study also reporting response to radiotherapy in a STK11 mutation-positive NSCLC patient who experienced hyperprogressive disease on pembrolizumab therapy [169, 136, 168, 450, 617].

Approved Drugs: None.

Phase 3: None.

Phase 2: A Phase 2 clinical trial of temsirolimus as a single agent in previously untreated NSCLC patients reported clinical benefit in 35% of patients, including partial response in 8% (4/52) and stable disease in 27% (14/52) of patients; however, grade 3 or 4 adverse events were reported in 63% (33/52) of patients and the study did not meet its pre-specified primary objective for efficacy. In this study, clinical response was not correlated with expression of p70S6K, phospho-p70S6K, Akt, phospho-Akt, or Pten [535]. A Phase 2 trial of everolimus as a monotherapy in 85 NSCLC patients reported an overall response rate of 5% and an overall disease control rate of 47%; 25% of patients experienced pneumonitis as an adverse effect. In this study, expression of p-Akt was predictive of decreased progression-free survival [610]. A Phase 2 study of everolimus in combination with docetaxel as second or third-line therapy in unselected NSCLC patients reported partial response and stable disease in 7% (2/28) and 54% (15/28) of patients, respectively, and a six-month progression-free survival rate of 5% [524].

Phase 1: N/A: Lower level clinical data are not presented when higher level data are available.

Preclinical: Treatment of Lkb1-deficient NSCLC cells with the Src inhibitor dasatinib or a Fak inhibitor reduced the invasive properties of the cells, and treatment of mice bearing STK11-deficient and KRAS-mutant tumors with a combination of dasatinib, mTOR-PI3K inhibitor (BEZ235) and MEK inhibitor (selumetinib) resulted in synergistic reduction of lung tumors [81].

SMARCA4 W764R

Gene: SMARCA4
Exon: 17
Nucleotide:
NM_001128844.3:
g.11012964T>A
c.2290T>A
Amino Acid: p.W764R
Allelic Fraction: 46.0% (of 120 reads)
Classification: Tier 2D
Assessment: Uncertain Significance

Biomarker summary: SMARCA4-W764R (NM_001128844) is an inactivating mutation.

Clinical relevance: Mutations in genes encoding components of the SWI/SNF chromatin remodeling complex, including SMARCA4, have been reported to be ubiquitous across various types of cancer, with a high fraction of these mutations considered to be deleterious (frameshift, nonsense, rearrangement, splice-site, and missense-damaging) [577]. The role of SMARCA4/Brg1 in cancer is unclear. Increased expression has been correlated with advanced stage in prostate cancer and melanoma; however, inactivation of Brg1 has been reported in several other types of cancer [624, 557, 544, 121, 531]. There are currently no therapies that target mutant SMARCA4 or loss of functional Brg1. However, the development of small molecule inhibitors targeting Brg1 and other components of the chromatin remodeling complex is an area of active investigation [685]. In addition, tumors with inactivating SMARCA4 mutations may have increased sensitivity to Ezh2 and Cdk4/6 inhibitors, which are currently in preclinical and clinical development [699, 698, 298, 161].

Disease summary: Loss of Brg1 activity, in cooperation with loss of TP53 and KRAS activation, has been reported to promote tumor development in NSCLC preclinical models, and SMARCA4-mutant NSCLC tumors and cell lines have been observed to exhibit increased oxidative phosphorylation [479, 605, 372].

Variants of potential clinical significance (4)

Molecular function: SMARCA4 W764R is a missense alteration located outside of several characterized domains of the Brg1 protein (UniProt). SMARCA4 W764R has been reported to impair dexamethasone-induced transcriptional activity and impair the inhibition of colony formation as compared with wild-type Brg1 in a cell model [544].

Incidence: SMARCA4 mutations have been reported in 0.0-13% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). SMARCA4 mutations have been reported in 8.5% (410 /4810) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). In addition, SMARCA4 mutations have been reported in 7-9% of NSCLC samples analyzed in the scientific literature [19, 329, 120].

