FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

COUNTRY CODE
ES

PRF#

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

Tumor Mutational Burden - 37 Muts/Mb
Microsatellite status - MS-Stable

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

MET S1268Y
STK11 loss exons 1-4
ERBB3 G582W
KEAP1 loss
CCNE1 amplification
CDKN2A/B p16INK4a V51fs*2 and p14ARF G65fs*107
CRKL amplification
SMARCA4 G883fs*4
TP53 H178fs*2

7 Disease relevant genes with no reportable alterations: ***EGFR, KRAS, ALK, BRAF, ERBB2, RET, ROS1***

10 Therapies approved in the EU
0 Therapies with Lack of Response
34 Clinical Trials

GENOMIC SIGNATURES	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 37 Muts/Mb	Atezolizumab [1]	Avelumab
	Durvalumab [1]	Cemiplimab
	Pembrolizumab [1]	
10 Trials *see p. 17*	Nivolumab [2A]	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Genomic Signatures section	

GENE ALTERATIONS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
MET - S1268Y	Crizotinib	Cabozantinib
10 Trials *see p. 22*		
STK11 - loss exons 1-4	none	Everolimus
10 Trials *see p. 25*		Temsirolimus
ERBB3 - G582W	none	none
2 Trials *see p. 20*		
KEAP1 - loss	none	none
4 Trials *see p. 21*		

[ ] *NCCN category*

Sample

Electronically signed by J. Keith Killian, M.D. | Julia Elvin, M.D., Ph.D., Laboratory Director | | Foundation Medicine, Inc. | Roche Customer Care: +49 7624 14 2098 or europe.foundationmedicine@roche.com

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Sample Analysis: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Alterations section.

CCNE1 - amplification ..... p. 7

CDKN2A/B - p16INK4a V51fs*2 and p14ARF G65fs*107 ..... p. 7

CRKL - amplification ..... p. 8

SMARCA4 - G883fs*4 ..... p. 8

TP53 - H178fs*2 ..... p. 9

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

Sample

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT
37 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3] and anti-PD-1 therapies[1-4]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb; similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb[1-2,5-15]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[16], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[17], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[18]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[19]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[20-21], several other large studies did find a strong association with increased TMB[22-25]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[26]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[20]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[27]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[27-28].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[29-30] and cigarette smoke in lung cancer[5,31], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[32-36], and microsatellite instability (MSI)[32,35-36]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,5-15,19,37-45].

GENOMIC SIGNATURE

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[46-48], including approved therapies nivolumab and pembrolizumab[49]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[50].

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[51-56], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[57-60]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Aug 2019). One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[51].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[61]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[61-63]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[64-66]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[61,63,65-66].

Sample

GENE
MET

ALTERATION
S1268Y

TRANSCRIPT NUMBER
NM_000245

CODING SEQUENCE EFFECT
3803C>A

POTENTIAL TREATMENT STRATEGIES

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, and foretinib have provided benefit to patients with MET-mutated papillary renal cell carcinoma[67-69], histiocytic sarcoma[70], NSCLC[71], lung adenocarcinoma[72-74], lung large cell carcinoma[70], and lung squamous cell carcinoma[70,75]. Patients with MET exon 14 alteration-harboring NSCLC who were treated with one of several MET inhibitors exhibited superior outcomes (median OS 24.6 vs. 8.1 months; HR 0.11, P=0.04) compared to patients who weren't treated with a MET inhibitor[76]. In an expansion cohort of the PROFILE 1001 study, crizotinib demonstrated anti-tumor activity in advanced MET exon 14-altered NSCLC with an ORR of 32% (3 CRs and 18 PRs) and a DCR of 77% (50/65) with an estimated median PFS and OS of 7.3 and 20.5 months at interim analysis, respectively[77]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations, achieving a mDOR of 14.3 months, an ORR of 47.5% (47/99) and a DCR of 69.7% (0 CR, 47 PR and 22 SD)[78]. Capmatinib demonstrated clinical efficacy in advanced NSCLC harboring MET exon 14 skipping alterations and elicited higher ORR (67.9% vs 40.6%) and DCR (96.4% vs 78.3%), and longer PFS (9.7 vs 5.4 months) and median DOR (11.4 vs 9.72 months) in treatment-naïve patients when compared with those who had prior therapies[79]. In another study, 11 patients with hereditary papillary renal cell carcinoma and germline MET mutations (4 of which were H1094R) experienced 5 PR and 5 SD after treatment with foretinib[67]. Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[72]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[70]. In the TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[80-81]. MET amplification has been reported at incidences of 14-48% in non-small cell lung cancer (NSCLC), is correlated with increased MET protein expression, and occurs more frequently following treatment with EGFR inhibitors[82-90]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[82,86,88,91-95], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[96].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[97-98]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

