CellMax LBx
Liquid Biopsy

Test Report
Lung cancer panel

CellMax Life

Test Report

CellMax LBx
Liquid Biopsy

Order Information

Requisition Number	SG001284
Patient Name	[redacted]
ID	[redacted]
Date of Birth	1963/07/29
Gender	M ☑ F ☐
Patient Phone Number	
Patient E-mail	
Name of Hospital or Clinic	
Lab Phone Number	
Name of Physician	[redacted]
Specimen Site	Peripheral blood
Disease	Non-small cell lung carcinoma (NSCLC)
SNOMED Concept ID	254637007
Date of Collection	2018/07/30
Date of Report	2018/08/22

Test Report

CellMax LBx Liquid Biopsy

Patient Test Results

Clinically Relevant Genomic Alterations Detected

TIER 1: VARIANTS OF STRONG CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
EGFR	E746_A750del	Afatinib (A), Osimertinib (A), Erlotinib (A), Gefitinib (A)	Neratinib (C)	None	Yes

TIER 2: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
EGFR	A750E	None	Neratinib (C), Afatinib (D), Osimertinib (D), Erlotinib (D), Gefitinib (D)	None	Yes
EGFR	amplification	None	Neratinib (C), Afatinib (D)	None	Yes
TP53	G245S	None	None	None	Yes

MSI Rresult

MSI-H	Not detected

Comments

For metastatic NSCLC patients with sensitizing EGFR mutation harboring tumors, the NCCN guidelines (v.5.2018) suggest treating with erlotinib, afatinib, gefitinib, or osimertinib (category 1) if the alteration is discovered prior to first-line chemotherapy or, if the alteration is discovered during first-line chemotherapy, interrupting/completing current therapy and treating with erlotinib, afatinib, gefitinib, or osimertinib (category 2A).

Electronic Signatures

Laboratory Manager

Leon Chen 陳律吾 Leon Chen.

Date

2018/08/22

Pathologist

Manana Kvezereli-Javey, MD, PhD

Date

2018/08/22

CellMax Life

CellMax LBx
Liquid Biopsy

LBx-Liquid Biopsy Test Report

Report outline:

CellMaxLife

Patient ID: SG001284
Report Date: Aug 21, 2018
Gender: male

Report ID: SG001284
Disease: Non-small cell lung carcinoma (NSCLC)

1. Summary

CLINICALLY RELEVANT ALTERATIONS

TIER 1: VARIANTS OF STRONG CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
EGFR	E746_A750del	Afatinib (A), Osimertinib (A), Erlotinib (A), Gefitinib (A)	Neratinib (C)	None	Yes

Prognostic and Diagnostic Variants: None

TIER 2: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
EGFR	A750E	None	Neratinib (C), Afatinib (D), Osimertinib (D), Erlotinib (D), Gefitinib (D)	None	Yes
EGFR	amplification	None	Neratinib (C), Afatinib (D)	None	Yes
TP53	G245S	None	None	None	Yes

Prognostic and Diagnostic Variants: None

GUIDELINES

Marker-Alteration	Summary
EGFR-E746_A750del	For NSCLC patients with metastatic disease and tumors harboring a sensitizing EGFR mutation, the NCCN guidelines (v.5.2018) suggest treating with erlotinib, afatinib, gefitinib, or osimertinib (category 1) if the alteration is discovered prior to first-line chemotherapy or, if the alteration is discovered during first-line chemotherapy, interrupting/completing current therapy and treating with erlotinib, afatinib, gefitinib, or osimertinib (category 2A). For NSCLC patients harboring an EGFR sensitizing mutation and exhibiting resistance to Egfr-targeted therapy, the NCCN Guidelines (v.5.2018) suggest high-sensitivity evaluation for EGFR T790M followed by testing for MET and ERBB2 amplification to assist in directing patients for additional therapies.

INTERACTIONS: NONE

VARIANTS NOT CURATED BY CELLMAX

Marker	Alteration
ROS1	p.Trp1856Cys (W1856C)

OTHER ALTERATIONS

TIER 3: VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE: NONE

TIER 4: BENIGN OR LIKELY BENIGN VARIANTS: NONE

CellMax Life

LABORATORY TECHNICAL DATA

Marker	Alteration	Map Location	Variant Allele Frequency	Coding Sequence Change	Transcript ID
EGFR	E746_A750del	chr7:55242464	59.08%	c.2235_2249delGGAATTAAGAGAAGC	NM_005228
EGFR	A750E	chr7:55242479	0.49%	c.2249C>A	NM_005228
EGFR	amplification	chr7:55241613-55259567		amplification	NM_005228
TP53	G245S	chr17:7577548	19.57%	c.733G>A	NM_000546
ROS1	W1856C	chr6:117645568	16.56%	c.5568G>T	NM_002944

The data in this table was generated by the laboratory in the course of molecular testing. It has not been altered in any way by CellMax.

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2. Detailed Biomarker Information

2.1. EGFR-E746_A750del (p.Glu746_Ala750del)

TIER 1: Variant of Strong Clinical Significance

2.1.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
EGFR	- MUTN (seq): p.Glu746_Ala750del (E746_A750del)	EGFR-E746_A750del 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 FDA approval in some tumor types (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883).

2.1.2 BIOLOGICAL RELEVANCE of EGFR-E746_A750del (p.Glu746_Ala750del)

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Molecular function	E746_A750del is located in the kinase domain of Egfr; this mutation and other exon 19 deletions have been shown to activate the tyrosine kinase activity of Egfr and confer sensitivity to Egfr tyrosine kinase inhibitors such as erlotinib and gefitinib (Lynch et al., 2004; 15118073, Paez et al., 2004; 15118125, Pao et al., 2004; 15329413).
Incidence in disease	EGFR mutations have been reported in 27% (24604/90800) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (Jun 2018). EGFR mutations have been reported in 10-29% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, Jun 2018). EGFR mutations have been reported in 14-36% of NSCLC cases, and found to be more common in East Asian patients as compared with other ethnicities (Zhang et al., 2018; 29543321, Riess et al., 2018; 29981927, Zhang et al., 2016; 27738317, Imyanitov et al., 2016; 27259329, Giannini et al., 2016; 27373829, Lee et al., 2016; 26992209, Han et al., 2017; 29110846).

2.1.3 CLINICAL RELEVANCE of EGFR-E746_A750del (p.Glu746_Ala750del)

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
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 (Ciardiello and Tortora, 2008; 18337605). EGFR mutations in NSCLC have been reported to occur more frequently in women, never-smokers, and in patients with adenocarcinoma histology (Rizzo et al., 2016; 25956936, Lee et al., 2015; 26359571, Naderi et al., 2015; 26362141, Zhou et al., 2016; 27039821, Lee et al., 2016; 26992209, Zhang et al., 2016; 27738317).

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Effect on 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 (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883, Rosell et al., 2012; 22285168). The Egfr TKIs erlotinib, afatinib, gefitinib, and osimertinib have been approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR mutations (Soria et al., 2018; 29151359, Shepherd et al., 2005; 16014882, Rosell et al., 2012; 22285168, Sequist et al., 2013; 23816960, Douillard et al., 2014; 24263064, Mok et al., 2009; 19692680). Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations (Yang et al., 2015; 26051236). Erlotinib, in combination with gemcitabine, has also been approved by the FDA for the treatment of locally advanced, unresectable, or metastatic pancreatic cancer (Moore et al., 2007; 17452677, Senderowicz et al., 2007; 18247017). For NSCLC patients with metastatic disease and tumors harboring a sensitizing EGFR mutation (defined as an exon 19 deletion or L858R) the NCCN guidelines (v.5.2018) suggest treating with erlotinib, afatinib, gefitinib or osimertinib (category 1) if the alteration is discovered prior to first-line chemotherapy or, if the alteration is discovered during first-line chemotherapy, interrupting/completing current therapy and treating with erlotinib, afatinib, gefitinib, or osimertinib (category 2A); the NCCN guidelines also note that less common EGFR mutations, such as exon 19 insertions, L861Q, G719X, and S768I, may also predict sensitivity to tyrosine kinase inhibitors.
Effect on 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 (Engelman et al., 2007; 17463250, Greulich et al., 2005; 16187797, Kwak et al., 2005; 15897464, Takezawa et al., 2012; 22956644, Yu et al., 2013; 23470965). Third generation irreversible Egfr TKIs that target the EGFR T790M mutation have shown efficacy in T790M-mutant NSCLC, including osimertinib, which has received FDA-approval for the treatment of EGFR T790M-mutant metastatic NSCLC (Jänne et al., 2011; 21220471, Jänne et al., 2015; 25923549, Greig, 2016; 26729184, Yang et al., 2016; 27198353, Wang et al., 2016; 27071706). 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 (Watanabe et al., 2013; 24012411, Chang et al., 2013; 24101933, Popat et al., 2013; 23312887, Sequist et al., 2011; 21430269). Preclinical studies have reported increased Smo expression in NSCLC cell lines resistant to first, second, and third generation Egfr inhibitors as compared with sensitive ones; treatment with Smo inhibitors was observed to restore sensitivity in the resistant cell lines (Della et al., 2015; 26124204, Bai et al., 2016; 26943330, Della et al., 2017; 28416737).

