ORDERING PHYSICIAN	**PATIENT**	**SPECIMEN**
Dr.	Name :	Site :
Registration No:	DOB :	Type :
Institution:	Patient ID :	ID :
Inst. No:	Age/Sex :	Collection date:
Tel No:	Ethnicity :	Sectioning date:
		Received date:
		Tumour cellularity:
		MDx Accession No:

Disease type Non-small cell lung carcinoma, Metastatic adenocarcinoma, Stage 4

Relevant history/ findings/ treatment provided by ordering physician
1st line targeted therapy [TAGRISSO] received.

RESULTS

GENOMIC FINDINGS RELEVANT TO THIS CANCER					POSSIBLE TREATMENT OPTIONS
Gene	**Alteration type**	**Genomic alteration**	**Allele fraction**	**Tier**[Refer to Table 1]	**Treatment**
EGFR	p.L833V (Exon 21)	c.2497T>G	44%	I	Afatinib Osimertinib
EGFR	p.H835L (Exon 21)	c.2504A>T	44%	I	**SEE NOTE 1, 2, 3, 4**

NOTE 1: The two EGFR mutations (L833V + H835L) are in cis position, meaning both mutations happened on one copy of the gene, while the other copy is not mutated.

NOTE 2: EGFR L833V/H835L (in cis) is an uncommon but activating EGFR mutation. Published clinical reports have demonstrated sensitivity to irreversible EGFR TKIs such as afatinib and osimertinib (PMID: 33116645, PMID: 37227041, PMID: 39604248). See **Note 6**.

NOTE 3: A 2025 multicenter analysis of 240 NSCLC patients with EGFR L833 and/or H835 mutations (57 treated with EGFR-TKIs) reported a median PFS of 16.4 months, comparable to that in classical EGFR L858R cases (PMID: 40886084). This supports that L833/H835 variants behave as sensitizing rather than resistance-conferring mutations.

NOTE 4: Based on the CHRYSALIS-2 study (cohort C) published in Dec 2025, amivantamab/lazertinib demonstrated clinically meaningful anti-tumor activity with no new safety signals in NSCLC patients harboring atypical EGFR mutations with ≤2 previous lines of therapy [https://ascopubs.org/doi/full/10.1200/JCO-24-02835].

No relevant genomic alterations detected in ALK, BRAF, ERBB2, KEAP1, KRAS, MET, NRG1, NTRK1, NTRK2, NTRK3, RET, ROS1, SMARCA4, STK11.

OTHER GENOMIC FINDINGS					POSSIBLE TREATMENT OPTIONS
Gene	**Alteration type**	**Genomic alteration**	**Allele fraction**	**Tier**[Refer to Table 1]	**Treatment**
PTEN	Deletion	-	0.57 copies	II	**SEE NOTE 5, 6**
TP53	p.K132R	c.395A>G	68%	II	**SEE NOTE 7**

NOTE 5: Please note that copy number loss is not clinically validated in this test. Result should be interpreted with caution.

NOTE 6: PTEN alterations have been associated with primary and acquired resistance to EGFR TKIs (PMID: 36765799) and linked to immunotherapy resistance (specifically anti-PD-1 therapy) (PMID: 36339554).

NOTE 7: The current tissue test is not able to inform germline status of the identified TP53 variant. Germline confirmation and genetic counselling should be considered, especially if the patient fulfils the NCCN Guideline's testing criteria for Li-Fraumeni Syndrome (LFS).

Quality This specimen meets the laboratory's quality requirements.

This sample achieved 98.11% uniformity of base coverage and 3062X average base coverage depth.

Coverage Assessment: All hotspot regions achieved adequate coverage depth of at least 250X.

The complete list of genes covered by APEX gene panel is listed below:
Base substitutions, insertions and deletions: *AKT1, AKT2, AKT3, ALK, AR, ARAF, BRAF, CDK4, CDKN2A, CHEK2, CTNNB1, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FOXL2*, GNA11, GNAQ, GNAS, H3F3A*, HRAS, IDH1, IDH2, KIT, KEAP1, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, PIK3CA, POLE, PTEN, RAF1, RB1*, RET, ROS1, SMO, SMARCA4*, STK11, TERT, TP53*
Amplifications and losses*: *ALK, AR, CD274 (PD-L1), CDKN2A, EGFR, ERBB2, ERBB3, FGFR1, FGFR2, KRAS, MET, PIK3CA, PTEN.*
Fusions, *Inter-genic: ALK, BRAF, ESR1, FGFR1, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, RET, ROS1, RSPO2, RSPO3. Intra-genic: AR, EGFR, MET*
**Clinical validation in progress*

Electronically signed by Molecular Pathologist

ABOUT THE TEST

The APEX tissue is a Next-Generation Sequencing test that uses Oncomine Precision Assay on the Ion Torrent Genexus system. This test is co-developed and offered by M Diagnostics, a company of the MiRXES Group, and Diagnostic Molecular Oncology Centre (DMOC), National University Hospital. The somatic variants reported are aligned with the hg19/GRCh37 human reference genome, analyzed by an intelligent bioinformatics knowledge base and ranked into levels of clinical significance (Table 1) adapted from the joint consensus recommendations of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists[1]. This is a laboratory developed test (LDT).

Limitations: This test uses at least 40 ng of high-quality DNA, and 80 ng RNA extracted from FFPE tissue specimens for good quality sequencing reads. Samples with amounts or quality lower than the recommended input could compromise sequencing results; using such samples may affect the performance characteristics of the assay. The test is limited to hotspot regions of the gene panel. The test has been validated for indels up to 25 base pairs. The limit of detection of this test is 5% allele frequency for single base substitutions, insertions and deletions, 25% tumour cellularity for inter-genic fusions and 20% tumor cellularity for ERBB2 amplifications and 25% tumor cellularity for other gene amplifications. Copy number loss is not clinically validated; results are for informational purposes only and should be interpreted with caution. This test detects specific gene fusion isoforms (Fusion gene list available on request) and is not designed for the detection of rare or novel gene fusions that are not included in the assay panel. This test is validated only for somatic variants and should not be used to infer or exclude any possible germline variants.
For breast cancer, the ASCO/CAP guidelines strongly recommends that specimens subject to HER2/neu (ERBB2) testing be placed in fixative within 1 hour of biopsy or resection (cold ischemia time) and remain in 10% neutral phosphate-buffered formalin for at least 6 hours and up to 72 hours (formalin fixation time) at room temperature. Decalcification solutions with strong acids should not be used. Negative results derived from specimens not meeting the above guidelines should be interpreted with caution.
Our pathologist has not reassessed the original diagnosis. The treatments mentioned in this report are suggested based on analyses of publications and information evidence at the time of search, and these treatments were not verified for their published indication. Listed treatments might not be exhaustive. The identified genetic alterations do not guarantee clinical benefit or lack thereof from specific treatment mentioned in this report.