Role in disease: The role of SMARCA4/Brg1 in cancer is unclear. Increased expression has been correlated with advanced stage in prostate cancer and melanoma; however, inactivation of Brg1 has been reported in several other types of cancer [624, 557, 544, 121, 531]. Loss of Brg1 activity, in cooperation with loss of TP53 and KRAS activation, has been reported to promote tumor development in NSCLC preclinical models, and SMARCA4-mutant NSCLC tumors and cell lines have been observed to exhibit increased oxidative phosphorylation [479, 605, 372].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: There are currently no therapies that target mutant SMARCA4 or loss of functional Brg1. However, the development of small molecule inhibitors targeting Brg1 and other components of the chromatin remodeling complex is an area of active investigation [685, 669]. Preclinical studies suggest that Brg1 and Ezh2 are reciprocally expressed in several cancer cell lines, and NSCLC cells and xenografts harboring SMARCA4 inactivating mutations treated with Ezh2 inhibitors exhibited enhanced sensitivity to etoposide [298, 161]. Ezh2 inhibitors are currently in clinical trials. In addition, SMARCA4 deficiency has been reported to increase sensitivity to Cdk4/6 inhibitors in preclinical cancer models [699, 698]. One study analyzing 133 NSCLC samples reported that reduced SMARCA4 mRNA expression was associated with increased sensitivity to platinum-based chemotherapy [43]. Depletion of SMARCA4 has been reported to sensitize lung cancer cells to ATR inhibition in cell lines and xenograft models [213].

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: A Phase 2 study (Lung-MAP sub-study SWOG S1400C) of palbociclib monotherapy in previously treated lung squamous cell carcinoma patients harboring cell cycle gene alterations reported partial response and stable disease in 6.3% (2/32) and 37.5% (12/32) of patients, respectively, as well as median progression-free survival of 1.7 months and median overall survival of 7.1 months [146]. A Phase 2 study of 16 evaluable NSCLC patients negative for p16INK4a expression and treated with palbociclib reported stable disease ranging from 16-42 weeks in 50% (8/16) of patients; no responses were reported. In the Phase 2 TAPUR trial, NSCLC patients harboring CDKN2A mutations and no RB1 mutations were assigned to receive palbociclib, with partial response and stable disease observed in 1/29 and 20.7% (6/29) of patients, respectively. Median progression-free and overall survival were 8.1 and 21.6 weeks, respectively, and 37.9% (11/29) of patients had at least one Grade 3/4 adverse event that was possibly treatment-related, with cytopenia being the most commonly noted [4].

Phase 1: A Phase 1 study of advanced NSCLC patients treated with abemaciclib reported a disease control rate (DCR) of 37% in KRAS wild-type patients (n=19) and a DCR of 54% in KRAS-mutant patients (n=26); the median duration of stable disease and progression-free survival were 5.6 months and 2.1 months, respectively. A Phase 1 study of ribociclib plus ceritinib in 27 non-small cell lung cancer patients with ALK-rearrangements has reported overall response rate of 37.0% and 50.0%, and median progression-free survival of 21.5 and 24.8 months in the overall cohort and in patients treated at the Phase 2 recommended dose, respectively [563]. A Phase 1 study of tazemetostat in 43 patients with solid tumors and 21 patients with B-cell non-Hodgkin lymphoma (NHL) has reported response rates of 5% (2/43) and 38% (8/21) in solid tumor and NHL patients, respectively. Grade 4 thrombocytopenia was the only dose-limiting toxicity observed [258].

Preclinical: Palbociclib treatment has been reported to confer sensitivity to gefitinib in preclinical NSCLC cell line and tumor models. In addition, clinical remission has been observed in a NSCLC patient with gefitinib resistance following treatment with gefitinib and palbociclib [379]. A preclinical study has reported that treatment of NSCLC cell lines with tazemetostat and dasatinib resulted in synergistic inhibition of cell proliferation [386].

Variants of biological significance (7)

CHD2 K1245fs*4

Gene: CHD2
Exon: 29
Nucleotide: NM_001271.4: g.92997086delA c.3734delA
Amino Acid: p.K1245fs*4
Allelic Fraction: 12.0% (of 482 reads)
Classification: Tier 3
Assessment: Likely Pathogenic

Biomarker summary: CHD2-K1245fs*4 (NM_001271) is predicted to be an inactivating mutation.

Clinical relevance: CHD2 encodes the Chromodomain-helicase-DNA binding protein 2, Chd2, which is an ATPase that binds to target gene promoters and regulates chromatin remodeling [378]. CHD2 alterations or inactivation have been associated with solid tumors and leukemia, as well as with lymphoid tumor formation and defective DNA damage repair in mouse models, suggesting a tumor suppressor role [542, 522, 453, 310]. There are currently no available therapies targeting CHD2 inactivating alterations.