2.1.4 CLINICAL EVIDENCE in Non-small cell lung carcinoma (NSCLC)

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
FDA Approved	Afatinib. Osimertinib. Erlotinib. Gefitinib.

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Phase III Data	A meta-analysis of six trials including 4675 EGFR-mutant patients reported no significant difference in overall survival, time to progression, or response rate with Egfr TKI monotherapy versus Egfr TKI treatment in combination with chemotherapy as first-line treatment (Yan et al., 2015; 26285137). 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 (Zhang et al., 2016; 26933807). Afatinib has been FDA-approved for the treatment of lung squamous cell carcinoma (SCC) following progression on platinum-based chemotherapy on the basis of the Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line treatment in 795 stage 3b/4 lung SCC patients. 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 (Soria et al., 2015; 26156651). 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 (Sequist et al., 2013; 23816960). Phase 3 studies of afatinib in unselected NSCLC patients previously treated with either erlotinib or gefitinib have reported significantly increased median progression-free survival, but similar overall survival and increased toxicity alone or in combination with chemotherapy, as compared with placebo or single agent chemotherapy (Schuler et al., 2016; 26646759, Miller et al., 2012; 22452896). 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) (Soria et al., 2018; 29151359). Erlotinib was approved by the FDA for unselected NSCLC patients based on a Phase 3 randomized trial demonstrating prolonged overall survival for unselected NSCLC patients treated with erlotinib compared with standard chemotherapy (Shepherd et al., 2005; 16014882). However, FDA 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 (FDA) (Cicènas et al., 2016; 27987585). 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 (Douillard et al., 2014; 24263064, Kazandjian et al., 2016; 26980062). The Phase 3 IPASS study compared gefitinib to carboplatin plus paclitaxel in 1,217 NSCLC patients with adenocarcinoma histology. Progression-free survival at 12 months was 24.9% in the gefitinib group and 6.7% in the carboplatin-paclitaxel group, and the objective response rates were 43% and 32.2%, respectively. In the 261 EGFR mutation positive patients, increased progression-free survival and objective response rates (71.2% and 47.3%, respectively) were reported in the gefitinib group as compared with the chemotherapy group (Mok et al., 2009; 19692680). A Phase 3 study of gefitinib monotherapy as compared

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
	with gefitinib, carboplatin, and pemetrexed in 344 untreated stage 3/4 or recurrent NSCLC patients with activating EGFR mutations has reported an improvement in median progression-free survival (20.9 versus 11.2 months) and overall survival (52.2 versus 38.8 months), but not in time to second disease progression (PFS2) (20.9 versus 21.1 months) in the combination arm as compared with the gefitinib monotherapy arm (Nakamura et al., 2018; ASCO 2018, Abstract 9005). 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 (Mok et al., 2018; 29864379, Mok et al., 2017; ASCO 2017, Abstract LBA9007, Wu et al., 2017; 28958502). 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 (Ramalingam et al., 2014; 25439691, Ramalingam et al., 2016; 26768165).
Phase II Data	A Phase 2 study of neratinib in NSCLC patients has reported limited clinical activity, with an overall response rate of 2% (3/158). 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 (Sequist et al., 2010; 20479403).
Phase I Data	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 (Heigener et al., 2015; 26354527). 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%) (Otsuka et al., 2015; 26349474).
Preclinical	Preclinical studies suggest that Hsp90 inhibitors may be effective in NSCLC cells that are resistant to Egfr inhibitors (Shimamura et al., 2012; 22806877, Kobayashi et al., 2012; 21767894, Wang et al., 2016; 27616574, Courtin et al., 2016; 27673365).

2.1.5 SAMPLE RELEVANT THERAPIES

Therapies targeting EGFR

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Afatinib	Gilotrif	A	Irreversible pan-ErbB kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Lung squamous cell carcinoma, EGFR-mutant NSCLC)
Erlotinib	Tarceva	A	Egfr tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Pancreatic carcinoma, Lung large cell neuroendocrine carcinoma, EGFR-mutant NSCLC)
Gefitinib	Iressa	A	Egfr tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (EGFR-mutant NSCLC)
Osimertinib	Tagrisso	A	Egfr T790M inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (EGFR-mutant NSCLC)

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Dacomitinib		B	Pan-ErbB family tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Lung cancer)
Neratinib	Nerlynx	C	Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Breast carcinoma)
Icotinib	Conmana	None found	Egfr inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Esophageal carcinoma)
Naquotinib		None found	EGFR mutant-specific inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
Pyrotinib		None found	Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
Poziotinib		None found	Egfr/Her2/ErbB4 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Breast carcinoma)
Avitinib		None found	EGFR mutant-specific inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Non-Hodgkin lymphoma (NHL))
CK-101		None found	Third generation EGFR-mutant-specific (T790M, L858R, exon 19 deletion) tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
AP32788		None found	EGFR/ERBB2 mutant-specific inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
AZD3759		None found	Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
Nazartinib		None found	Third generation EGFR mutant-specific (T790M, L858R, exon 19 deletion) tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
Olmutinib		None found	Egfr inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
Varlitinib		None found	Egfr/Her2 inhibitor.	Phase 2 (Gastric carcinoma, Pancreatic carcinoma)
PF-06747775		None found	EGFR T790M-specific inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
Pirotinib		None found	ErbB family inhibitor.	Phase 1 (Solid Tumor)

2.1.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT02448251	Safety, Pharmacokinetic and Preliminary Efficacy Study of AC0010MA in Advanced Non Small Cell Lung Cancer	Phase 1	EGFR	•Overall contact: Liming Liu, MD, PhD, limingliu@aceabio.com, 858-249-9120 •CA (2), GA (1), TX (1), Madrid (2), Marseille (1)

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
2	EGFR	NCT02411448	A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Participants With EGFR Mutation-Positive Metastatic NSCLC	Phase 3	EGFR, ERBB3, ERBB4, KDR	•Overall contact: There may be multiple sites in this clinical trial. 1-877-CTLILLY (1-877-285-4559) or, 1-317-615-4559 •Greece (2), Hong Kong (2), Italy (1), Japan (28), Korea, Republic of (4), Taiwan (3)
3	EGFR	NCT02633189	Study Comparing Bevacizumab + Erlotinib vs Erlotinib Alone as First Line Treatment of Patients With EGFR Mutated Advanced Non Squamous Non Small Cell Lung Cancer	Phase 3	EGFR, VEGFA	•Overall contact: Francesco Perrone, M.D., f.perrone@istitutotumori.na.it, +39 081 5903522 •Italy (55)
4	EGFR	NCT01553942	Afatinib With CT and RT for EGFR-Mutant NSCLC	Phase 2	EGFR, ERBB2, ERBB3, ERBB4	•Overall contact: Lecia V Sequist, MD MPH, lvsequist@partners.org, 617-724-4000 •Dana-Farber Cancer Institute: Massachusetts, USA, Geoffrey Oxnard, MD, goxnard@partners.org, (MA) •Massachusetts General Hospital: Massachusetts, USA, Lecia V Sequist, MD MPH, lvsequist@partners.org, (MA)
5	EGFR	NCT01859026	A Phase I/IB Trial of MEK162 in Combination With Erlotinib in NSCLC Harboring KRAS or EGFR Mutation	Phase 1	EGFR, MEK	•H. Lee Moffitt Cancer Center and Research Institute: Florida, USA, Germaine Gonzalez-Vazquez, germaine.gonzalezvazquez@moffitt.org, (FL)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT02511106	AZD9291 Versus Placebo in Patients With Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy.	Phase 3	EGFR	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (5), CO (1), CT (2), FL (3), GA (2), HI (1), IL (1), MD (1), NJ (2), NY (2), RI (1), TN (2), TX (1), VA (1), WA (1), Australia (8), Belgium (6), Brazil (13), Canada (1), China (31), France (5), Germany (13), Hong Kong (2), Hungary (5), Israel (5), Italy (14), Japan (22), Netherlands (4), Poland (8), Romania (4), Russian Federation (14), Spain (13), Sweden (1), Taiwan (11), Thailand (3), Turkey (8), Ukraine (9), Vietnam (3)
2	EGFR	NCT02143466	AZD9291 in Combination With Ascending Doses of Novel Therapeutics	Phase 1	CD274, CTLA-4 obsolete - see CTLA4, CTLA4, EGFR, MEK, MET	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (1), GA (1), MA (2), NY (1), PA (1), TN (1), Canada (2), China (10), Japan (6), Korea, Republic of (6), Poland (5), Russian Federation (9), Taiwan (6), Ukraine (5)

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
3	EGFR	NCT02448251	Safety, Pharmacokinetic and Preliminary Efficacy Study of AC0010MA in Advanced Non Small Cell Lung Cancer	Phase 1	EGFR	•Overall contact: Liming Liu, MD, PhD, limingliu@aceabio.com, 858-249-9120 •CA (2), GA (1), TX (1), Madrid (2), Marseille (1)
4	EGFR	NCT03381274	Oleclumab (MEDI9447) EGFRm NSCLC Novel Combination Study	Phase 1/Phase 2	ADORA2A, EGFR	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (2), CO (1), CT (1), FL (1), MD (1), NY (1), TX (1), Seoul (3)
5	EGFR	NCT02424617	A Study of BGB324 in Combination With Erlotinib in Patients With Non-Small Cell Lung Cancer	Phase 1/Phase 2	AXL, EGFR	•Overall contact: Dr. Murray Yale, MD, murray.yule@bergenbio.com, 47 535 01 564 •CA (2), FL (1), IN (1), MI (1), TN (1), TX (4)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

2.2. EGFR-A750E (p.Ala750Glu)

TIER 2: Variant of Potential Clinical Significance

2.2.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
EGFR	- MUTN (seq): p.Ala750Glu (A750E)	EGFR-A750E is predicted to be 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 FDA approval in some tumor types (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883).