Sample

GENE
STK11

ALTERATION
loss exons 1-4

POTENTIAL TREATMENT STRATEGIES

STK11 alteration is associated with poorer response to immune checkpoint inhibitors for patients with NSCLC, including those with tumors harboring co-occurring KRAS or KEAP1 mutations. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS and STK11 co-mutated tumors than for those whose tumors were STK11 wild-type (6.4 vs. 16.1 months, HR=1.99)[99] as well as markedly fewer objective responses for patients with KRAS/STK11 co-mutated versus KRAS/TP53 co-mutated tumors in the CheckMate-057 (0% [0/6], vs. 57% [4/7])[99] and GEMINI (0% [0/6], vs. 53% [9/17])[100] trials. Similar objective responses were observed for patients receiving combination anti-PD-1 and anti-CTLA-4 treatment in CheckMate-012 (0% [0/3] KRAS/STK11, vs. 78% [7/9] KRAS/TP53)[11], although a case study reported ongoing response in 1 patient with KRAS/STK11 co-mutations treated with nivolumab and ipilimumab[101]. Patients with NSCLC and concurrent mutation of STK11 and KEAP1 (n=39) who received treatment with a PD-L1 inhibitor experienced significantly shorter PFS (1.6 vs. 2.5 months; HR=1.5) and OS (4 vs. 11 months; HR=1.9) compared with patients with STK11- and KEAP1-wild-type tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 mut/Mb)[102]. Lower ORR (31.3% vs. 60.6%) and shorter median PFS (6.4 vs. 11 months) and OS (9.8 vs. 22.4 months) have also been reported in patients with NSCLC harboring STK11/LKB1 mutations compared with wild-type STK11/LKB1[103]. In multiple Phase 1 and 2 trials, durvalumab-based treatments were associated with lower ORRs for patients with STK11-mutated versus STK11-wild-type NSCLC (0–6% vs. 16–25%)[104]. STK11 mutation is an independent predictor of shorter treatment duration on nivolumab for patients with NSCLC[105] and correlates with reduced PD-L1 expression[106-109] and T-cell infiltration[108-112]. Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations[113-117]. A PJS patient with pancreatic cancer and an STK11 mutation experienced a partial response to the mTOR inhibitor everolimus[118]. Loss of STK11 also leads to activation of the downstream kinase SRC, suggesting that inhibitors such as dasatinib or bosutinib may be relevant for the treatment of LKB1-deficient tumors[119].

FREQUENCY & PROGNOSIS

Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), with alterations more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%)[24,81,90,114,120-122]. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases[80] and was not observed in any of 178 lung squamous cell carcinoma cases[81]. STK11 mutations in NSCLC often co-occur with activating KRAS mutations[121-122]. In transgenic mouse models, animals expressing mutant KRAS developed lung adenocarcinomas, whereas the KRAS-mutant/LKB1-deficient mice developed an expanded histological spectrum of tumors that included large cell and squamous cell carcinomas[114]. Strongly decreased or absent expression of LKB1 correlated with inferior outcome in patients with NSCLC treated with bevacizumab-containing chemotherapy; expression of LKB1 was not prognostic in patients treated with chemotherapy without bevacizumab[123].