Cost: The cost of the test is the sole responsibility of the patient and there is no guarantee that a healthcare provider or insurer will reimburse the patient for such costs.

Disclaimer: The biomarker-matched drugs (covered under POSSIBLE TREATMENT OPTIONS) are recommended as per industry standards in accordance with US FDA, EMA, and/or professional guidelines.
The pharmaceutical companies have no influence on the drugs recommended in the report. Such recommendations are solely based on the biomarkers analyzed in this test. The inclusion of certain drugs in this report should not be construed as an endorsement or guarantee of their efficacy or appropriateness for a particular patient, as individual patient responses to drugs and/or medication may vary. Thus, this should not be solely relied upon or considered as a substitute for professional medical advice, diagnosis, or treatment.

Physician Responsible for Treatment Decisions: Any drugs selected based on potential (or lack of) clinical benefit for the treatment of a patient's disease are the responsibility of the physician. Any relevant patient information and applicable local standard of care guidelines must be considered in combination with information in this report, before the physician decides an appropriate course of treatment.

Table 1. Clinical Significance of variants used in this report

Strong clinical significance	Tier I	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis
		Biomarker is prognostic or diagnostic for this diagnosis based on professional guidelines or well-powered studies
Potential clinical significance	Tier II	Biomarker predicts response or resistance to an FDA or EMA approved or investigational therapy, according to (i) drug label or professional guidelines but only for different diagnosis, or (ii) case or clinical studies
		Biomarker is prognostic or diagnostic based on multiple small studies
Uncertain clinical significance	Tier III	Biomarker has uncertain clinical significance and not known to be likely benign or benign

1 Li MM et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23. doi: 10.1016/j.jmoldx.2016.10.002. PMID: 27993330

ADDITIONAL INFORMATION INCLUDED IN THIS REPORT

GUIDELINES

None

INTERACTIONS

None

POSSIBLE TREATMENT OPTIONS

OSIMERTINIB

Osimertinib, a kinase inhibitor, is FDA- and EMA-approved for treating adult patients with non-small cell lung cancer (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; 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; and for treating 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 also FDA-approved, in combination with pemetrexed and platinum-based chemotherapy, for the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.

Sensitive

Gene	Tier	HGVS.p	HGVS.c	Assessment
EGFR	II	p.L833V	c.2497T>G	Pathogenic
EGFR	II	p.H835L	c.2504A>T	Pathogenic

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.

Sensitive

Gene	Tier	HGVS.p	HGVS.c	Assessment
EGFR	II	p.L833V	c.2497T>G	Pathogenic
EGFR	II	p.H835L	c.2504A>T	Pathogenic

VARIANT DETAILS

EGFR

Exon:
21
Nucleotide:
NM_005228.5
g.55259439T>G
c.2497T>G
Amino Acid:
p.L833V
Assessment:
Pathogenic

Biomarker summary: EGFR-L833V (NM_005228) is an activating mutation.
Clinical relevance: EGFR activating mutations or amplification may predict sensitivity to Egfr-targeted therapies, including inhibitors of multiple ErbB family members, and several have received agency approval in some tumor types [106, 135, 168]. The Egfr TKIs erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib, as well as the combination of amivantamab plus lazertinib, have been approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR mutations; osimertinib has additionally been approved for the treatment of NSCLC with EGFR T790M [155, 183, 105, 148, 134, 147, 29, 106, 120]. Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations [192]. The combination of erlotinib and ramucirumab as well as osimertinib plus platinum-based chemotherapy have been FDA-approved for the treatment of metastatic NSCLC patients with tumors harboring an EGFR exon 19 deletion or the exon 21 L858R mutation [108, 124]. Amivantamab in combination with carboplatin and pemetrexed has been FDA-approved for the treatment of adult patients with locally advanced or metastatic NSCLC harboring EGFR Exon 19 deletions or Exon 21 L858R substitution mutations whose disease has progressed on or after treatment with an EGFR TKI [120]. Amivantamab has also been approved by the FDA for NSCLC patients with EGFR exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy and as frontline therapy in combination with carboplatin and pemetrexed. The accelerated FDA approval of mobocertinib for NSCLC patients with EGFR exon 20 insertions has been withdrawn due to lack of progression-free survival benefit in the confirmatory Phase 3 trial [133, 207]. The Trop-2-directed antibody and topoisomerase inhibitor conjugate datopotamab deruxtecan-dlnk has been FDA-approved for the treatment of adults with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy [1, 140].
Disease summary: Studies have reported non-squamous NSCLC patients with metastatic disease and tumors harboring an EGFR exon 19 deletion or L858R mutation to be sensitive to osimertinib, erlotinib, afatinib, gefitinib, dacomitinib, and the combination of erlotinib plus ramucirumab [193, 134, 183, 106, 29, 155, 108]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors [114]. Some patients with EGFR-mutant NSCLC exhibit resistance to Egfr inhibition; resistance has been associated with insertions in EGFR exon 20, the T790M mutation in EGFR, and amplification of either MET or ERBB2 [31, 38, 74, 162, 200]. Several studies have reported that resistance to Egfr TKIs in non-small cell lung cancer (NSCLC) is mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features; these transformed SCLC cases

have been shown to be responsive to standard SCLC therapy regimens involving platinum and etoposide–based chemotherapy [14, 146, 52, 76].

Molecular function: EGFR L833V is a missense alteration located within exon 21 of the Egfr protein, within the kinase domain (UniProt) [196]. This mutation has been shown to lead to activation of Egfr and confer sensitivity to gefitinib [16]. In addition, a preclinical study performing a screen of cancer related mutations has reported that EGFR L833V resulted in enhanced cell growth in 2/2 cell lines tested [109]. EGFR L833V has been found in combination with other EGFR mutations in lung adenocarcinoma patients, including with G719A and an exon 19 deletion; these complex alterations also conferred sensitivity to gefitinib [150, 158, 196, 142, 122]. Separate case studies have also reported clinical responses in non-small cell lung carcinoma patients harboring L833V as a double mutation with other EGFR alterations, including L858R, H835L and G719A, following treatment with afatinib, erlotinib, icotinib, aumolertinib, furmonertinib, or osimertinib [86, 182, 152, 205, 201, 117, 80].