Disease summary: CHD2 mutations have been reported in 3.7% (77/2105) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). CHD2 mutations have been reported in 0.0-6.3% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). CHD2 in Non-small cell lung carcinoma (NSCLC) has not been a significant subject of study reported in the scientific literature (PubMed, May 2021). Please note: This gene has not been recently reviewed in the context of this specific cancer type by N-of-One.

Molecular function: The CHD2 frameshift alteration reported here is predicted to lead to a loss of function due to nonsense-mediated decay [366, 513, 455, 538].

Incidence: CHD2 mutations have been reported in 3.7% (77/2105) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). CHD2 mutations have been reported in 0.0-6.3% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023).

Role in disease: Inactivating CHD2 alterations have been identified in chronic lymphocytic leukemia, suggesting that Chd2 plays a tumor suppressor role [542]. Studies have reported that CHD2 heterozygous mutant mice were highly susceptible to spontaneous lymphoid tumor formation and that CHD2 mutant cells showed defective DNA damage repair induced by ionizing and ultraviolet radiation [522, 453]. Please note: This gene has not been recently reviewed in the context of this specific cancer type by N-of-One.

Diagnostic significance: Please note: This gene has not been recently reviewed in the context of this specific cancer type by N-of-One.

Prognostic significance: Please note: This gene has not been recently reviewed in the context of this specific cancer type by N-of-One.

Drug sensitivity: There are currently no available therapies targeting CHD2 inactivating alterations. Please note: This gene has not been recently reviewed in the context of this specific cancer type by N-of-One.

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

EPHA3 G766E

Gene: EPHA3
Exon: 13
Nucleotide: NM_005233.6: g.89431310G>A c.2297G>A
Amino Acid: p.G766E
Allelic Fraction: 34.0% (of 137 reads)
Classification: Tier 3
Assessment: Likely Pathogenic

Biomarker summary: EPHA3-G766E (NM_005233) is an inactivating mutation.

Clinical relevance: Eph family receptors are believed to play several roles in cancer, including adhesion, invasion, migration, growth and metastasis, and Eph receptors have therefore been proposed as cancer therapy targets [9, 693]. Preclinical studies in cell lines with EPHA3 amplification and EphA3 overexpression have reported inhibition of EphA3 expression and activity with the tyrosine kinase inhibitor dasatinib [611]. EPHA3 may have either an oncogenic or a tumor suppressive role, dependent on the tumor type and the context [301, 735, 370, 29]. Therefore, the use of EphA3 inhibition must be carefully considered in each context. In addition, in the case of an inactivating mutation, therapeutic approaches targeting EphA3 activity are not expected to be relevant.

Disease summary: One study reported that ectopic EphA3 expression induced apoptosis and inhibited cell growth in three NSCLC cell lines and reduced tumor growth in two xenograft models of NSCLC [735]. Another study reported that homozygous loss of EPHA3 did not accelerate tumorigenesis in KRAS-mutant or TP53-

Variants of biological significance (7)

deficient lung adenocarcinoma mouse models [331]. EPHA3 mutation has been significantly associated with high tumor mutational burden in one analysis of 499 NSCLC cases [520].

Molecular function: EPHA3 G766E is a missense alteration within the kinase domain of the EphA3 protein (UniProt). EPHA3 G766E has been reported in cancer and preclinical studies have indicated that EPHA3 G766E is associated with decreased kinase activity, tyrosine phosphorylation, and cell surface localization as compared with wild-type protein [370, 735, 330].

Incidence: EPHA3 mutations have been reported in 7.7% (343/4435) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). EPHA3 mutations have been reported in 0.0-10% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). Literature studies have reported EPHA3 mutations in 1-6% of non-small cell lung carcinoma samples overall, and specifically in 6% (11/188) and 1/40 lung adenocarcinoma and in none of 44 squamous cell lung carcinoma samples [520, 133, 123, 521].

Role in disease: Eph family receptors are believed to play several roles in cancer, including adhesion, invasion, migration, growth, and metastasis; Eph receptors have therefore been proposed as cancer therapy targets [9, 693]. The role of ephrins and their receptors in cancer is complex in that both upregulation and downregulation of expression has been documented, and multiple mechanisms of signaling are present for each complex [500, 152]. One study reported that ectopic EphA3 expression induced apoptosis and inhibited cell growth in three NSCLC cell lines and reduced tumor growth in two xenograft models of NSCLC [735]. Another study reported that homozygous loss of EPHA3 did not accelerate tumorigenesis in KRAS-mutant or TP53-deficient lung adenocarcinoma mouse models [331]. EPHA3 mutation has been significantly associated with high tumor mutational burden in one analysis of 499 NSCLC cases [520].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Preclinical studies in cell lines with EPHA3 amplification and EphA3 overexpression have reported inhibition of EphA3 expression and activity with the tyrosine kinase inhibitor dasatinib [611]. EPHA3 may have either an oncogenic or a tumor suppressive role, dependent on the tumor type and the context [301, 735, 370, 29]. Therefore, the use of EphA3 inhibition must be carefully considered in each context. In addition, in the case of an inactivating mutation, therapeutic approaches targeting EphA3 activity are not expected to be relevant.