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels[113]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis[119,124]. Functional disruption of the STK11 kinase domain (amino acids 49-309) or STRAD binding domain (amino acids 320-343) through mutation or loss, such as observed here, is predicted to be inactivating[125-136]. Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation[137]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly[137-139]. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers[137-139], and individuals with this syndrome have a 30-50% risk of developing breast cancer[137,139]. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

Sample

GENE
ERBB3

ALTERATION
G582W

TRANSCRIPT NUMBER
NM_001982

CODING SEQUENCE EFFECT
1744G>T

POTENTIAL TREATMENT STRATEGIES

ERBB3 cooperates with other ERBB family members, in particular ERBB2, for efficient signaling[140-143]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, including antibodies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), and dual EGFR/HER2 TKIs such as lapatinib and afatinib. Antibodies targeting ERBB3 are also being studied in clinical trials. Preclinical studies support the sensitivity of cells with ERBB3 activating mutations to various anti-ERBB2 agents[142,144-145]. In a Phase 2 study of afatinib in platinum-refractory urothelial cancer, 2 patients with activating ERBB3 mutations but no EGFR or HER2 activating alterations experienced clinical benefit and PFS > 6 months[146]. Other studies in solid tumors have reported mixed efficacy for afatinib for patients with uncharacterized ERBB3 mutations[147-148]. Case studies report clinical benefit from lapatinib combined with either capecitabine[147] or trastuzumab[147,149] for patients with breast cancer harboring activating ERBB3 mutations. However, Phase 2 trials have suggested limited efficacy of other ERBB2-targeting TKIs against ERBB3 mutations, with no objective response to neratinib in any of 16 patients with ERBB3-mutated solid tumors[150] or dacomitinib in either of 2 patients with ERBB3-mutated cutaneous squamous cell carcinoma[151]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

ERBB3 mutations have been reported in up to 1% of lung adenocarcinomas[80,142] and in 1-2% of lung squamous cell carcinomas (cBioPortal, COSMIC, Apr 2019). However, ERBB3 mRNA has been detected in over 75% of NSCLC tumors[152] and ERBB3 protein expression has been reported in 51% (32/63) of lung squamous cell carcinomas, compared to 18% (9/51) of lung adenocarcinomas and 9% (1/11) of large cell carcinomas[153], whereas a conflicting study reported higher ERBB3 mRNA expression in lung adenocarcinoma compared to squamous cell carcinoma[154]. High-level expression of ERBB3 mRNA has been associated with distant site metastases and poor overall survival in NSCLC[152]. In a study of 844 solid tumors, ERBB3 kinase domain mutations, but not non-kinase domain mutations, correlated with improved survival in univariate, but not multivariate analysis; patients treated with ERBB-targeted agents achieved 1 PR and 7 SD (1 PR and 3 SD for mutations in tyrosine kinase domain)[147].

FINDING SUMMARY

ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family[155]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
KEAP1

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to address KEAP1 inactivating alterations. Preclinical data suggest that KEAP1 inactivation increases tumor demand for glutamine and increases tumor sensitivity to glutaminase inhibitors like telaglenastat, which is in clinical development in multiple tumor types[156-159]. Loss of KEAP1 function may stabilize NRF2, and a number of compounds that inhibit NRF2 are being evaluated preclinically[160]. Additionally, KEAP1 mutation has been identified as a potential biomarker for sensitivity to combined AKT- and TXNRD1-inhibition in lung cancer[161]. Based on limited clinical evidence, KEAP1 mutation may be associated with poor response to immunotherapy in non-small cell lung cancer (NSCLC). Patients with NSCLC and concurrent mutation of STK11 and KEAP1 (n=39) who received treatment with a PD-L1 inhibitor experienced significantly shorter PFS (1.6 vs. 2.5 months; HR=1.5) and OS (4 vs. 11 months; HR=1.9) compared with patients with STK11- and KEAP1-wild-type tumors (n=210) despite significantly higher TMB in the dual mutant group (median 9.4 vs. 6.1 mut/Mb)[102].

FREQUENCY & PROGNOSIS

Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[162]. KEAP1 mutations are rare in hematological malignancies, occurring in fewer than 1% of samples analyzed (COSMIC, 2020). NRF2 activation has been associated with poor prognosis in head and neck squamous cell carcinomas (HNSCC)[163].

FINDING SUMMARY

KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate-specificity for a CUL3-dependent ubiquitin ligase[164]. KEAP1 is a negative regulator of NRF2, a transcription factor encoded by NFE2L2[165-167]. KEAP1 inactivation is hypothesized to promote tumor survival through constitutive activation of cytoprotective proteins normally regulated as part of the oxidative stress response. This hypothesis is strengthened by the observation that many tumors lacking KEAP1 mutations instead exhibit NFE2L2 mutations, which prevent NRF2 recognition, and therefore polyubiquitination, by KEAP1/CUL3 E3 ligase[168]. KEAP1 mutations may be hypomorphic with respect to activating NRF2 but have been associated with DPP3 overexpression, which can result in a more complete activation of NRF2[167].