Incidence: EGFR mutations have been reported in 27% (26714/99814) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). EGFR mutations have been reported in 6.3-29% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). EGFR mutations have been reported in 14-41% of NSCLC cases [84, 51, 204].

Role in disease: The presence of an EGFR abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Egfr protein, which can lead to excessive proliferation [19].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: The presence of a sensitizing EGFR mutation in a tumor is the strongest biological predictor of sensitivity to an Egfr tyrosine kinase inhibitor (TKI). Compared with conventional chemotherapy, Egfr TKIs have been shown to improve progression-free survival in non-small cell lung cancer patients whose tumors harbor EGFR mutations [106, 135, 168, 134]. The Egfr TKIs erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib, as well as the combination of amivantamab plus lazertinib, have been approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR mutations; osimertinib has additionally been approved for the treatment of NSCLC with EGFR T790M [155, 183, 105, 148, 134, 147, 29, 106, 120, 89]. Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations [192]. The combination of erlotinib and ramucirumab as well as osimertinib plus platinum-based chemotherapy have been FDA-approved for the treatment of metastatic NSCLC patients with tumors harboring an EGFR exon 19 deletion or the exon 21 L858R mutation [108, 124]. Amivantamab in combination with carboplatin and pemetrexed has been FDA-approved for the treatment of adult patients with locally advanced or metastatic NSCLC harboring EGFR Exon 19 deletions or Exon 21 L858R substitution mutations whose disease has progressed on or after treatment with an EGFR TKI [120]. Amivantamab has also been approved by the FDA for NSCLC patients with EGFR exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy and as frontline therapy in combination with carboplatin and pemetrexed. The accelerated FDA approval of mobocertinib for NSCLC patients with EGFR exon 20 insertions has been withdrawn due to lack of progression-free survival benefit in the confirmatory Phase 3 trial [133, 207]. The Trop-2-directed antibody and topoisomerase inhibitor conjugate datopotamab deruxtecan-dlnk has been FDA-approved for the treatment of adults with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy [1, 140]. Studies have reported non-squamous NSCLC patients with metastatic disease and tumors harboring an EGFR exon 19 deletion or L858R mutation to be sensitive to osimertinib, erlotinib, afatinib, gefitinib, dacomitinib, and the combination of erlotinib plus ramucirumab [193, 134, 183, 106, 29, 155, 108]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors [114]. Afatinib has been FDA-approved for the treatment of lung squamous cell carcinoma following progression on platinum-based chemotherapy [154, 36].

Drug resistance: Some patients with EGFR-mutant NSCLC exhibit resistance to Egfr inhibition; resistance has been associated with insertions in EGFR exon 20, the T790M mutation in EGFR, and amplification of either MET or ERBB2 [31, 38, 74, 162, 200]. Third generation irreversible Egfr TKIs that target the EGFR T790M mutation have shown efficacy in T790M-mutant NSCLC, including osimertinib, which has received approval by the FDA, EMA, and PMDA for the treatment of EGFR T790M-mutant metastatic NSCLC [54, 56, 37, 190, 177]. Several studies have reported that resistance to Egfr TKIs in NSCLC is mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features [180, 14, 125, 146]. In addition, EGFR mutations have been associated with reduced efficacy of immune checkpoint inhibitor therapy in NSCLC patients [123, 191, 85, 67, 208].

Approved Drugs: Datopotamab deruxtecan (NSCLC with actionable EGFR alterations). (Afatinib approved for NSCLC with EGFR exon 19 deletion, L858R, G719X, L861Q, and/or S768I). (Dacomitinib approved for NSCLC with EGFR exon 19 deletion or EGFR L858R). (Osimertinib approved for NSCLC with EGFR exon 19 deletion, EGFR L858R, or EGFR T790M). (Erlotinib approved for NSCLC with EGFR exon 19 deletion or EGFR L858R). (Gefitinib approved for NSCLC with EGFR exon 19 deletion or EGFR L858R). (Amivantamab approved for NSCLC with EGFR exon 20 insertion). (Sunvozertinib approved for NSCLC with EGFR exon 20 insertion). (Erlotinib+ramucirumab approved for NSCLC with EGFR exon 19 deletion or L858R). (Amivantamab+lazertinib approved for NSCLC with EGFR exon 19 deletion or EGFR L858R).

Phase 3: A meta-analysis of 16 Phase 3 trials including 2962 patients with EGFR-mutant advanced NSCLC evaluated the efficacy of afatinib, erlotinib, and gefitinib. In the overall population, all therapies showed superior outcome as compared with chemotherapy for overall response rate (ORR), disease control rate (DCR), and one-year progression-free survival (PFS). In chemotherapy-naive patients, afatinib had improved overall survival (OS) and one-year PFS, and erlotinib showed the best DCR. In previously treated patients, gefitinib had enhanced ORR, and erlotinib showed the most improved one- and two-year OS, as compared with gefitinib and second line chemotherapy [203]. A Phase 3 trial (TROPION-Lung01) of datopotamab deruxtecan (Dato-DXd) versus docetaxel in 604 patients with advanced NSCLC reported objective response rates of 26.4% and 12.8%, median progression-free survival of 4.4 and 3.7 months, and median overall survival of 12.9 and 11.8 months in the Dato-DXd and docetaxel arms, respectively. Grade 3-4 adverse events were reported in 25.6 and 42.1% of patients, respectively [1]. The approval of afatinib for first-line therapy of NSCLC patients with EGFR exon 19 deletions or the exon 21