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

KMT2C K2797fs*26

Gene: KMT2C
Exon: 38
Nucleotide:
NM_170606.3:
g.152177063delT
c.8390delA
Amino Acid: p.K2797fs*26
Allelic Fraction: 7.16% (of 335 reads)
Classification: Tier 3
Assessment: Pathogenic

Biomarker summary: KMT2C-K2797fs (NM_170606) is an inactivating mutation.

Clinical relevance: KMT2C, which is more commonly known as MLL3 (mixed-lineage leukemia 3), encodes a histone methyltransferase enzyme involved in the regulation of gene transcription [15, 344]. There are no therapies specifically targeting MLL3-deficient tumors. Preclinical work suggests that inactivation of another member of the MLL family, MLL, may predict sensitivity to HDAC inhibitors, although it is unclear if this approach would be relevant for MLL3 aberrations [620]. In addition, a preclinical study in acute myeloid leukemia (AML) with MLL3 suppression reported inhibition of cell and tumor growth with a bromodomain and extra-terminal (BET) inhibitor, suggesting another possible therapeutic approach for MLL3 alterations [93]. However, further research is needed to clarify the relevance of this therapeutic approach.

Disease summary: KMT2C mutation, alone or in combination with TP53 mutation, has been significantly associated with higher tumor mutational burden while KMT2C and TP53 co-mutation has been significantly associated with PD-L1 positivity in one analysis of 637 NSCLC cases [391]. KMT2C mutation, or KMT2C mutation combined with TP53 mutation has been associated with increased clinical benefit from immune checkpoint inhibitor therapy NSCLC studies [584, 376, 210, 668].

Variants of biological significance (7)

Molecular function: The alteration reported here is expected to result in the loss of several functional domains of the MLL-3 protein, including the S-adenosyl-L-methionine binding catalytic region and the SET domain (UniProt). Mutations resulting in the truncation of the MLL SET domain have been reported to disrupt gene regulation and to result in widespread histone methylation disturbances [643]. Therefore, this alteration is predicted to lead to a loss of protein function.

Incidence: KMT2C mutations have been reported in 11% (400/3768) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). KMT2C mutations have been reported in 0.0-16% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). In the scientific literature, KMT2C mutations have been reported in 2-17% of NSCLC cases, including 7% (2/30) and 15% (3 /20) of lung squamous cell carcinoma cases [380, 578, 27, 277, 729, 90].

Role in disease: MLL3, as part of a transcriptional coactivator complex, is a tumor suppressor involved in a number of cellular processes, including regulation of homeostasis and hormone receptor signaling [47, 15, 305]. Inactivating mutations in MLL3 and downregulation of MLL-3 protein expression have been reported in a number of tumor types and found to play a role in tumorigenesis and leukemogenesis [477, 713, 93, 694, 289, 337]. KMT2C mutation, alone or in combination with TP53 mutation, has been significantly associated with higher tumor mutational burden while KMT2C and TP53 co-mutation has been significantly associated with PD-L1 positivity in one analysis of 637 NSCLC cases [391].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: There are no therapies specifically targeting MLL3-deficient tumors. Preclinical work suggests that inactivation of another member of the MLL family, MLL, may predict sensitivity to HDAC inhibitors, although it is unclear if this approach would be relevant for MLL3 aberrations [620]. In addition, a preclinical study in acute myeloid leukemia (AML) with MLL3 suppression reported inhibition of cell and tumor growth with a bromodomain and extra-terminal (BET) inhibitor, suggesting another possible therapeutic approach for MLL3 alterations [93]. However, further research is needed to clarify the relevance of this therapeutic approach. KMT2C mutation, or KMT2C mutation combined with TP53 mutation has been associated with increased clinical benefit from immune checkpoint inhibitor therapy NSCLC studies [584, 376, 210, 668]. Depletion of KMT2C has been reported to increase sensitivity to olaparib in a NSCLC xenograft model [527].