2.2.2 BIOLOGICAL RELEVANCE of EGFR-A750E (p.Ala750Glu)

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Molecular function	EGFR A750E is a missense alteration that occurs in exon 19, within the kinase domain of the Egfr protein (UniProt). This alteration falls within a small region of frequent in-frame deletions in non-small cell lung carcinoma (NSCLC) shown to lead to activation of Egfr kinase activity and confer sensitivity to Egfr inhibitors (Tam et al., 2006; 16533793, Lynch et al., 2004; 15118073, Paez et al., 2004; 15118125, Pao et al., 2004; 15329413). Another alteration at this location, A750P, has been shown to result in constitutive activation of Egfr and lead to tumor formation in mice (Sun et al., 2009; 19625781). Therefore, although EGFR A750E specifically has not been functionally characterized, it is also predicted to be an activating mutation.
Incidence in disease	EGFR mutations have been reported in 27% (24604/90800) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (Jun 2018). EGFR mutations have been reported in 10-29% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, Jun 2018). EGFR mutations have been reported in 14-36% of NSCLC cases, and found to be more common in East Asian patients as compared with other ethnicities (Zhang et al., 2018; 29543321, Riess et al., 2018; 29981927, Zhang et al., 2016; 27738317, Imyanitov et al., 2016; 27259329, Giannini et al., 2016; 27373829, Lee et al., 2016; 26992209, Han et al., 2017; 29110846).

2.2.3 CLINICAL RELEVANCE of EGFR-A750E (p.Ala750Glu)

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
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 (Ciardiello and Tortora, 2008; 18337605). EGFR mutations in NSCLC have been reported to occur more frequently in women, never-smokers, and in patients with adenocarcinoma histology (Rizzo et al., 2016; 25956936, Lee et al., 2015; 26359571, Naderi et al., 2015; 26362141, Zhou et al., 2016; 27039821, Lee et al., 2016; 26992209, Zhang et al., 2016; 27738317).

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Effect on 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 (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883, Rosell et al., 2012; 22285168). The Egfr TKIs erlotinib, afatinib, gefitinib, and osimertinib have been approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR mutations (Soria et al., 2018; 29151359, Shepherd et al., 2005; 16014882, Rosell et al., 2012; 22285168, Sequist et al., 2013; 23816960, Douillard et al., 2014; 24263064, Mok et al., 2009; 19692680). Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations (Yang et al., 2015; 26051236). Erlotinib, in combination with gemcitabine, has also been approved by the FDA for the treatment of locally advanced, unresectable, or metastatic pancreatic cancer (Moore et al., 2007; 17452677, Senderowicz et al., 2007; 18247017). For NSCLC patients with metastatic disease and tumors harboring a sensitizing EGFR mutation (defined as an exon 19 deletion or L858R) the NCCN guidelines (v.5.2018) suggest treating with erlotinib, afatinib, gefitinib or osimertinib (category 1) if the alteration is discovered prior to first-line chemotherapy or, if the alteration is discovered during first-line chemotherapy, interrupting/completing current therapy and treating with erlotinib, afatinib, gefitinib, or osimertinib (category 2A); the NCCN guidelines also note that less common EGFR mutations, such as exon 19 insertions, L861Q, G719X, and S768I, may also predict sensitivity to tyrosine kinase inhibitors.
Effect on 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 (Engelman et al., 2007; 17463250, Greulich et al., 2005; 16187797, Kwak et al., 2005; 15897464, Takezawa et al., 2012; 22956644, Yu et al., 2013; 23470965). Third generation irreversible Egfr TKIs that target the EGFR T790M mutation have shown efficacy in T790M-mutant NSCLC, including osimertinib, which has received FDA-approval for the treatment of EGFR T790M-mutant metastatic NSCLC (Jänne et al., 2011; 21220471, Jänne et al., 2015; 25923549, Greig, 2016; 26729184, Yang et al., 2016; 27198353, Wang et al., 2016; 27071706). 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 (Watanabe et al., 2013; 24012411, Chang et al., 2013; 24101933, Popat et al., 2013; 23312887, Sequist et al., 2011; 21430269). Preclinical studies have reported increased Smo expression in NSCLC cell lines resistant to first, second, and third generation Egfr inhibitors as compared with sensitive ones; treatment with Smo inhibitors was observed to restore sensitivity in the resistant cell lines (Della et al., 2015; 26124204, Bai et al., 2016; 26943330, Della et al., 2017; 28416737).

2.2.4 CLINICAL EVIDENCE in Non-small cell lung carcinoma (NSCLC)

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
FDA Approved	(Afatinib approved for NSCLC with EGFR exon 19 deletion, L858R, G719X, L861Q, and/or S768I). (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).

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Phase III Data	A meta-analysis of six trials including 4675 EGFR-mutant patients reported no significant difference in overall survival, time to progression, or response rate with Egfr TKI monotherapy versus Egfr TKI treatment in combination with chemotherapy as first-line treatment (Yan et al., 2015; 26285137). 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 (Zhang et al., 2016; 26933807). Afatinib has been FDA-approved for the treatment of lung squamous cell carcinoma (SCC) following progression on platinum-based chemotherapy on the basis of the Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line treatment in 795 stage 3b/4 lung SCC patients. 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 (Soria et al., 2015; 26156651). 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 (Sequist et al., 2013; 23816960). Phase 3 studies of afatinib in unselected NSCLC patients previously treated with either erlotinib or gefitinib have reported significantly increased median progression-free survival, but similar overall survival and increased toxicity alone or in combination with chemotherapy, as compared with placebo or single agent chemotherapy (Schuler et al., 2016; 26646759, Miller et al., 2012; 22452896). 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) (Soria et al., 2018; 29151359). Erlotinib was approved by the FDA for unselected NSCLC patients based on a Phase 3 randomized trial demonstrating prolonged overall survival for unselected NSCLC patients treated with erlotinib compared with standard chemotherapy (Shepherd et al., 2005; 16014882). However, FDA 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 (FDA) (Cicènas et al., 2016; 27987585). 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 (Douillard et al., 2014; 24263064, Kazandjian et al., 2016; 26980062). The Phase 3 IPASS study compared gefitinib to carboplatin plus paclitaxel in 1,217 NSCLC patients with adenocarcinoma histology. Progression-free survival at 12 months was 24.9% in the gefitinib group and 6.7% in the carboplatin-paclitaxel group, and the objective response rates were 43% and 32.2%, respectively. In the 261 EGFR mutation positive patients, increased progression-free survival and objective response rates (71.2% and 47.3%, respectively) were reported in the gefitinib group as compared with the chemotherapy group (Mok et al., 2009; 19692680). A Phase 3 study of gefitinib monotherapy as compared

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
	with gefitinib, carboplatin, and pemetrexed in 344 untreated stage 3/4 or recurrent NSCLC patients with activating EGFR mutations has reported an improvement in median progression-free survival (20.9 versus 11.2 months) and overall survival (52.2 versus 38.8 months), but not in time to second disease progression (PFS2) (20.9 versus 21.1 months) in the combination arm as compared with the gefitinib monotherapy arm (Nakamura et al., 2018; ASCO 2018, Abstract 9005). 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 (Mok et al., 2018; 29864379, Mok et al., 2017; ASCO 2017, Abstract LBA9007, Wu et al., 2017; 28958502). 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 (Ramalingam et al., 2014; 25439691, Ramalingam et al., 2016; 26768165).
Phase II Data	A Phase 2 study of neratinib in NSCLC patients has reported limited clinical activity, with an overall response rate of 2% (3/158). 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 (Sequist et al., 2010; 20479403).
Phase I Data	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 (Heigener et al., 2015; 26354527). 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%) (Otsuka et al., 2015; 26349474).
Preclinical	Preclinical studies suggest that Hsp90 inhibitors may be effective in NSCLC cells that are resistant to Egfr inhibitors (Shimamura et al., 2012; 22806877, Kobayashi et al., 2012; 21767894, Wang et al., 2016; 27616574, Courtin et al., 2016; 27673365).