L858R mutation is based on a randomized Phase 3 study of 345 patients with EGFR mutations comparing afatinib to chemotherapy with pemetrexed and cisplatin. The median progression-free survival (PFS) for patients treated with afatinib was 11.1 months, compared to 6.9 months for patients treated with chemotherapy. Among patients with exon 19 or 21 mutations, the median PFS for patients treated with afatinib was 13.6 months, compared to 6.9 months for chemotherapy [147]. Combined analysis of three Phase 3b studies of afatinib in 1108 NSCLC patients not previously treated with Egfr tyrosine kinase inhibitors reported an objective response rate of 55.5%, time to symptomatic progression of 14.8 months, and a median progression-free survival of 13.0 months. Treatment-related adverse events were reported in 97.2%, with diarrhea and rash being common, and dose reduction due to adverse events occurred in 41.6% of patients [119]. The Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line treatment in 795 stage 3b/4 lung SCC patients has reported patients treated with afatinib had increased median progression-free survival as compared with erlotinib treatment (2.6 versus 1.9 months), increased median overall survival (7.9 versus 6.8 months), and improved disease control and median duration of objective response. Adverse events were cited in 99% (390/392) and 97% (385/395) of patients in the afatinib and erlotinib groups, respectively, with grades 3/4 adverse events reported in 57% of both groups [154]. Final survival analysis of the Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line treatment in 795 stage 3b/4 lung SCC patients has reported that afatinib significantly prolonged overall survival (7.8 vs 6.8 months). Long-term clinical benefit was observed in 5.3% (21/398) of patients treated with afatinib compared with 3.3% (13/397) of patients treated with erlotinib and was more common in patients with tumors harboring ERBB mutations [36]. The Phase 3 ARCHER 1050 trial of dacomitinib versus gefitinib as first-line treatment in 452 NSCLC patients with EGFR exon 19 deletion or L858R mutations, with or without T790M, has reported similar overall response rates of 75% and 72% in the dacomitinib and gefitinib arms, respectively, but a significantly improved progression-free survival (14.7 versus 9.2 months) and overall survival (34.1 versus 26.8 months) with dacomitinib as compared with gefitinib [105, 183]. The Phase 3 ARCHER 1009 trial of dacomitinib or erlotinib in advanced or metastatic NSCLC patients previously treated with chemotherapy reported an overall median progression-free survival time of 2.6 months in both groups, and 2.6 months in KRAS wild-type patients specifically treated with either drug; serious adverse events were reported in 12% and 9% of those treated with dacomitinib and erlotinib, respectively [127, 128]. The randomized Phase 3 FLAURA trial of osimertinib versus gefitinib or erlotinib in TKI-naïve advanced NSCLC harboring EGFR exon 19 deletion or L858R mutation, has reported progression-free survival (PFS) of 18.9 months, an overall response rate of 80% (223/279), and a median duration of response (DoR) of 17.2 months in the osimertinib arm, while the other treatment arm reported PFS of 10.2 months, an overall response rate of 76% (211/277), and median DoR of 8.5 months. Also, grade 3 or higher adverse events were less common in the osimertinib arm (34%, 95/279) as compared with the other treatment arm (45%, 125/277) [155]. Furthermore, the Phase 3 study of osimertinib versus gefitinib or erlotinib in 556 patients with untreated advanced NSCLC with an EGFR L858R mutation or exon 19 deletion has reported a median overall survival of 38.6 and 31.8 months as well as grade 3 or higher adverse events in 42% and 47% of patients in the osimertinib and comparator groups, respectively [130]. A preplanned subgroup analysis of the Phase 3 FLAURA trial of osimertinib versus gefitinib or erlotinib in 128 untreated EGFR-mutated advanced NSCLC patients with measurable and/or nonmeasurable CNS lesions at baseline reported a median CNS progression-free survival (PFS) of 13.9 months with gefitinib or erlotinib, while CNS PFS was not reached with osimertinib; in patients with at least one measurable CNS lesion, CNS objective response rates of 91% and 68% were reported with osimertinib and standard TKIs, respectively [132]. An interim analysis of the Phase 3 double-blind, randomized ADAURA trial of adjuvant osimertinib versus placebo in 682 previously resected stage 1-3a EGFR-mutated NSCLC patients who had already received adjuvant chemotherapy reported a two-year disease-free survival rate of 89% and 52% in the overall population, and 90% and 40% in stage 2-3a patients in the osimertinib and placebo arms, respectively [184]. Further exploratory analysis of the Phase 3 trial (ADAURA) of osimertinib or placebo in 682 patients with resected, EGFR-mutant, stage 1b-3a NSCLC has reported median disease-free survival (DFS) of 65.8 and 21.9 months in the osimertinib and placebo arms, respectively. In patients with stage 2-3a disease, the four-year DFS was 70% with 9% (22/223) CNS recurrence in the osimertinib arm and 29% with 17% (41/237) CNS recurrence in the placebo arm. In the overall study population, the DFS was 73% with osimertinib and 38% with placebo [44]. Overall survival analysis of the Phase 3 trial (ADAURA) of osimertinib or placebo in 682 patients with resected, EGFR-mutated, stage 1b-3a NSCLC reported five-year overall survival rates of 88% and 78% in the osimertinib and placebo arms, respectively. Median overall survival was not reached [169]. The Phase 3 FLAURA2 study of osimertinib with chemotherapy as compared with osimertinib monotherapy in 557 treatment-naive NSCLC patients with EGFR exon 19 deletion or L858R mutation has reported objective response in 83% and 76% of patients, median progression-free survival (PFS) of 25.5 and 16.7 months, 24-months PFS rate of 57% and 41%, and grade 3 and higher adverse events in 64% and 27% of patients in the osimertinib plus chemotherapy and osimertinib monotherapy arms, respectively [124]. The Phase 3 LAURA study of osimertinib or placebo in 216 unresectable EGFR-mutated stage 3 NSCLC patients without progression during or after chemoradiotherapy has reported significant improvement in median progression-free survival (39.1 months versus 5.6 months) in the osimertinib arm, with 36-month overall survival rate of 84% and 74%, and grade 3 or higher adverse events in 35% and 12% of patients in the osimertinib and placebo arms, respectively [89]. Erlotinib approval for unselected NSCLC patients was based on a Phase 3 randomized trial demonstrating prolonged overall survival for unselected NSCLC patients treated with erlotinib compared with standard chemotherapy [148]. However, approval has been modified to include only NSCLC patients harboring either an exon 19 deletion mutation or the exon 21 L858R mutation based on the results of a double-blind placebo-controlled Phase 3 trial that excluded patients harboring these mutations; this study (NCT01328951) found that in patients without these mutations, erlotinib had no benefit compared with placebo on overall survival of 643 NSCLC patients with no disease progression or unacceptable toxicity during four cycles of platinum-based first-line chemotherapy [20]. The approval of gefitinib for NSCLC patients with EGFR exon 19 deletions or the exon 21 L858R mutation is based on a Phase 4 trial of gefitinib as a first-line treatment in 106 EGFR mutation positive NSCLC patients, including 69 patients harboring an exon 19 deletion, 33 with L858R, and two each with L861Q and G719X mutations. The overall response rate based on investigator assessment was 69.8% (74/106), including two complete and 72 partial responses, and 50% (58/106) by a secondary, central review; the disease control rate was 90.6%, and median progression-free and overall survival times were 9.7 and 19.2 months,