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

LRP1B E3468*

Gene: LRP1B
Exon: 66
Nucleotide:
NM_018557.3:
g.140442516C>A
c.10402G>T
Amino Acid: p.E3468*
Allelic Fraction: 66.0% (of 311 reads)
Classification: Tier 3
Assessment: Likely Pathogenic

Biomarker summary: LRP1B-E3468* (NM_018557) is an inactivating mutation.

Clinical relevance: LRP1B encodes the low-density lipoprotein receptor-related protein 1B (Lrp1B). LRP1B is subject to frequent mutation, deletion, and silencing in cancer, and has been found to inhibit cell growth, migration, and invasion, in preclinical studies [133, 456, 514, 607]. LRP1B is a very large gene, which spans 1.9 Mb and lies within the common fragile site, FRA2F. Common fragile sites are regions of extreme genomic instability [600]. There are currently no available therapies that directly compensate for LRP1B inactivation.

Disease summary: LRP1B mutations have been associated with high tumor mutational burden, smoking, and male gender in studies of non-small cell lung carcinoma (NSCLC), and have been reported to be mutually exclusive with EGFR mutations [94, 692, 695, 578, 72, 98]. In addition, expression of Lrp1b in NSCLC cell lines has been reported to result in inhibition of proliferation, while depletion of Lrp1B resulted in increased cell proliferation [40].

Variants of biological significance (7)

Molecular function: The nonsense alteration reported here is expected to truncate the Lrp1B protein, resulting in the loss of a portion of the extracellular domain as well as the entire transmembrane helical and cytoplasmic domains (UniProt). Preclinical studies have reported that disruption of the transmembrane and cytoplasmic domains can inactivate Lrp1B [131, 375]. Therefore, this alteration is predicted to be inactivating.

Incidence: LRP1B mutations have been reported in 30% (759/2489) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). LRP1B mutations have been reported in 0.0-35% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). In addition, LRP1B mutations have been reported in 9-31% of NSCLC cases reported in the scientific literature [133, 692, 94].

Role in disease: LRP1B is located within a “common fragile site” (CFS) of human DNA, which is defined as a large region of genomic instability that spans genes commonly altered across multiple cancer types [600]. LRP1B is subject to frequent mutation, deletion and silencing in cancer, suggesting a tumor suppressor function [133, 600, 640, 607]. LRP1B has been found to play a role in inhibiting cell growth, migration, and invasion in preclinical studies [607, 465, 115, 514]. LRP1B mutations have been associated with high tumor mutational burden, smoking, and male gender in studies of non-small cell lung carcinoma (NSCLC), and have been reported to be mutually exclusive with EGFR mutations [94, 692, 695, 578, 72, 98]. In addition, expression of Lrp1b in NSCLC cell lines has been reported to result in inhibition of proliferation, while depletion of Lrp1B resulted in increased cell proliferation [40].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: There are currently no available therapies that directly compensate for LRP1B inactivation.

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

LRP1B G1801*

Gene: LRP1B
Exon: 33
Nucleotide:
NM_018557.3:
g.140776197C>A
c.5401G>T
Amino Acid: p.G1801*
Allelic Fraction: 45.0% (of 58 reads)
Classification: Tier 3
Assessment: Likely Pathogenic

Biomarker summary: LRP1B-G1801* (NM_018557) is an inactivating mutation.

Clinical relevance: LRP1B encodes the low-density lipoprotein receptor-related protein 1B (Lrp1B). LRP1B is subject to frequent mutation, deletion, and silencing in cancer, and has been found to inhibit cell growth, migration, and invasion, in preclinical studies [133, 456, 514, 607]. LRP1B is a very large gene, which spans 1.9 Mb and lies within the common fragile site, FRA2F. Common fragile sites are regions of extreme genomic instability [600]. There are currently no available therapies that directly compensate for LRP1B inactivation.

Disease summary: LRP1B mutations have been associated with high tumor mutational burden, smoking, and male gender in studies of non-small cell lung carcinoma (NSCLC), and have been reported to be mutually exclusive with EGFR mutations [94, 692, 695, 578, 72, 98]. In addition, expression of Lrp1b in NSCLC cell lines has been reported to result in inhibition of proliferation, while depletion of Lrp1B resulted in increased cell proliferation [40].