2.2.5 SAMPLE RELEVANT THERAPIES

Therapies targeting EGFR

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Neratinib	Nerlynx	C	Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Breast carcinoma)
Afatinib	Gilotrif	D	Irreversible pan-ErbB kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Lung squamous cell carcinoma, EGFR-mutant NSCLC)
Erlotinib	Tarceva	D	Egfr tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Pancreatic carcinoma, Lung large cell neuroendocrine carcinoma, EGFR-mutant NSCLC)
Gefitinib	Iressa	D	Egfr tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (EGFR-mutant NSCLC)
Osimertinib	Tagrisso	D	Egfr T790M inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (EGFR-mutant NSCLC)

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Dacomitinib		D	Pan-ErbB family tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Lung cancer)
Icotinib	Conmana	None found	Egfr inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Esophageal carcinoma)
Pyrotinib		None found	Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
Poziotinib		None found	Egfr/Her2/ErbB4 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Breast carcinoma)
AP32788		None found	EGFR/ERBB2 mutant-specific inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
AZD3759		None found	Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
Varlitinib		None found	Egfr/Her2 inhibitor.	Phase 2 (Gastric carcinoma, Pancreatic carcinoma)
Pirotinib		None found	ErbB family inhibitor.	Phase 1 (Solid Tumor)

2.2.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT03381274	Oleclumab (MEDI9447) EGFRm NSCLC Novel Combination Study	Phase 1/Phase 2	ADORA2A, EGFR	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (2), CO (1), CT (1), FL (1), MD (1), NY (1), TX (1), Seoul (3)
2	EGFR	NCT02411448	A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Participants With EGFR Mutation-Positive Metastatic NSCLC	Phase 3	EGFR, ERBB3, ERBB4, KDR	•Overall contact: There may be multiple sites in this clinical trial. 1-877-CTLILLY (1-877-285-4559) or, 1-317-615-4559 •Greece (2), Hong Kong (2), Italy (1), Japan (28), Korea, Republic of (4), Taiwan (3)
3	EGFR	NCT02633189	Study Comparing Bevacizumab + Erlotinib vs Erlotinib Alone as First Line Treatment of Patients With EGFR Mutated Advanced Non Squamous Non Small Cell Lung Cancer	Phase 3	EGFR, VEGFA	•Overall contact: Francesco Perrone, M.D., f.perrone@istitutotumori.na.it, +39 081 5903522 •Italy (55)
4	EGFR	NCT01553942	Afatinib With CT and RT for EGFR-Mutant NSCLC	Phase 2	EGFR, ERBB2, ERBB3, ERBB4	•Overall contact: Lecia V Sequist, MD MPH, lvsequist@partners.org, 617-724-4000 •Dana-Farber Cancer Institute: Massachusetts, USA, Geoffrey Oxnard, MD, goxnard@partners.org, (MA) •Massachusetts General Hospital: Massachusetts, USA, Lecia V Sequist, MD MPH, lvsequist@partners.org, (MA)

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
5	EGFR	NCT01859026	A Phase I/IB Trial of MEK162 in Combination With Erlotinib in NSCLC Harboring KRAS or EGFR Mutation	Phase 1	EGFR, MEK	•H. Lee Moffitt Cancer Center and Research Institute: Florida, USA, Germaine Gonzalez-Vazquez, germaine.gonzalezvazquez@moffitt.org, (FL)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT02511106	AZD9291 Versus Placebo in Patients With Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy.	Phase 3	EGFR	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (5), CO (1), CT (2), FL (3), GA (2), HI (1), IL (1), MD (1), NJ (2), NY (2), RI (1), TN (2), TX (1), VA (1), WA (1), Australia (8), Belgium (6), Brazil (13), Canada (1), China (31), France (5), Germany (13), Hong Kong (2), Hungary (5), Israel (5), Italy (14), Japan (22), Netherlands (4), Poland (8), Romania (4), Russian Federation (14), Spain (13), Sweden (1), Taiwan (11), Thailand (3), Turkey (8), Ukraine (9), Vietnam (3)
2	EGFR	NCT02143466	AZD9291 in Combination With Ascending Doses of Novel Therapeutics	Phase 1	CD274, CTLA-4 obsolete - see CTLA4, CTLA4, EGFR, MEK, MET	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (1), GA (1), MA (2), NY (1), PA (1), TN (1), Canada (2), China (10), Japan (6), Korea, Republic of (6), Poland (5), Russian Federation (9), Taiwan (6), Ukraine (5)
3	EGFR	NCT03381274	Oleclumab (MEDI9447) EGFRm NSCLC Novel Combination Study	Phase 1/Phase 2	ADORA2A, EGFR	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (2), CO (1), CT (1), FL (1), MD (1), NY (1), TX (1), Seoul (3)
4	EGFR	NCT02917993	An Open-Label Phase 1/2 Study of INCB039110 in Combination With Osimertinib in Subjects With Non-Small Cell Lung Cancer	Phase 1/Phase 2	EGFR, JAK1	•Overall contact: Incyte Corporation Call Center, 1.855.463.3463 •AZ (1), CA (3), CO (1), DC (1), FL (1), MA (1), MI (2), NJ (1), NY (2), OH (1), OR (1), PA (1), TX (4), UT (1), VA (1), WV (1), Barcelona (1), Madrid (1), Seoul (3), Taipei (1), Taipei City (1), Valencia (1)
5	EGFR	NCT03239340	A Molecular Profiling Study of Patients With EGFR Mutation-positive Locally Advanced or Metastatic NSCLC Treated With Osimertinib	Phase 2	EGFR	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (1), CT (1), GA (2), IL (1), MA (1), Italy (7), Korea, Republic of (8), Malaysia (5), Spain (6)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

2.3. EGFR-amplification

TIER 2: Variant of Potential Clinical Significance

2.3.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
EGFR	- MUTN (seq): amplification	EGFR-amplification is an activating alteration.
	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 FDA approval in some tumor types (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883).

2.3.2 BIOLOGICAL RELEVANCE of EGFR-amplification

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Molecular function	High-level EGFR gene amplification has been correlated with elevated Egfr protein expression, as measured by immunohistochemistry, although this correlation is not consistent for low-level gene amplification (Hemmings et al., 2009; 19404848, Liang et al., 2010; 20637128, Yang et al., 2012; 22490401, Bhargava et al., 2005; 15920544, Miyai et al., 2010; 20608935).
Incidence in disease	Putative high-level amplification of EGFR has been reported in 5.0-6.0% of Non-small cell lung carcinoma (NSCLC) cases (cBioPortal for Cancer Genomics, Jun 2018). Amplification of EGFR has been reported in 6-10% of non-small cell lung carcinoma (NSCLC) samples in several large studies (Genova et al., 2018; 29158193, Park et al., 2012; 22207554, Grob et al., 2013; 23238037, Liang et al., 2010; 20637128, Zhang et al., 2014; 24452282, Schrock et al., 2016; 27343443). However, smaller studies of less than 100 samples have detected higher incidences of EGFR amplification in NSCLC, citing it in 35-64% of cases, with one study reporting EGFR amplification in 72% (16/22) and 64% (16/25) of adenocarcinoma and squamous cell carcinoma samples, respectively (Russell et al., 2014; 24300726, Liang et al., 2010; 20637128, Tochigi et al., 2011; 21502435, Oakley and Chiosea, 2011; 21587084, Jia et al., 2015; 26400330). One study reported positive EGFR mRNA expression in the peripheral blood of 69% (29/42) of non-small cell lung carcinoma (NSCLC) patients, as compared with 12.5% (5/40) of control patients without lung cancer (Zhang et al., 2014; 24396405). Egfr expression has been reported in 19-69% of NSCLC cases (Ludovini et al., 2013; 23314677, Dobashi et al., 2011; 21040950, Traynor et al., 2013; 23628526, Watzka et al., 2010; 20353893, Liang et al., 2010; 20637128, Grob et al., 2013; 23238037, Park et al., 2012; 22207554, Hao et al., 2015; 26648997).

2.3.3 CLINICAL RELEVANCE of EGFR-amplification

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
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 (Ciardiello and Tortora, 2008; 18337605). EGFR mutations in NSCLC have been reported to occur more frequently in women, never-smokers, and in patients with adenocarcinoma histology (Rizzo et al., 2016; 25956936, Lee et al., 2015; 26359571, Naderi et al., 2015; 26362141, Zhou et al., 2016; 27039821, Lee et al., 2016; 26992209, Zhang et al., 2016; 27738317).