respectively. In patients with an exon 19 deletion and the L858R mutation, the overall response rates based on investigator assessment were 72.5% (50/69) and 63.6% (21/33), respectively [29, 66]. Two Phase 3 studies of combined gefitinib, carboplatin, and pemetrexed versus gefitinib monotherapy in NSCLC patients have reported that combined treatment is associated with significantly longer median progression-free survival and overall survival as compared with gefitinib monotherapy. In addition, one of these trials reported that combined treatment was associated with a significantly higher radiologic response rate and a significantly higher rate of Grade 3 or higher adverse events as compared with treatment using gefitinib alone [112, 111]. A Phase 3 study of gefitinib with or without chemotherapy in 161 untreated EGFR mutation-positive NSCLC patients with brain metastasis has reported intracranial and overall objective response rates of 85.0% and 80.0% in the gefitinib plus chemotherapy arm, respectively, versus 63.0% and 64.2% in the gefitinib monotherapy arm, respectively. In addition, the median intracranial and overall progression-free survival were 15.6 and 16.3 months in the gefitinib plus chemotherapy arm, respectively, versus 9.1 and 9.5 months in the gefitinib monotherapy arm, respectively [47]. The Phase 3 PAPILLON study of chemotherapy with or without amivantamab in 308 patients with NSCLC harboring EGFR exon 20 insertions has reported a median progression-free survival (PFS) of 11.4 and 6.7 months, a PFS at 18 months in 31% and 3%, and a complete or partial response in 73% and 47% of patients treated with or without amivantamab, respectively; 7% of patients discontinued amivantamab due to adverse effects [207]. The randomized Phase 3 RELAY study of erlotinib plus ramucirumab (E+R) or placebo (E+P) in 449 untreated metastatic NSCLC patients with EGFR mutations has reported increased median progression-free survival in the E+R as compared with the E+P arm in patients with common exon 19 deletion variants (15.2 versus 9.9 months), in patients with uncommon exon 19 deletion variants (19.4 versus 13.9 months), in patients with E746del (15.4 versus 9.9 months), and in patients with L747del (18.0 versus 12.5 months). Increased median duration of response was reported in the E+R as compared with the E+P arm in patients with common exon 19 deletion variants (14.1 versus 8.4 months), in patients with uncommon exon 19 deletion variants (13.8 versus 11.3 months), in patients with E746del (14.1 versus 9.6 months), and in patients with L747del (13.8 versus 11.0 months). Slightly increased frequency of grade 3 or higher treatment-related adverse events were reported in the erlotinib plus ramucirumab as compared with the erlotinib plus placebo arm [110]. Final analysis of the Phase 3 RELAY study of erlotinib plus ramucirumab or placebo in 449 untreated metastatic NSCLC patients with EGFR mutations, at a median follow-up of 45.1 months, has reported no significant improvement with similar long overall survival durations in both treatment arms (51.1 vs 46.0 months). No new safety signals were identified [107]. The Phase 3 MARIPOSA-2 study of amivantamab plus chemotherapy with or without lazertinib versus chemotherapy alone in 657 NSCLC patients who experienced disease progression on osimertinib has reported significantly longer progression-free survival (PFS) for the amivantamab-associated treatment groups. PFS of 6.3, 8.3, and 4.2 months, respectively, and objective response rates of 63%, 64%, and 36%, respectively, were reported for amivantamab plus chemotherapy, amivantamab plus chemotherapy with lazertinib, and chemotherapy alone, respectively. However, the presence of amivantamab induced increased adverse events as well, namely in hematologic, EGFR- and MET- related toxicities [120]. The Phase 3 MARIPOSA trial of amivantamab plus lazertinib versus osimertinib versus lazertinib alone in 1074 patients with previously untreated advanced NSCLC harboring EGFR ex19 deletion or L858R mutations has reported a median progression-free survival of 23.7 and 16.6 months and an objective response rate of 86% and 85% in the amivantamab-lazertinib and osimertinib arms, respectively. Treatment-related adverse events were predominantly EGFR-related toxic effects, with 10% of patients discontinuing amivantamab-lazertinib due to adverse events compared with 3% for osimertinib [17]. The Phase 3 MARIPOSA-2 study of subcutaneous (SC) versus intravenous (IV) amivantamab combined with lazertinib has reported that SC administration exhibited non-inferiority compared with IV. Overall response rates of 30% and 33% as well as progression-free survival of 6.1 and 4.3 months were reported in the SC and IV groups, respectively. Additionally, infusion-related reactions were reported to be fewer in the subcutaneous group [77]. The Phase 3 EXCLAIM-2 study of mobocertinib versus platinum-based chemotherapy as first-line treatment in 354 advanced/metastatic NSCLC patients with EGFR exon 20 mutations has reported confirmed objective response per blinded independent central review in 32% (26/40) and 30% (24/38) of patients in the mobocertinib and chemotherapy cohorts, respectively. Frequent grade 3 or higher adverse events included diarrhea (20%, 1%), anemia (6%, 10%), increased lipase (6%, 0%), and decreased neutrophil count (1%, 7%) in the mobocertinib and chemotherapy cohorts, respectively [55].

Phase 2: A Phase 2 trial (TROPION-Lung05) of datopotamab deruxtecan in patients with advanced NSCLC with actionable genomic alterations reported confirmed disease control and objective response (ORR) rates of 78.8% and 35.8%; ORR of 23.5% and 43.6% were reported in patients with ALK rearrangements and EGFR mutation, respectively. Grade 3-4 adverse events were reported in 28.5% of patients [140]. A Phase 2 study of osimertinib in 37 patients with metastatic or recurrent NSCLC with an EGFR mutation other than L858R, T790M, exon 19 deletion, or exon 20 insertion has reported an objective response rate of 50% (18/36), a median progression-free survival of 8.2 months, and a median duration of response of 11.2 months in evaluable patients; the median overall survival was not reached [18]. A Phase 2 study testing the use of circulating tumor DNA (ctDNA) analysis as a selection criterion for first-line gefitinib treatment has reported detection of EGFR mutations in 44% (188/426) of cases screened. Among 183 evaluable patients who received treatment, the overall response rate was 72% and the median progression-free survival (PFS) was 9.5 months. Additionally, a significantly increased PFS of 11.0 months was reported among 147 patients who showed clearance of EGFR mutations in ctDNA at eight weeks as compared with 2.1 months in 20 patients whose mutations persisted [179]. A Phase 2 study of neratinib in NSCLC patients has reported limited clinical activity, with an overall response rate of 2%. Specifically, responses were reported in 3.4% (3/88) of previously treated EGFR-mutant NSCLC patients, with all responding patients harboring EGFR G719X alterations, while no responses were reported in any of 12 EGFR T790M mutant patients, 48 EGFR wild-type patients, including two with EGFR amplification, or 28 TKI naive patients, including 11 with EGFR mutation and five with EGFR amplification [145]. The Phase 2 SUMMIT trial in 31 NSCLC patients harboring exon 18 mutations has reported an objective response rate (ORR) at eight weeks of 19.4% with six partial responses. The confirmed ORR by RECIST and median progression-free survival were 32.3% and 5.75 months, respectively. The most common treatment-related adverse event was diarrhea [35]. A Phase 1/2 study of mobocertinib (TAK-788) in 28 NSCLC patients with EGFR exon 20 insertions has reported objective response rate (ORR) of 43%, with median progression-