Molecular function: The nonsense alteration reported here is expected to truncate the Lrp1B protein, resulting in the loss of a portion of the extracellular domain as well as the entire transmembrane helical and cytoplasmic domains (UniProt). Preclinical studies have reported that disruption of the transmembrane and cytoplasmic domains can inactivate Lrp1B [131, 375]. Therefore, this alteration is predicted to be inactivating.

Incidence: LRP1B mutations have been reported in 30% (759/2489) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). LRP1B mutations have been reported in 0.0-35% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). In addition, LRP1B mutations have been reported in 9-31% of NSCLC cases reported in the scientific literature [133, 692, 94].

Role in disease: LRP1B is located within a “common fragile site” (CFS) of human DNA, which is defined as a large region of genomic instability that spans genes commonly altered across multiple cancer types [600].

Variants of biological significance (7)

LRP1B is subject to frequent mutation, deletion and silencing in cancer, suggesting a tumor suppressor function [133, 600, 640, 607]. LRP1B has been found to play a role in inhibiting cell growth, migration, and invasion in preclinical studies [607, 465, 115, 514]. LRP1B mutations have been associated with high tumor mutational burden, smoking, and male gender in studies of non-small cell lung carcinoma (NSCLC), and have been reported to be mutually exclusive with EGFR mutations [94, 692, 695, 578, 72, 98]. In addition, expression of Lrp1b in NSCLC cell lines has been reported to result in inhibition of proliferation, while depletion of Lrp1B resulted in increased cell proliferation [40].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: There are currently no available therapies that directly compensate for LRP1B inactivation.

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

TGFBR2 K128fs*35

Gene: TGFBR2
Exon: 3
Nucleotide: NM_003242.6: g.30650380delA c.383delA
Amino Acid: p.K128fs*35
Allelic Fraction: 15.0% (of 166 reads)
Classification: Tier 3
Assessment: Pathogenic

Biomarker summary: TGFBR2-K128fs (NM_003242) is an inactivating mutation.

Clinical relevance: TGFBR2 encodes the TGF-beta receptor type-2 protein, or TGF-beta receptor II, a transmembrane serine/threonine kinase that transduces signals from TGF-beta cytokines to regulate processes such as cellular proliferation, extracellular matrix production, angiogenesis, and immune responses [461, 364]. Inactivating TGFBR2 mutations and loss of TGF-beta receptor II expression have been identified in several types of tumors, which could confer resistance to TGF-beta-induced growth arrest [350, 413, 498, 447, 311, 260, 452, 200, 308, 341]. There are currently no targeted therapies in development or in use for patients with inactivation of TGFBR2.

Disease summary: Decreased TGFBR2 mRNA or TGF-beta receptor II expression has been correlated with poor tumor differentiation, lymph node metastases, and higher clinical stage in NSCLC cases [403, 354, 95, 54]. Loss of TGFBR2 has been reported to increase lymph node metastases and reduce survival, as compared with control mice with wild-type TGFBR2, in a KRAS-driven lung cancer mouse model [54].

Molecular function: TGFBR2 K128fs is expected to lead to a truncation of the Tgfbr2 protein at amino acid 128 of 567, resulting in the loss of the entire helical and cytoplasmic domains, including the protein kinase domain (UniProt). Therefore, this alteration is predicted to be inactivating.

Incidence: TGFBR2 mutations have been reported in 1.7% (77/4558) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). TGFBR2 mutations have been reported in 0.0-3.3% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023).

Role in disease: Germline mutations in TGFBR2 have been associated with inherited disorders such as Marfan syndrome and Loeys-Dietz syndrome [440, 720, 143, 592, 448]. Some inactivating TGFBR2 frameshift mutations have been associated with microsatellite instability and identified in several types of cancers; such mutations may confer resistance to TGF-beta-induced growth arrest [350, 413, 498, 447, 311, 260, 452]. Loss of TGF-beta receptor II protein expression has also been seen in cancer, including of the bladder, breast, and prostate, and has been reported to correlate with higher tumor grade [200, 308, 341]. Decreased TGFBR2 mRNA or TGF-beta receptor II expression has been correlated with poor tumor differentiation, lymph node metastases, and higher clinical stage in NSCLC cases [403, 354, 95, 54]. Loss of TGFBR2 has been reported to increase lymph node metastases and reduce survival, as compared with control mice with wild-type TGFBR2, in a KRAS-driven lung cancer mouse model [54].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Variants of biological significance (7)

Drug sensitivity: There are currently no targeted therapies in development or in use for patients with inactivation of TGFBR2.

Drug resistance: None.