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Effect on drug sensitivity	EGFR amplification or increased copy number may result in elevated Egfr protein expression and thus predict sensitivity to Egfr targeted therapies. The Egfr tyrosine kinase inhibitors (TKIs) erlotinib, afatinib, and gefitinib have been FDA approved for the treatment of non-small cell lung carcinoma (NSCLC) with specific EGFR mutations; however, only modest clinical benefit for gefitinib or erlotinib has been reported in patients harboring EGFR amplification without concurrent sensitizing mutations (Cappuzzo et al., 2015; 25514804, Kelly et al., 2015; 26324372, Ahn et al., 2008; 18559606, Fukuoka et al., 2011; 21670455, Douillard et al., 2010; 20038723, Yang et al., 2015; 26051236). Anti-Egfr monoclonal antibodies are also approved in some indications, including cetuximab, which is an approved therapy for head and neck and colorectal cancer, panitumumab, which is approved in colorectal cancer, and necitumumab, which has received approval for the treatment of advanced squamous NSCLC (Cunningham et al., 2004; 15269313, Vermorken et al., 2008; 18784101, Van Cutsem et al., 2007; 17470858, Thatcher et al., 2015; 26045340). However, the NCCN guidelines (v.2.2018) state that the addition of necitumumab is not beneficial based on toxicity, cost, and limited improvement in efficacy when compared with cisplatin/gemcitabine. In addition, afatinib and erlotinib have been removed as recommended second-line therapies for squamous NSCLC due to limited improvements in overall survival and quality of life when compared with other available agents (NCCN Guidelines, v.2.2018).

2.3.4 CLINICAL EVIDENCE in Non-small cell lung carcinoma (NSCLC)

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
FDA Approved	Afatinib (approved in lung squamous cell carcinoma independent of EGFR). Necitumumab (approved in lung squamous cell carcinoma).
Phase III Data	Afatinib has been FDA-approved for the treatment of lung squamous cell carcinoma (SCC) following progression on platinum-based chemotherapy on the basis of the Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line treatment in 795 stage 3b/4 lung SCC patients. 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 (Soria et al., 2015; 26156651). 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 (Sequist et al., 2013; 23816960). Phase 3 studies of afatinib in unselected NSCLC patients previously treated with either erlotinib or gefitinib have reported significantly increased median progression-free survival, but similar overall survival and increased toxicity alone or in combination with chemotherapy, as compared with placebo or single agent chemotherapy (Schuler et al., 2016; 26646759, Miller et al., 2012; 22452896). A Phase 3 randomized study in 1093 stage 4 squamous NSCLC patients reported that treatment with first-line necitumumab in combination with gemcitabine (G) and cisplatin (C) compared with GC alone was associated with an increase in overall survival (11.5 and 9.9 months, respectively) and an increase in median progression free survival (5.7 and 5.5 months, respectively); the objective response rates were similar between the two groups (31% and 29%, respectively), although necitumumab in combination with GC showed an increased disease control rate (82% versus 77%, respectively). An increase in grade 3 or higher adverse events was also reported in the cohort treated with necitumumab plus GC (72%, 388/5387) compared with cohort treated with GC alone (62%, 333/541) (Thatcher et al., 2015; 26045340). A subgroup analysis of 982 stage 4 squamous NSCLC patients reported expression of Egfr in 95% (935/982) of cases; in Egfr-positive patients, the combination of necitumumab and GC resulted in a significantly increased median overall survival time of 11.7 months as compared with 10.0 months with GC alone. No differences in survival between treatments were reported in patients with no Egfr protein expression (Paz-Ares et al., 2016; 27198355, Paz-Ares et al., 2016; 27207107).

EGFR alterations in Non-small cell lung carcinoma (NSCLC)	
Phase II Data	A Phase 2 study of afatinib in NSCLC patients with EGFR copy number gain or amplification has reported an overall response rate of 13% (9/69) with progression-free and overall survival times of 8.4 and 50.4 weeks, respectively. The response rate was also reported to be higher in patients harboring additional EGFR mutations (25%, 3/12) as compared with EGFR wild-type patients (9%, 4/43) (Cappuzzo et al., 2015; 25514804). A Phase 2 study of neratinib in NSCLC patients has reported limited clinical activity, with an overall response rate of 2% (3/158). 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 (Sequist et al., 2010; 20479403). A Phase 2 trial of nimotuzumab in combination with chemotherapy (docetaxel and carboplatin) versus chemotherapy alone in 110 stage 3b/4 NSCLC patients reported an increased overall response rate in the nimotuzumab-treated group as compared with the chemotherapy-treated group (54% and 34.5%, respectively). Complete and partial responses were reported in 3.6% and 50% of nimotuzumab-treated patients, and in 4% and 30.9% in the chemotherapy group, respectively; no significant differences between the groups were observed in median progression-free survival, overall survival, and safety profile (Prabhash et al., 2013; ASCO 2013, Abstract 8053). A Phase 1b/2 study of afatinib and nimotuzumab in 43 evaluable patients with advanced NSCLC and acquired resistance to gefitinib or erlotinib reported median progression-free survival and overall survival of 4.0 and 11.7 months, respectively, and an overall response rate of 23% (10/43) in all evaluable patients and 30% (9/35) in patients harboring EGFR-activating mutations; combination treatment was deemed to have an acceptable toxicity profile (Lee et al., 2016; 26667485).
Phase I Data	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 (Heigener et al., 2015; 26354527).
Preclinical	N/A: Lower level clinical data are not presented when higher level clinical data are available.

2.3.5 SAMPLE RELEVANT THERAPIES

Therapies targeting EGFR

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Neratinib	Nerlynx	C	Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Breast carcinoma)
Afatinib	Gilotrif	D	Irreversible pan-ErbB kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Lung squamous cell carcinoma, EGFR-mutant NSCLC)
Nimotuzumab	Theraloc	D	Egfr inhibitory antibody.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Gastric carcinoma, Glioblastoma, Glioma, Pancreatic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, and various other cancers)
Necitumumab	Portrazza	E	Anti-Egfr monoclonal antibody.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved (Lung squamous cell carcinoma)
Pyrotinib		None found	Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
ABT-414		None found	Anti-Egfr monoclonal antibody drug conjugate.	Phase 1 (Solid Tumor) Phase 3 (Glioblastoma)
Poziotinib		None found	Egfr/Her2/ErbB4 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Breast carcinoma)
Sym004		None found	Anti-Egfr antibody mixture.	Phase 2 (Glioma, Head and neck squamous cell carcinoma (HNSCC), Colorectal carcinoma (CRC))

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Varlitinib		None found	Egfr/Her2 inhibitor.	Phase 2 (Gastric carcinoma, Pancreatic carcinoma)
ABBV-321		None found	Anti-Egfr antibody conjugated to monomethyl auristatin F.	Phase 1 (Solid Tumor) Phase 1 (Glioblastoma, Head and neck squamous cell carcinoma (HNSCC), Brain and Central Nervous System Tumors, Lung squamous cell carcinoma)
MM-151		None found	Anti-Egfr monoclonal antibody mixture.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
SYN004		None found	Anti-Egfr monoclonal antibody.	Phase 1 (Solid Tumor) Phase 1 (Lung squamous cell carcinoma)
ABBV-221		None found	Anti-Egfr antibody drug conjugate.	Phase 1 (Solid Tumor)
JNJ-61186372		None found	Bispecific anti-Met, anti-Egfr antibody.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
Pirotinib		None found	ErbB family inhibitor.	Phase 1 (Solid Tumor)
D2C7-IT		None found	Immunotoxin targeting both wild-type Egfr and Egfr-vIII.	Phase 1 (Glioblastoma)
EGFR(V)-EDV-Dox		None found	Doxorubicin-loaded EGFR-targeting nanocells.	Phase 1 (Glioblastoma)

Therapies targeting EGFR

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
ABT806		None found	Anti-Egfr and EGFRvIII antibody.	Phase 1 (Solid Tumor) Phase 2 (Gastroesophageal junction carcinoma)

2.3.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT03054038	Afatinib and Necitumumab in Patients With EGFR Mutation Positive Advanced or Metastatic Non-small Cell Lung Cancer	Phase 1	EGFR, ERBB2, ERBB3, ERBB4	•Overall contact: Clinical Trials Information Program, cip@vanderbilt.edu, 800-811-8480 •Vanderbilt-Ingram Cancer Center: Tennessee, USA, (TN) •City of Hope National Medical Center: California, USA, Thomas Fok Fok, tfok@coh.org, (CA)
2	EGFR	NCT01553942	Afatinib With CT and RT for EGFR-Mutant NSCLC	Phase 2	EGFR, ERBB2, ERBB3, ERBB4	•Overall contact: Lecia V Sequist, MD MPH, lvsequist@partners.org, 617-724-4000 •Dana-Farber Cancer Institute: Massachusetts, USA, Geoffrey Oxnard, MD, goxnard@partners.org, (MA) •Massachusetts General Hospital: Massachusetts, USA, Lecia V Sequist, MD MPH, lvsequist@partners.org, (MA)