	free survival (PFS) of 7.3 months and median duration of response of 14 months. The only grade 3 or higher treatment-related adverse event was diarrhea [133]. Analysis of the EXCLAIM extension cohort of 96 additional patients and 114 platinum-pretreated (PPP) patients from the same study of mobocertinib in NSCLC patients with EGFR exon 20 insertions has reported ORR by independent review committee of 25% and 28%, ORR by investigator of 32% and 35%, and median PFS of 7.3 and 7.3 months, respectively. Grade 3 or higher adverse events were reported in 68% (142/210) of all patients, with ten and 19 patients discontinuing treatment in the extension and PPP arms, respectively [206]. A Phase 2 trial of mobocertinib in patients with EGFR exon 20 insertion mutation-positive NSCLC reported an objective response rate of 18.2%, including complete and partial responses in 1/33 and 15.2% (5/33) of patients, respectively. Grade 3-4 adverse events were reported in 63.6% (21/33) of patients; the most common adverse events were stomatitis, diarrhea, nausea, and paronychia. Enrollment was terminated due to futility [199]. **Phase 1:** A study assessed the efficacy of afatinib in patients with "uncommon EGFR mutations" with metastatic NSCLC progressing after previous treatment with chemotherapy and one line of Egfr TKI treatment. In the 60 enrolled patients, 30 cases of T790M were reported. Median time to treatment failure was 3.8 and 5.1 months in the uncommon and common mutation groups, respectively, with activity noted in patients harboring E709X and T790M mutations, and exon 20 insertions [42]. A study of 24 NSCLC patients previously treated with gefitinib, erlotinib, or afatinib who developed resistance assessed the efficacy of bevacizumab in combination with either erlotinib (n=22) or gefitinib (n=2). The response and disease control rates were 13% and 88%, respectively, with three partial responses and 18 patients showing stable disease; median progression-free and overall survival times were 4.1 and 13.5 months, respectively. Increased response rate and disease control rates were also reported in T790M-negative patients as compared with those harboring the T790M mutation (18% versus 0%, 88% versus 86%) [116]. Preliminary analysis of the ongoing Phase 1 CHRYSALIS trial of amivantamab in 114 NSCLC patients with EGFR exon 20 insertions has reported an overall response rate of 37%, with median progression-free and overall survival of 6.9 and 23 months, respectively. Grade 3-4 adverse events included neutropenia, diarrhea, rash, hypokalemia, and pulmonary embolism. Treatment is ongoing in 15% of patients, with median treatment duration of 2.6 years. Preliminary analysis of the ongoing Phase 1 CHRYSALIS trial of amivantamab in 36 advanced NSCLC patients with MET exon 14 skipping mutations has reported overall responses in 33% (12/36) of patients, including partial responses in 12 patients and stable disease in 17 patients. Treatment-related adverse events including dose reduction and discontinuation were reported in three patients, each. The Phase 1 CHRYSALIS study of the EGFR-MET bispecific antibody amivantamab in combination with lazertinib in 71 NSCLC patients with EGFR exon 19del/L858R mutations has reported an overall response rate of 43.5% in 23 evaluable patients, with partial response in ten patients and stable disease in nine patients. In the expansion cohort of post-osimertinib patients, early clinical response was observed in 14 out of 20 evaluable patients, including six patients with stable disease. Grade 3 or higher treatment-related adverse events were reported in 7% of patients in the overall trial. Analysis of the Phase 1 CHRYSALIS-2 study cohort A of amivantamab and lazertinib in 162 patients with NSCLC with EGFR exon 19del/L858R mutations following progression on osimertinib and platinum-based chemotherapy has reported a blinded independent central review-assessed overall response rate of 35%, a median duration of response of 8.3 months, a clinical benefit rate of 58%, a median progression-free and overall survival of 4.5 and 14.8 months, respectively, and a duration of response of at least six months in 57% (32/56) of patients; grade 3 or higher treatment-related adverse events were reported in 50% of patients [9]. **Preclinical:** N/A: Preclinical data are not presented when higher level data are available.
EGFR **Exon:** 21 **Nucleotide:** NM_005228.5 g.55259446A>T c.2504A>T **Amino Acid:** p.H835L **Assessment:** Pathogenic	**Biomarker summary:** The functional consequences of EGFR-H835L (NM_005228) are unknown. **Clinical relevance:** EGFR activating mutations or amplification may predict sensitivity to Egfr-targeted therapies, including inhibitors of multiple ErbB family members, and several have received agency approval in some tumor types [106, 135, 168]. The Egfr TKIs erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib, as well as the combination of amivantamab plus lazertinib, have been approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR mutations; osimertinib has additionally been approved for the treatment of NSCLC with EGFR T790M [155, 183, 105, 148, 134, 147, 29, 106, 120]. Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations [192]. The combination of erlotinib and ramucirumab as well as osimertinib plus platinum-based chemotherapy have been FDA-approved for the treatment of metastatic NSCLC patients with tumors harboring an EGFR exon 19 deletion or the exon 21 L858R mutation [108, 124]. Amivantamab in combination with carboplatin and pemetrexed has been FDA-approved for the treatment of adult patients with locally advanced or metastatic NSCLC harboring EGFR Exon 19 deletions or Exon 21 L858R substitution mutations whose disease has progressed on or after treatment with an EGFR TKI [120]. Amivantamab has also been approved by the FDA for NSCLC patients with EGFR exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy and as frontline therapy in combination with carboplatin and pemetrexed. The accelerated FDA approval of mobocertinib for NSCLC patients with EGFR exon 20 insertions has been withdrawn due to lack of progression-free survival benefit in the confirmatory Phase 3 trial [133, 207]. The Trop-2-directed antibody and topoisomerase inhibitor conjugate datopotamab deruxtecan-dlnk has been FDA-approved for the treatment of adults with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy [1, 140]. As the alteration reported here has not been functionally characterized, the relevance of any available therapeutic approaches is unknown. **Disease summary:** Studies have reported non-squamous NSCLC patients with metastatic disease and tumors harboring an EGFR exon 19 deletion or L858R mutation to be sensitive to osimertinib, erlotinib, afatinib, gefitinib, dacomitinib, and the combination of erlotinib plus ramucirumab [193, 134, 183, 106, 29, 155, 108]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors [114]. Some patients with EGFR-mutant NSCLC exhibit resistance to Egfr inhibition; resistance has been associated with insertions in EGFR exon 20, the T790M mutation in EGFR, and amplification of either MET or ERBB2 [31, 38, 74, 162, 200]. Several studies have reported that resistance to Egfr TKIs in non-small cell lung cancer (NSCLC) is mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features; these transformed SCLC cases