SAMPLE

GENE
CCNE1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies that directly target CCNE1 alterations. Because amplification or overexpression of CCNE1 leads to increased genomic instability though the ATR-CHK1 pathway[169] and cyclin E1 promotes cell cycle progression in a complex with CDK2[170], clinical and preclinical studies have investigated inhibitors of CHK1, ATR, and CDK2 as potential therapeutic approaches for tumors with CCNE1 activation. Clinical benefit has been reported for patients with recurrent high-grade ovarian carcinoma with CCNE1 amplification or expression in response to treatment with the CHK1 inhibitor prexasertib[171].

Preclinical studies have demonstrated that cell lines with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR[172-173] or CDK2[174]. However, other studies have shown that sensitivity of various cell lines to CDK2 inhibitors, including SNS-032, dinaciclib, and seliciclib, at clinically achievable doses, is largely independent of CCNE1 copy number or expression[175-178]. One study has reported a reduction in tumor CCNE1 levels in 4/6 lung and esophageal cancer cases following treatment with the HDAC inhibitor vorinostat[179].

FREQUENCY & PROGNOSIS
In the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets, putative high-level CCNE1 amplification has been reported in 2.6%[80] and 5.6%[81] of cases, respectively. CCNE1 amplification was identified in 6% (6/98) of patients with non-small cell lung cancer (NSCLC) and was associated with TP53 mutation[180]. A study of 68 NSCLC samples observed cyclin E1 overexpression to significantly correlate with centrosome abnormalities[181]. Published data investigating the prognostic implications of CCNE1 in NSCLC are limited (PubMed, Jul 2019).

FINDING SUMMARY
CCNE1 encodes the protein cyclin E1, which plays a role in the regulated transition from the G1 to S phase by binding to and activating cyclin-dependent protein kinase 2 (CDK2). It also has a direct role in initiation of replication and the maintenance of genomic stability[170]. Amplification of chromosomal region 19q12-q13 has been demonstrated in many types of cancer, and CCNE1 is a well-studied gene within this amplicon[182-183]. Increased copy number of CCNE1 is highly associated with overexpression of the cyclin E1 protein[184-185]. Cyclin E1 overexpression can lead to cell transformation as a result of an increase in cyclin E1 activity[170,186].

GENE
CDKN2A/B

ALTERATION
p16INK4a V51fs*2 and p14ARF G65fs*107

TRANSCRIPT NUMBER
NM_000077

CODING SEQUENCE EFFECT
151delG

POTENTIAL TREATMENT STRATEGIES
Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[187-190]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[191-192], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[193-199]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[200-201], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS
CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[80]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[81]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[81,202-207]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[204,208-210].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[211-212]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[203,213]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[214-215]. This alteration is predicted to result in p16INK4a[216-237] loss of function. This alteration is predicted to result in p14ARF[220,237-240] loss of function. This alteration does not affect the function of p15INK4b.

Sample

GENE
CRKL

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies that directly target CRKL[241-242]. Preclinical studies report that some cancer cell lines with CRKL amplification are sensitive to tyrosine kinase inhibitor (TKI) dasatinib[241-243]. However, a patient with CRKL-amplified pancreatic cancer did not respond to dasatinib[244]. CRKL amplification has been shown to be a mechanism of acquired resistance to EGFR TKIs[242,245].

FREQUENCY & PROGNOSIS

CRKL amplification has been identified in various solid tumor types, including uterine carcinosarcoma (7%), pancreatic ductal adenocarcinoma (5.5%)[246], lung squamous cell carcinoma (4.5%)[81], sarcoma (4%), ovarian serous cystadenocarcinoma (3.8%), bladder urothelial carcinoma (3%)[247], and melanoma (2%)(cBioPortal, 2020). Increased CRKL expression has been reported in many tumor types, including lung[248-249], breast[250-251], ovarian[251-252], pancreatic[253], skin[251], colon[251,254], hepatocellular[255], and gastric cancers[241]. CRKL overexpression has been shown to significantly correlate with reduced overall survival in patients with NSCLC or hepatocellular carcinoma[249,255] and with tumor size and metastasis in patients with breast cancer[250].