Approved Drugs: None.

Phase 3: None.

Phase 2: None.

Phase 1: None.

Preclinical: None.

TP53 E62*

Gene: TP53
Exon: 4
Nucleotide: NM_000546.6: g.7676185C>A c.184G>T
Amino Acid: p.E62*
Allelic Fraction: 61.0% (of 165 reads)
Classification: Tier 3
Assessment: Pathogenic

Biomarker summary: TP53-E62* (NM_000546) is an inactivating mutation.

Clinical relevance: TP53 is a tumor suppressor that encodes the p53 protein; alterations in TP53 may result in a loss of p53 function, yet an increase in the expression and stability of the mutant p53 protein in the nucleus, sometimes leading to oncogenic effects, including genomic instability and excessive cell proliferation [349, 670, 315, 296, 245, 476]. 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 [570, 657, 555]. Tumors with TP53 mutations may be sensitive to the Wee1 inhibitor adavosertib (MK-1775), and clinical trials are currently underway for patients with solid tumors and hematologic malignancies [239, 63]. Aurora kinase A inhibitors are another therapeutic approach under investigation for TP53-mutated cancers [658, 362, 295, 642, 286].

Disease summary: TP53 is one of the most commonly mutated genes in lung cancer; scientific studies have reported TP53 mutations in 27-46% of non-small cell lung carcinoma (NSCLC) cases [449, 270, 635, 399]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis [89]. 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 [270, 420, 50, 312]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples [140, 565, 6, 407, 282]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients [654].

Molecular function: The nonsense alteration reported here is expected to truncate the p53 protein within the N-terminus, resulting in the loss of all of the DNA-binding domain (DBD) and tetramerization domain [275]. DBD mutations are thought to result in loss of function via the loss of transactivation of p53-dependent genes [296]. In addition, the tetramerization domain is thought to be critical to normal p53 function [287]. Therefore, this mutation is predicted to lead to a loss of function.

Incidence: TP53 mutations have been reported in 42% (5051/12103) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). TP53 mutations have been reported in 43-68% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). TP53 is one of the most commonly mutated genes in lung cancer; scientific studies have reported TP53 mutations in 27-67% of non-small cell lung carcinoma (NSCLC) cases [449, 270, 635, 559, 324, 248, 399]. Specifically, TP53 mutations have been reported in 74% (8887/12079) of KRAS wild-type and in 37-55% of KRAS mutant NSCLC samples [279].

Role in disease: Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers [67]. 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 [402, 616, 562]. 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 [670, 315, 296, 245, 476]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis [89]. 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 [270, 420, 50, 312]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples [140, 565, 6, 407, 282]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients [654].

Variants of biological significance (7)

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: 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 [570, 657, 555]. 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 [395, 239, 63]. 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 [658, 362, 295, 642, 211, 416].

Drug resistance: Mutations in TP53 may increase resistance to ionizing radiation therapy [149, 439].

Approved Drugs: None.

Phase 3: None.

Phase 2: A Phase 2 study of radical surgery with or without recombinant adenovirus human p53 (rAd-p53) gene therapy in NSCLC patients reported that the addition of rAd-p53 resulted in a post-surgical recurrence rate of 29.3% (24/82) as compared with 45.7% (37/81) in patients who received surgery alone. In addition, the three-year progression-free (PFS) and overall survival (OS) rates for patients receiving rAd-p53 were 71.9% and 88.4%, respectively, which were both significantly higher as compared with the three-year PFS and OS rates in patients who received surgery alone (46.9% and 67.0%, respectively) [129].

Phase 1: N/A: Lower level clinical data are not presented when higher level data are available.

Preclinical: N/A: Preclinical data are not presented when higher level data are available.

Variants of uncertain significance (31)