have been shown to be responsive to standard SCLC therapy regimens involving platinum and etoposide–based chemotherapy [14, 146, 52, 76].

Molecular function: EGFR H835L is a missense alteration located within the kinase domain of the Egfr protein (UniProt). This alteration has been reported in combination with the EGFR L833V mutation in lung adenocarcinoma patients who responded to gefitinib, osimertinb, or aumolertinib; a preclinical study also reported that the H835L mutation alone showed sensitivity to gefitinib [13, 197, 80, 57, 90, 152, 3, 16, 196]. This alteration has also been reported in combination with EGFR L833V and E709K in a lung adenocarcinoma patient who responded to afatinib [86, 33]. Other studies have reported stable disease in L833V/H835L and L833V/H835L/R670W mutation-positive lung adenocarcinoma patients who were treated with afatinib for 13.5 months and over seven months, respectively. EGFR T790M was detected upon resistance [81, 126]. Additionally, a study has reported that EGFR H835L and H835L/L833V exhibited reduced receptor autophosphorylation, while EGFR L833V alone exhibited increased receptor autophosphorylation both in the presence and absence of Egf as compared with the wild-type protein [136]. In one preclinical study, EGFR H835L was reported to be activating in one cell line, but to have a neutral effect in another [109]. Therefore, its effect on Egfr function is unclear.

Incidence: EGFR mutations have been reported in 27% (26714/99814) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (May 2023). EGFR mutations have been reported in 6.3-29% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, May 2023). EGFR mutations have been reported in 14-41% of NSCLC cases [84, 51, 204].

PTEN

Assessment:
Pathogenic

Biomarker summary: PTEN-loss is an inactivating alteration.

Clinical relevance: PTEN loss or inactivating mutation may lead to increased activation of the PI3K/Akt/mTOR pathway. Therefore, inhibitors of this pathway may be relevant in a tumor with loss or mutation of PTEN [21, 181, 151]. The PI3K inhibitors alpelisib and copanlisib, the Akt inhibitor capivasertib, and the mTOR inhibitors everolimus and temsirolimus have been approved in specific cancer indications. These and other PI3K, Akt, and mTOR inhibitors, as well as dual PI3K/mTOR inhibitors are also currently in clinical trials, alone or in combination with other therapies [5, 99, 53, 39]. The Akt inhibitor capivasertib has been approved by the FDA in combination with fulvestrant for the treatment of adult patients with hormone receptor positive, Her2 negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Disease summary: Loss of Pten protein expression has been associated with higher stage, lymph node metastases, and poorly differentiated disease in NSCLC patients [137, 82, 149, 167, 58, 202]. Deletion of PTEN has been shown to lead to the formation of lung squamous cell carcinoma tumors in preclinical studies [96, 187].

Molecular function: PTEN deletion, which occurs at chromosome 10q23, has been correlated with reduced Pten expression in clinical cancer tissues [174, 32, 41, 88].

Incidence: Putative homozygous deletion of PTEN has been reported in 0.4-3.1% of Non-small cell lung carcinoma (NSCLC) cases (cBioPortal for Cancer Genomics, May 2023). In the scientific literature, one study reported homozygous deletion of PTEN in 1/124 non-small cell lung carcinoma (NSCLC) samples [189]. Decreased PTEN mRNA expression has been reported in non-small cell lung carcinoma (NSCLC) samples as compared with normal tissue samples [185, 195, 188, 198, 186]. In addition, loss of Pten protein expression has been reported in 35-70% of NSCLC samples [153, 137, 149, 113, 165].

Role in disease: Loss of PTEN (through mutation or deletion) can lead to uncontrolled cell growth and suppression of apoptosis [160]. PTEN haploinsufficiency has been associated with tumorigenesis in some tumor types, including astrocytoma and prostate cancer [22, 75, 73, 172]. PTEN germline mutations are found in several cancer-predisposition syndromes, such as Cowden syndrome and Proteus syndrome [46]. Loss of Pten protein expression has been associated with higher stage, lymph node metastases, and poorly differentiated disease in NSCLC patients [137, 82, 149, 167, 58, 202]. Deletion of PTEN has been shown to lead to the formation of lung squamous cell carcinoma tumors in preclinical studies [96, 187].

Diagnostic significance: Unknown.

Prognostic significance: Unknown.

Drug sensitivity: Because PTEN negatively regulates the PI3K/Akt/mTOR pathway, PTEN loss or mutation leads to activation of the PI3K pathway and may therefore predict sensitivity to inhibitors of the PI3K/Akt/mTOR pathway [181]. The PI3K inhibitors alpelisib and copanlisib, the Akt inhibitor capivasertib, and the mTOR inhibitors everolimus and temsirolimus have been approved in specific cancer indications. These and other PI3K, Akt, and mTOR inhibitors, as well as dual PI3K/mTOR inhibitors are also currently in clinical trials, alone or in combination with other therapies [5, 99, 53, 39]. The Akt inhibitor capivasertib has been approved by the FDA in combination with fulvestrant for the treatment of adult patients with hormone receptor positive, Her2 negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. In addition, preclinical studies have shown that PTEN-deficient tumors may be sensitive to PARP inhibitors, and PARP inhibitors are in clinical trials for patients with PTEN-deficient tumors [102, 26, 101].