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
3	EGFR	NCT03065387	Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification or HER3/4 Mutation	Phase 1	CDK4, CDK6, EGFR, ERBB2, MEK, MTOR	•Overall contact: Sarina Piha-Paul, MD, spihapau@mdanderson.org, 713-563-1930 •University of Texas MD Anderson Cancer Center: Texas, USA, (TX)
4	EGFR	NCT02364609	Pembrolizumab and Afatinib in Patients With Non-small Cell Lung Cancer With Resistance to Erlotinib	Phase 1	EGFR, ERBB2, ERBB3, ERBB4, PDCD1	•University of California Davis Comprehensive Cancer Center: California, USA, Jonathan W. Riess, jwriess@ucdavis.edu, (CA)
5	EGFR	NCT02795156	Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations	Phase 2	AXL, BRAF, EGFR, ERBB2, ERBB3, ERBB4, FLT1, FLT3, FLT4, KDR, KIT, MET, PDGFRA, PDGFRB, RAF1, RET, ROS1, TEK	•Overall contact: Sarah Cannon Development Innovations, LLC, CANN.InnovationsMedical@sarahcannon.com, 844-710-6157 •CO (1), FL (3), MO (1), TN (2), WI (1)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT03054038	Afatinib and Necitumumab in Patients With EGFR Mutation Positive Advanced or Metastatic Non-small Cell Lung Cancer	Phase 1	EGFR, ERBB2, ERBB3, ERBB4	•Overall contact: Clinical Trials Information Program, cip@vanderbilt.edu, 800-811-8480 •Vanderbilt-Ingram Cancer Center: Tennessee, USA, (TN) •City of Hope National Medical Center: California, USA, Thomas Fok Fok, tfok@coh.org, (CA)
2	EGFR	NCT02364609	Pembrolizumab and Afatinib in Patients With Non-small Cell Lung Cancer With Resistance to Erlotinib	Phase 1	EGFR, ERBB2, ERBB3, ERBB4, PDCD1	•University of California Davis Comprehensive Cancer Center: California, USA, Jonathan W. Riess, jwriess@ucdavis.edu, (CA)

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
3	EGFR	NCT02465060	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)	Phase 2	ABL1, AKT, ALK, BRAF, BTK, CDK4, CDK6, CSF1R, EGFR, EPHA2, EPHA3, ERBB2, ERBB3, ERBB4, FGFR1, FGFR2, FGFR3, FLT3, KDR, KIT, MEK, MET, MTOR, mTORC1, mTORC2, NTRK1, NTRK2, NTRK3, PDCD1, PDGFRA, PDGFRB, PI3K, PIK3CB, PTK2, RET, ROS1, RPS6KB1, SMO, SRC, VEGFR1, VEGFR3, WEE1, YES1	•AK (8), AL (2), AR (3), AZ (3), CA (108), CO (42), CT (13), DC (2), DE (9), FL (18), GA (19), HI (16), IA (22), ID (13), IL (61), IN (13), KS (18), KY (16), LA (20), MA (10), MD (16), ME (9), MI (93), MN (37), MO (34), MS (8), MT (10), NC (28), ND (7), NE (18), NH (5), NJ (19), NM (6), NV (32), NY (21), OH (72), OK (6), OR (15), PA (44), RI (4), SC (29), SD (3), TN (14), TX (15), UT (13), VA (10), VT (3), WA (59), WI (63), WV (7), WY (3), Bayamon (1), Manati (1), San Juan (2)
4	EGFR	NCT02609776	A Dose Escalation Study of JNJ-61186372 in Participants With Advanced Non-Small Cell Lung Cancer	Phase 1	EGFR, MET	•Overall contact: Use link at the bottom of the page to see if you qualify for an enrolling site (see list). If you still have questions:, JNJ.CT@sylogent.com •CA (2), FL (1), MA (1), MO (1), NY (2), OR (1), PA (1), VA (1), Cheongju-Si (1), Goyang-Si (1), Incheon (1), Seongnam-Si (1), Seoul (4)
5	EGFR	NCT03234712	A Study Evaluating the Safety, Pharmacokinetics, and Anti-tumor Activity of ABBV-321 in Subjects With Advanced Solid Tumors Associated With Overexpression of the Epidermal Growth Factor Receptor (EGFR) or Its Ligands	Phase 1	EGFR	•Overall contact: ABBVIE CALL CENTER, abbvieclinicaltrials@abbvie.com, 847.283.8955 •AR (1), CA (1), IL (3), NC (1), NY (1), RI (1), TX (1), Heidelberg (1), Ramat Gan (1), St Leonards (1)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

CellMaxLife

2.4. TP53-G245S (p.Gly245Ser)

TIER 2: Variant of Potential Clinical Significance

2.4.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
TP53	- MUTN (seq): p.Gly245Ser (G245S)	TP53-G245S exhibits altered function compared to wild-type.
	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 (Levine, 1997; 9039259, Wang et al., 2005; 15625370, Koga et al., 2001; 11400116, Kato et al., 2003; 12826609, Houben et al., 2011; 21760960, Olivier et al., 2009; 18802452). 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 (Schuler et al., 2014; 24583792, Vermeij et al., 2011; 21541192, Saito et al., 2014; 24982341). Tumors with TP53 mutations may be sensitive to the Wee1 inhibitor MK-1775, and clinical trials are currently underway for patients with solid tumors and hematologic malignancies (Hirai et al., 2010; 20107315, Bridges et al., 2011; 21799033). Aurora kinase A inhibitors are another therapeutic approach under investigation for TP53-mutated cancers (Vilgelm et al., 2015; 25398437, Li et al., 2015; 25512615, Katayama and Sen, 2011; 21761334, Tentler et al., 2015; 25758253, Kalous et al., 2013; 24091768). However, as the alteration reported here has been shown to have oncogenic effects, these therapeutic approaches are not expected to be relevant. Some studies suggest that Hsp90 inhibitors may be effective in tumors with oncogenic TP53 alterations (Alexandrova et al., 2015; 26009011, Lin et al., 2008; 17982489).

2.4.2 BIOLOGICAL RELEVANCE of TP53-G245S (p.Gly245Ser)

TP53 alterations in Non-small cell lung carcinoma (NSCLC)	
Molecular function	TP53 G245 in the transcript NM_000546 used in COSMIC corresponds to G113 and G206 in other TP53 transcripts (Integrated Genomics Viewer, v.2.3). G245S is located at a mutational hotspot and is considered to be a structural mutation, affecting the local structure of the DNA-binding domain (DBD), rather than a contact site mutation (Wong et al., 1999; 10411893). DBD mutations are thought to result in loss of function via the loss of transactivation of p53-dependent genes (Kato et al., 2003; 12826609). TP53 G245S has been reported to result in substantially reduced transactivation capacity, as compared with wild-type TP53, and to have dominant negative activity, in yeast assays (IARC TP53 Database, release R18) (Kato et al., 2003; 12826609, Petitjean et al., 2007; 17311302, Brachmann et al., 1996; 8633021, Inga et al., 1997; 9364015, Monti et al., 2002; 11896595). In addition, a preclinical study reported that mice expressing G245S showed tumor latency and survival characteristics that were similar to p53 null mice, with modest increases in tumor spectrum and Akt signaling as compared to null mice, suggesting that this alteration also results in gain of function (Hanel et al., 2013; 23538418).
Incidence in disease	TP53 mutations have been reported in 35% (2633/7559) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (Jun 2018). TP53 mutations have been reported in 54-68% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, Jun 2018). TP53 is one of the most commonly mutated genes in lung cancer; scientific studies have reported TP53 mutations in 29-42% of non-small cell lung carcinoma (NSCLC) cases, with a higher incidence cited in tumors of the squamous cell carcinoma subtype as compared with the adenocarcinoma subtype (Mogi and Kuwano, 2011; 21331359, Tekpli et al., 2013; 23011884, Vignot et al., 2013; 23630207, Ma et al., 2014; 24495481, Maeng et al., 2013; 24222160, Molina-Vila et al., 2014; 24696321, Mattioni et al., 2015; 25884692, Kim et al., 2014; 24323028).

2.4.3 CLINICAL RELEVANCE of TP53-G245S (p.Gly245Ser)

TP53 alterations in Non-small cell lung carcinoma (NSCLC)	
Role in disease	

TP53 alterations in Non-small cell lung carcinoma (NSCLC)	
	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (Brown et al., 2009; 19935675). 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 (Malkin et al., 1990; 1978757, Srivastava et al., 1991; 2259385, Santibáñez-Koref et al., 1991; 1683921). 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 (Wang et al., 2005; 15625370, Koga et al., 2001; 11400116, Kato et al., 2003; 12826609, Houben et al., 2011; 21760960, Olivier et al., 2009; 18802452). TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis (Chang et al., 2011; 20811949). 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 (Mattioni et al., 2015; 25884692, Bircan et al., 2010; 20349288, Kim et al., 2014; 24323028).
Effect on drug sensitivity	Some studies suggest that Hsp90 inhibitors may be effective in tumors with oncogenic TP53 alterations (Alexandrova et al., 2015; 26009011, Lin et al., 2008; 17982489, Li et al., 2011; 21478269).
Effect on drug resistance	Mutations in TP53 may increase resistance to ionizing radiation therapy (El-Deiry, 2003; 14576853). Indeed, a study reported that the TP53 G245S mutation rendered cells resistant to UV radiation (Menendez et al., 2006; 16508005).