Gene	Variant	Allelic fraction	Classification
AR	c.204_239delGCAGCAGCAGCAGCAGCAG CAGCAGCAGCAGCAGCA p.Q69_Q80del	21.0% (of 193 reads)	Tier 3, Uncertain Significance
ARID2	c.4988A>G p.Y1663C	60.0% (of 386 reads)	Tier 3, Uncertain Significance
ATR	c.6394T>G p.Y2132D	100.0% (of 296 reads)	Tier 3, Uncertain Significance
ATR	c.6005C>G p.A2002G	35.0% (of 231 reads)	Tier 3, Uncertain Significance
E2F3	c.550G>T p.G184C	63.0% (of 186 reads)	Tier 3, Uncertain Significance
EPHA5	c.571C>G p.R191G	36.0% (of 586 reads)	Tier 3, Uncertain Significance
ETV1	c.115T>A p.L39M	24.0% (of 462 reads)	Tier 3, Uncertain Significance
FGF14	c.655C>A p.P219T	50.0% (of 313 reads)	Tier 3, Uncertain Significance
FGF3	c.668C>G p.S223C	62.0% (of 422 reads)	Tier 3, Uncertain Significance
GATA2	c.49C>A p.L17M	27.0% (of 272 reads)	Tier 3, Uncertain Significance
GNAS	c.342C>A p.F114L	80.0% (of 567 reads)	Tier 3, Uncertain Significance
GRM3	c.827T>A p.M276K	43.0% (of 1020 reads)	Tier 3, Uncertain Significance
IKZF1	c.1297C>A p.R433S	47.0% (of 474 reads)	Tier 3, Uncertain Significance
IL7R	c.1217T>G p.L406R	29.0% (of 915 reads)	Tier 3, Uncertain Significance
KDR	c.5A>G p.Q2R	98.0% (of 231 reads)	Tier 3, Uncertain Significance
KEL	c.136A>T p.R46W	80.0% (of 345 reads)	Tier 3, Uncertain Significance
LATS2	c.119G>A p.G40E	48.0% (of 461 reads)	Tier 3, Uncertain Significance
LRP1B	c.150G>T p.W50C	31.0% (of 281 reads)	Tier 3, Uncertain Significance
NOTCH2	c.3G>A p.M1I	29.0% (of 392 reads)	Tier 3, Uncertain Significance
NTRK3	c.713T>A p.L238Q	65.0% (of 685 reads)	Tier 3, Uncertain Significance
PGR	c.307G>T p.D103Y	58.0% (of 529 reads)	Tier 3, Uncertain Significance
PLK2	c.232G>A p.G78S	51.0% (of 863 reads)	Tier 3, Uncertain Significance
PREX2	c.1818_1819delATinsGC p. G606_L607delinsGL	100.0% (of 121 reads)	Tier 3, Uncertain Significance
PRKDC	c.496delA p.I166fs*6	17.0% (of 124 reads)	Tier 3, Uncertain Significance
RAD51C	c.790G>A p.G264S	77.0% (of 386 reads)	Tier 3, Uncertain Significance
RARA	c.472G>A p.A158T	26.0% (of 356 reads)	Tier 3, Uncertain Significance
REL	c.10+3G>T	52.0% (of 527 reads)	Tier 3, Uncertain Significance

Variants of uncertain significance (31)

Gene	Variant	Allelic fraction	Classification
SDHA	c.469T>C p.Y157H	100.0% (of 388 reads)	Tier 3, Uncertain Significance
SETD2	c.5666T>C p.M1889T	100.0% (of 224 reads)	Tier 3, Uncertain Significance
SPTA1	c.2077G>A p.E693K	66.0% (of 200 reads)	Tier 3, Uncertain Significance
SPTA1	c.1186G>T p.D396Y	26.0% (of 324 reads)	Tier 3, Uncertain Significance

REPORT INFORMATION

Genes tested

Methods and limitations

Genomic DNA and RNA was extracted from the specimen, and an amplicon library with Unique Molecular Indices (UMI) was generated using the QIAseq PanCancer Multiomodal Panel. Variants were identified using the *Perform QIAseq Multimodal Analysis with TMB and MSI* workflow in CLC Genomics Workbench software.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools: QIAGEN Clinical Insight Interpret (9.1.1.20230406), Ingenuity Knowledge Base (H-release), CADD (v1.6), NCBI Gene (2022-02-22), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2022-02-22), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2023-04-16 07:41:41.298), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (H-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Dec 16 09:34), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 37), CentoMD (5.3), dbVar (2021_04), OMIM (April 13, 2022), gnomAD (GRCh37 (hg19) 2.1.1, GRCh38 (hg38) 3.1.2), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2023-04-25), DGV (2016-05-15), COSMIC (v95), HGMD (2023.1), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 154, GRCh38 154), SIFT4G (2016-02-23)

Disclaimer
The QIAseq PanCancer Multimodal Panel is for molecular biology applications. This product is not intended for the diagnosis, prevention or treatment of a disease.

Clinical significance of variants based on AMP / ASCO / CAP guidelines*

Strong clinical significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential clinical significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain clinical significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

*Adapted from PMID:27993330 jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf

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