Drug resistance: Preclinical studies have associated decreased expression of Pten with gefitinib and erlotinib resistance in EGFR-mutant NSCLC cell lines [157, 194, 161, 93]. Mutation of PTEN has been reported to be associated with a low objective response rate (ORR) to Egfr tyrosine kinase inhibitors in lung adenocarcinomas harboring EGFR mutations, with 7.3% ORR in PTEN-mutated cases compared to 70.9% ORR in wild-type PTEN lung adenocarcinomas [68].

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 [131]. 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 [156]. 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% [129]. Preliminary analysis of a Phase 2 trial of everolimus in combination with avutometinib in 16 KRAS-mutated NSCLC patients has reported progression-free survival of 5.3 months, and objective response in 3/14 patients with tumor size reduction reported in 11/14 patients. A Phase 2 multi-arm study in patients with advanced thoracic malignancies, including NSCLC, SCLC, and thymic malignancies, treated patients based on genomic characterization. In four NSCLC patients with alterations in PTEN, AKT1, or PIK3CA, no clinical responses were reported with MK-2206 treatment [87]. The Phase 2 BASALT-1 study evaluated the efficacy of single agent buparlisib in 63 patients with PI3K-activated, metastatic NSCLC. The 12-week progression-free survival rates were 23.3% and 20% in the squamous and nonsquamous NSCLC groups, respectively; the second phase of this study was not conducted due to failure to meet its primary endpoint of a 12-week progression-free survival rate of at least 50% [171]. Results from the Phase 1b/2 BASALT-3 trial evaluating the efficacy of buparlisib combined with docetaxel in 27 patients with previously treated squamous NSCLC reported overall response rates of 6% and 18% in patients receiving 80 mg or 100 mg of buparlisib, respectively. The median progression-free survival was reported to be 2.8 months at both doses with all patients discontinuing treatment, predominately due to disease progression.

Phase 1: A Phase 1 trial of capivasertib (AZD5363) in 90 solid tumor patients has reported stable disease for more than six and 12 weeks in 30% (27/90) and 7% (6/90) of patients, respectively, and one partial response in a cervical cancer patient with a PIK3CA mutation. In an expansion cohort of patients with PIK3CA mutations, confirmed RECIST responses were observed in 1/28 and 8% (2/26) of breast and gynecologic cancer patients, respectively, resulting in termination of further enrollment [6]. A Phase 1 study of capivasertib (AZD5363) in 41 Japanese solid tumor patients has reported confirmed partial responses in 5% (2/37) of evaluable patients, both with the AKT1 E17K mutation, and stable disease in 27% (10/37) of patients. Grade 3 or higher treatment-related adverse events were observed in 58.5% of patients [164]. A Phase 1 study of alpelisib in PIK3CA-altered advanced solid tumors has reported an overall response rate of 6%, including one complete and seven partial responses, as well as stable disease in 52% (70/134) of patients. The safety profile was also reported to be tolerable [61]. A Phase 1 study of alpelisib monotherapy in 33 Japanese patients with advanced solid tumors has reported overall response rate, disease control rate, and median progression-free survival at 350 mg/day of 3%, 57.6%, and 3.4 months, respectively. The most common treatment-related adverse events were hyperglycemia, maculopapular rash, and diarrhea observed in 48.5%, 48.5%, and 45.5%, of patients, respectively [4]. A Phase 1b study of alpelisib in combination with everolimus, with or without exemestane, in advanced solid tumor patients, with expansion cohorts in renal cell carcinoma (RCC), pancreatic neuroendocrine tumor (pNET), and solid tumor patients pretreated with mTOR inhibitors has reported 16-week progression-free survival rates of 52.4%, 35.3%, and 30.0% in patients in the RCC, pNET, and prior mTOR inhibitor cohorts, respectively [23]. A Phase 1 study in 14 evaluable NSCLC patients that had previously failed chemotherapy and Egfr tyrosine kinase therapy reported two patients with minor responses and symptomatic improvement for eight and 27 weeks following treatment with MK-2206 in combination with gefitinib. A Phase 1 study of copanlisib in 48 patients with advanced solid tumors reported one complete response in an endometrial carcinoma patient with PIK3CA activation and PTEN loss, as well as two partial responses in metastatic breast cancer patients [121]. A Phase 1b trial of buparlisib and trametinib in patients with advanced solid cancer reported stable disease in 53% (9/17) of NSCLC cases, and a partial response in one NSCLC patient with a KRAS mutation; median progression-free survival for NSCLC was four months, and grade 3/4 adverse events were reported in 65% (73/113) of all study patients [8]. 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 [7].

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

TP53

Exon:
5
Nucleotide:
NM_000546.6
g.7578535T>C
c.395A>G
Amino Acid:
p.K132R
Assessment:
Pathogenic

Biomarker summary: TP53-K132R (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 [79, 178, 70, 65, 48, 115]. 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 [144, 173, 138]. 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 [45, 11]. Aurora kinase A inhibitors are another therapeutic approach under investigation for TP53-mutated cancers [175, 83, 64, 166, 63].

Disease summary: 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 [94, 59, 163, 139, 72, 50, 92]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis [15]. 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 [59, 100, 10, 69]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples [28, 143, 2, 97, 62]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients [170].

Molecular function: TP53 K132R corresponds to c.376-2A>G in transcript ENST00000604348 (IGV). TP53 K132R is a missense mutation located within the L1 loop of the DNA-binding domain (DBD) of the p53 protein [78]. DBD mutations are thought to result in loss of function via the loss of transactivation of p53-dependent genes [65]. Codon K132 has been identified as a hot spot mutation site [176]. TP53 K132R has been reported to result in substantially

reduced transactivation capacity, as compared with wild-type TP53, in yeast assays (The TP53 Database) [24]. K132R demonstrated loss of activity, as well as a dominant negative effect on wild-type TP53 in a yeast functional assay [25]. TP53 K132R has also been reported as a likely loss of function mutation in mutagenesis assays in human cell lines [34, 71].

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 NSCLC cases [94, 59, 163, 139, 72, 50, 49, 92]. Specifically, TP53 mutations have been reported in 74% (8887/12079) of KRAS wild-type and in 37-55% of KRAS mutant NSCLC samples [60].

Role in disease: Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers [12]. 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 [95, 159, 141]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [178, 70, 65, 48, 115]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis [15]. 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 [59, 100, 10, 69]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples [28, 143, 2, 97, 62]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients [170].

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 [144, 173, 138]. 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 [91, 45, 11]. 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 [175, 83, 64, 166, 40, 98].

Drug resistance: Mutations in TP53 may increase resistance to ionizing radiation therapy [30, 104].

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) [27].

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.

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