2.4.4 CLINICAL EVIDENCE in Non-small cell lung carcinoma (NSCLC)

TP53 alterations in Non-small cell lung carcinoma (NSCLC)	
FDA Approved	None.
Phase III Data	None.
Phase II Data	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) (Deng et al., 2017; 29291013). A Phase 2 study of ganetespib in NSCLC patients reported progression-free survival at 16 weeks in 13.3% (2/15), 5.9% (1/17), and 19.7% (13/66) of cases harboring mutant EGFR, mutant KRAS, or no EGFR or KRAS mutations, respectively; stable disease was reported in 4% (4/98) of cases, all of which harbored ALK rearrangements (Socinski et al., 2013; 23553849). The randomized Phase 2 GALAXY-1 study in previously treated NSCLC patients reported that in 253 evaluable lung adenocarcinoma patients, the combination of ganetespib and docetaxel, compared with docetaxel alone, did not improve progression free survival, and therefore did not meet the primary endpoint of the trial (Ramalingam et al., 2015; 25997818).
Phase I Data	A Phase 1 study of AT13387 in 62 patients with advanced solid tumors or lymphoma has reported one partial response in a patient with a gastrointestinal stromal tumor, stable disease in 34% (21/62) of patients, and an acceptable safety profile (Shapiro et al., 2015; 25336693). A Phase 1 study of SNX-5422 in 32 evaluable patients with refractory solid tumors reported one durable complete response in a prostate cancer patient, partial responses in a Her2-positive breast cancer patient and an adrenal gland cancer patient, and three patients with stable disease for greater than or equal to six months (Infante et al., 2014; 25262379). A Phase 1 study of SNX-5422 in 32 patients with refractory solid tumors and lymphomas reported no objective responses, stable disease in 47% (15/32), progressive disease in 53% (17/32), and that the treatment was well tolerated (Rajan et al., 2011; 21908572).
Preclinical	AT13387 has been reported to inhibit NSCLC cell growth in vitro and in a tumor xenograft model (Graham et al., 2012; 22181674).

2.4.5 SAMPLE RELEVANT THERAPIES

Therapies targeting HSP90

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Ganetespib		D	Small molecule inhibitor	Phase 3 (Non-small cell lung carcinoma (NSCLC))

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
			of Hsp90, also may inhibit Kit/Egfr/Bcr-Abl.	Phase 3 (Acute myelocytic leukemia (AML), Lung cancer, Myelodysplastic Syndrome (MDS))
AT13387		D	Small molecule inhibitor of Hsp90.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (GIST (Gastrointestinal stromal tumor), Prostate carcinoma, Lung cancer, Diffuse large B-cell lymphoma (DLBCL))
SNX-5422		D	Hsp90 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor)
Luminespib		None found	Hsp90 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (GIST (Gastrointestinal stromal tumor), Pancreatic carcinoma, Breast carcinoma)
PU-H71		None found	Hsp90 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Lymphoma, Solid Tumor, Non-Hodgkin lymphoma (NHL))
XL888		None found	Small molecule inhibitor of Hsp90.	Phase 1 (Melanoma)

2.4.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	TP53	NCT02898207	Olaparib and Onalespib in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery or Recurrent Ovarian, Fallopian Tube, Primary Peritoneal, or Triple-Negative Breast Cancer	Phase 1	HSP90, HSP90AA1, HSP90AB1, PARP	•AZ (2), FL (1), MA (4), MN (1)
2	TP53	NCT02503709	Onalespib and CDKI AT7519 in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	Phase 1	CDKs, HSP90, HSP90AA1, HSP90AB1	•DC (1), MA (2), MD (2), OH (1)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	TP53	NCT02898207	Olaparib and Onalespib in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery or Recurrent Ovarian, Fallopian Tube, Primary Peritoneal, or Triple-Negative Breast Cancer	Phase 1	HSP90, HSP90AA1, HSP90AB1, PARP	•AZ (2), FL (1), MA (4), MN (1)
2	TP53	NCT02503709	Onalespib and CDKI AT7519 in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	Phase 1	CDKs, HSP90, HSP90AA1, HSP90AB1	•DC (1), MA (2), MD (2), OH (1)

*Note: the trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.

2.5. ROS1-W1856C (p.Trp1856Cys)

2.5.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
ROS1	- MUTN (seq): p.Trp1856Cys (W1856C)	The effect of ROS1-W1856C has not been determined by CellMax.
	Clinical relevance	Tumors with Ros1 activation may benefit from receptor tyrosine kinase inhibitor (TKI) therapy. Crizotinib is a TKI approved for ALK-positive and ROS1-altered non-small cell lung cancer (NSCLC) (Solomon et al., 2014; 25470694, Shaw et al., 2013; 23724913, Mazières et al., 2015; 25667280). Several other tyrosine kinase inhibitors have also been reported to have activity against Ros1, including cabozantinib, entrectinib, lorlatinib, and merestinib (Davare et al., 2015; 26372962, Yan et al., 2013; 23275061, Drilon et al., 2016; 26673800, Drilon et al., 2017; 28183697, Facchinetti et al., 2016; 27401242). Activating mutations and rearrangements of ROS1, including fusions, lead to the activation of the Ros1 protein and several oncogenic signaling pathways, including the ERK1/2, PI3K, Met, Stat3, and Akt pathways (Acquaviva et al., 2009; 18778756). However, ROS1-W1856C has not been analyzed by CellMax, and therefore the relevance of any therapeutic approaches is uncertain.

2.5.2 BIOLOGICAL RELEVANCE of ROS1-W1856C (p.Trp1856Cys)

ROS1 alterations in Non-small cell lung carcinoma (NSCLC)	
Molecular function	ROS1-W1856C has not been analyzed by CellMax; therefore its effect on protein function cannot be described.
Incidence in disease	ROS1 mutations have been reported in 5.1% (75/1479) of Non-small cell lung carcinoma (NSCLC) samples analyzed in COSMIC (Jun 2018). ROS1 mutations have been reported in 0.0-5.5% of Non-small cell lung carcinoma (NSCLC) samples (cBioPortal for Cancer Genomics, Jun 2018). Literature studies have reported ROS1 rearrangements in approximately 1-3% of NSCLC cases; one meta-analysis has reported ROS1 rearrangements in 3% (116/3898) of lung adenocarcinoma samples and in less than 1% (7/3181) of lung non-adenocarcinoma samples (Zhao et al., 2018; 29600072, Zhu et al., 2015; 26207220, Wang et al., 2015; 26486077, Song et al., 2016; 27544536, Zhou et al., 2016; 27648828).

2.5.3 CLINICAL RELEVANCE of ROS1-W1856C (p.Trp1856Cys)

ROS1 alterations in Non-small cell lung carcinoma (NSCLC)	
Role in disease	ROS1 fusions, which lead to constitutive activation of Ros1, have been reported to play a role in the development of several cancers, including NSCLC, melanoma and colorectal cancer (Davies and Doebele, 2013; 23719267, Wiesner et al., 2014; 24445538, Aisner et al., 2014; 24296758). ROS1 rearrangements in NSCLC patients have been associated with lung adenocarcinoma as compared with other histological types of NSCLC; additionally, ROS1 rearrangements have been associated with increased tumor stage in NSCLC patients (Zhao et al., 2018; 29464758, Bergethon et al., 2012; 22215748, Zhu et al., 2015; 26207220).
Effect on drug sensitivity	Tumors with Ros1 activation may benefit from receptor tyrosine kinase inhibitor (TKI) therapy. Crizotinib is a TKI approved for ALK-positive and ROS1-altered non-small cell lung cancer (NSCLC) (Solomon et al., 2014; 25470694, Shaw et al., 2013; 23724913, Mazières et al., 2015; 25667280). Several other tyrosine kinase inhibitors have also been reported to have activity against Ros1, including cabozantinib, entrectinib, lorlatinib, and merestinib (Davare et al., 2015; 26372962, Yan et al., 2013; 23275061, Drilon et al., 2016; 26673800, Drilon et al., 2017; 28183697, Facchinetti et al., 2016; 27401242). Preclinical and clinical studies have reported that NSCLC with ROS1 rearrangements are sensitive to treatment with crizotinib and cabozantinib (Heigener and Reck, 2014; 24756793, Komiya et al., 2012; 22891268, Yasuda et al., 2012; 22617245, Katayama et al., 2015; 25351743, Bergethon et al., 2012; 22215748, Drilon et al., 2016; 26673800). However, the functional consequences of ROS1-W1856C have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

ROS1 alterations in Non-small cell lung carcinoma (NSCLC)	
Effect on drug resistance	Despite initial sensitivity to crizotinib in NSCLC harboring ROS1 rearrangements, acquired mutations in ROS1 have been reported to develop, which confer resistance to crizotinib; preclinical studies and one case study have reported that tumors with these resistance mutations retain sensitivity to cabozantinib and other preclinical studies reported similar results with foretinib (Davies et al., 2013; 24349229, Davare et al., 2013; 24218589, Katayama et al., 2015; 25351743, Heigener and Reck, 2014; 24756793, Drilon et al., 2016; 26673800).

2.5.4 CLINICAL EVIDENCE in Non-small cell lung carcinoma (NSCLC)

ROS1 alterations in Non-small cell lung carcinoma (NSCLC)	
FDA Approved	None.
Phase III Data	A retrospective study of crizotinib in patients with ROS1-rearranged NSCLC has reported an objective response in 24/30 (80%) evaluable patients, including five complete responses; median progression-free survival (PFS) was 9.1 months and PFS at 12 months was 44% (Mazières et al., 2015; 25667280).
Phase II Data	A Phase 2 study of ceritinib in 32 NSCLC patients harboring ROS1 rearrangements has reported an overall response rate of 62%, including one complete and 19 partial responses, with a median duration of response lasting 21 months. In addition, intracranial disease control was reported in 5/8 cases with brain metastases (Lim et al., 2017; 28520527). Preliminary analysis on 32 Ros1 inhibitor-naive locally advanced or metastatic NSCLC patients with ROS1 fusions across Phase 1 and 2 studies of entrectinib has reported an objective response rate of 75% (24/32) overall, with three complete responses, and 64% (7/11) in patients with CNS disease, with confirmed RECIST intracranial responses in 71% (5/7) of evaluable patients. Median duration of response and progression-free survival were 17.2 and 19.1 months, respectively (Li et al., 2017; IASLC 18th World Conference on Lung Cancer 2017, Abstract OA 14.06). A Phase 2 basket trial of ceritinib monotherapy in patients with solid tumors harboring ALK or ROS1 alterations has reported a clinical benefit rate at 16 weeks of 19.1% (9/47), including partial responses in 6.4% (3/47) of patients (Slosberg et al., 2018; 29765547). A Phase 2 randomized discontinuation trial of cabozantinib in metastatic NSCLC has reported a 10% response rate by RECIST, though a 64% rate of overall tumor regression in heavily pretreated patients, with a safety profile similar to that of other TKI inhibitors (Hellerstedt, 2012; ASCO 2012, Abstract 7514). A Phase 2 randomized trial of cabozantinib, erlotinib, or the combination in 111 EGFR wild-type NSCLC patients reported significantly improved median progression-free survival in the cabozantinib and combination groups as compared with the erlotinib group (4.3, 4.7, and 1.8 months, respectively), as well as longer median overall survival; Met expression was detected in 85% of cases and was not correlated with progression-free survival (Neal et al., 2016; 27825638).
Phase I Data	A Phase 1 study of crizotinib in 50 patients with ROS1-rearranged NSCLC reported an objective response rate of 72%, with three complete responses and 33 partial responses. Median progression-free survival was 19.2 months, with 50% (25/50) of patients still in follow-up (Shaw et al., 2014; 25264305). A Phase 1 trial of lorlatinib in NSCLC patients with ALK or ROS1 rearrangements has reported objective responses in 50% (6/12), 46% (19/41) and 42% (11/26) of ROS1-rearranged patients, ALK-rearranged patients, and ALK-rearranged patients previously treated with two or more TKIs, respectively (Shaw et al., 2017; 29074098). A Phase 1 clinical trial of crizotinib in pediatric solid tumors reported objective responses in 17.7% (14/79) of patients, including nine complete responses and five partial responses; response was enriched in patients with activating alterations in ALK (Mossé et al., 2013; 23598171). A Phase 1 study of ceritinib in solid tumors has reported responses in 4/6 crizotinib-treated patients and 2/10 crizotinib-naïve patients, with all responses seen in NSCLC patients (Mehra et al., 2012; ASCO 2012, Abstract 3007). Combined evaluation of two Phase 1 studies, ALKA-372-001 and STARTRK-1, of entrectinib in solid tumor patients including those with active CNS disease has reported durable (more than two years) response in NSCLC, colorectal cancer, renal cell carcinoma, melanoma, and mammary analog secretory carcinoma patients harboring NTRK1/2/3, ROS1, or ALK fusions that had not received prior tyrosine kinase inhibitor therapy (Drilon et al., 2017; 28183697).
Preclinical	N/A: Preclinical data are not presented when higher level data are available.

2.5.5 SAMPLE RELEVANT THERAPIES

The functional consequences of ROS1-W1856C have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

2.5.6 BIOMARKER-MATCHED CLINICAL TRIALS

The functional consequences of ROS1-W1856C have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3. Glossary of Biomarkers

Marker	Description
EGFR	EGFR encodes the Epidermal growth factor receptor (Egfr), a receptor tyrosine kinase that passes biochemical messages to the cell that stimulate it to grow and divide. Amplification, mutation, and overexpression of EGFR may cause excessive proliferation and tumor formation.
ROS1	ROS1 is a receptor tyrosine kinase of the insulin receptor family that is related to ALK. The Ros1 protein plays a role in cellular growth and differentiation, and activates several signaling pathways, including the MAPK, PI3K, Akt, Stat3, and Vav3 signaling pathways. ROS1 has been reported to be overexpressed and/or mutated in several cancer types, and ROS1 activating gene fusions have also been commonly reported in variety of cancers, including glioblastoma, non-small cell lung cancer (NSCLC), ovarian cancer, gastric adenocarcinoma, and colorectal cancer.
TP53	The TP53 gene encodes the tumor suppressor p53. p53 is involved in the DNA-damage cell cycle checkpoint; it causes a cell-cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes, or induce apoptosis in the presence of DNA damage. It has been called the "cellular gatekeeper".

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5. Definitions of Variant Tiers and Levels of Evidence

Tier 1: Variants of Strong Clinical Significance

Level A	**Predictive of response:** Therapy is FDA-approved in this disease, based on the presence of this biomarker. **Predictive of resistance:** Biomarker is included in professional guidelines as providing resistance to therapy. **Diagnostic:** Biomarker is included in professional guidelines as pathognomonic (required for diagnosis; characteristic of a particular disease). **Prognostic:** Biomarker is included in professional guidelines for clinical decision-making; specifically, the molecular criteria is included in an accepted, clinically relevant prognostic scoring system.
Level B	**Predictive of response:** Strong evidence (well-powered studies, consensus from experts) that biomarker predicts sensitivity to therapy. **Predictive of resistance:** Well-powered studies with expert consensus or smaller studies repeatedly confirmed or reproduced by different groups that variant predicts resistance to therapy. **Diagnostic:** Well-powered studies with expert consensus or repeatedly reported in smaller studies with consistent results or reproduced by different groups indicating diagnostic relevance. These markers may be mentioned in professional guidelines, but are suggestive of, rather than conclusive for, a specific diagnosis. **Prognostic:** Well-powered studies with expert consensus or smaller studies repeatedly with consistent results or reproduced by different groups indicating prognostic relevance.
Level B/C	**Predictive of response:** Consensus from experts, but lacking well-powered studies that biomarker predicts sensitivity to therapy. Not applicable for drug resistance, prognostic, or diagnostic levels of evidence.

Tier 2: Variants of Potential Clinical Significance

Level C	**Predictive of response:** Therapy is FDA-approved for a different disease, based on the presence of this biomarker; or, criteria for a clinical trial. **Predictive of resistance:** Preclinical data strongly suggests resistance; reported in clinical cases. **Diagnostic:** Small studies, diagnostic for a group of related cancers or variants that are supportive of a diagnosis along with other genomic variants. **Prognostic:** Multiple small studies providing prognostic relevance.
Level C/D	**Predictive of response:** Case reports or small case series including exceptional responders that indicate sensitivity to therapy. Not applicable for drug resistance, prognostic, or diagnostic levels of evidence.
Level D	**Predictive of response:** Plausible sensitivity to therapy based on preclinical studies, which do not need to be disease specific. **Predictive of resistance:** Limited preclinical data suggesting resistance; no clinical reports. **Diagnostic:** Small studies or a few case reports support this variant alone or in combination with other biomarkers as assisting diagnosis of this disease. **Prognostic:** : Small studies or a few case reports support this variant alone or in combination with other biomarkers as assisting with prognostic assessment in this disease.
Level E	**Predictive of response:** Poor evidence that biomarker predicts sensitivity to an approved therapy. Not applicable for drug resistance, prognostic, or diagnostic levels of evidence.

Tier 3: Variants of Uncertain Clinical Significance

Tier 4: Benign or Likely Benign Variants

Disclaimer

DNA studies do not constitute a definitive test for any disease conditions in any tested individual. This test is developed and its performance characteristics determined by CellMax Life laboratory. This assay provides information on somatic alterations present in the sample, and microsatellite high instability (MSI-H). No further comments are made on low microsatellite instability (MSI-L), or microsatellite stable (MSS) status. Clinical decisions regarding care and treatment of customers should not be solely based on this test. How this information is used to guide customer care is the responsibility of the physician.

The CellMax Life test is designed to assist health care practitioners in providing additional clinical information. The information therein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. Medical knowledge develops rapidly and new evidence may emerge between the time information is developed to when it is published or read.

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