FINDING SUMMARY

CRKL encodes an adaptor protein that has been shown to mediate growth, motility, and adhesion in solid tumor cells[256]. Studies in non-small cell lung cancer (NSCLC) and pancreatic cancer cells have linked CRKL amplification and overexpression with increased cell proliferation and with tumorigenesis[242,248-249,253].

GENE
SMARCA4

ALTERATION
G883fs*4

TRANSCRIPT NUMBER
NM_003072

CODING SEQUENCE EFFECT
2648delG

POTENTIAL TREATMENT STRATEGIES

Clinical[257] and preclinical[258-264] data suggest that patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with EZH2 inhibitors, including tazemetostat. In addition, preclinical data have demonstrated that SMARCA4-deficient non-small cell lung cancer (NSCLC) and SCCOHT patient-derived xenografts and cell lines are highly sensitive to CDK4/6 inhibition through a synthetic lethal mechanism of reduced cyclin D1 expression[265-266]. Notably, similar drug sensitivity was detected in SMARCA4-deficient lung and ovarian tumors, thereby suggesting that SMARCA4-deficient tumors are likely to be sensitive to CDK4/6 inhibition regardless of tissue of origin[265-266]. Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells[267]. In vitro studies have shown that SCCOHT cell lines are sensitive to treatment with epothilone B, methotrexate, and topotecan, compared to treatment with other chemotherapies such as platinum-containing compounds; similar sensitivity was not observed for treatment with ixabepilone, a compound closely related to epothilone B[268].

FREQUENCY & PROGNOSIS

In the TCGA datasets, SMARCA4 mutations have been reported in 6% of lung adenocarcinomas[80] and in 5% of lung squamous cell carcinomas[81]. Loss of BRG1 protein expression has been observed in 10-15% of non-small cell lung cancer (NSCLC) cases in the scientific literature[269-271]. Loss of expression of BRG1 and BRM, another catalytic subunit in SWI/SNF chromatin remodeling complexes, has been correlated with poor prognosis in patients with NSCLC[269-270,272].

FINDING SUMMARY

SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[273]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[274]. Alterations in SMARCA4 that disrupt or remove the ARID1A-interaction domain (aa 476-587)[275], ATP-binding domain (aa 766-931), or the bromodomain (aa 1477-1547)[276] are predicted to result in loss of SMARCA4 function. Certain point mutations have also been characterized to inactivate SMARCA4[277-278].

Sample

GENE
TP53

ALTERATION
H178fs*2

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
531_532delCC

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[279-282], or p53 gene therapy and immunotherapeutics such as SGT-53[283-287] and ALT-801[288]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 10% (17/176) and SDs in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53 wild-type[289]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR in patients with platinum refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[290]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[291]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[292]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate in patients with TP53 alterations[293]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[287]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutant, but not TP53-wild-type, breast cancer xenotransplant mouse model[294].

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[80-81,206,295-299], including 38-54% of lung adenocarcinomas and 47-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Sep 2019)[24-25,80-81]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[109]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[300].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[301]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[302-304]. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[305-307], including sarcomas[308-309]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[310] to 1:20,000[309]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[311]. In the appropriate clinical context, germline testing of TP53 is recommended.

Sample

Atezolizumab

Assay findings association

Tumor Mutational Burden
37 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is available in the EU to treat patients with advanced or metastatic urothelial carcinoma following platinum-based chemotherapy or patients who are not eligible for cisplatin-containing chemotherapy and whose tumors have PD-L1 expression ≥ 5%. It is also available as a first-line treatment in combination with bevacizumab, paclitaxel, and carboplatin or in combination with nab-paclitaxel and carboplatin for patients with metastatic non-squamous NSCLC without EGFR or ALK alterations and as monotherapy to treat patients with metastatic NSCLC following chemotherapy. Patients whose tumors harbor EGFR or ALK alterations should also have received targeted therapy for these alterations. It is additionally available in combination with carboplatin and etoposide as first-line treatment for patients with extensive-stage small cell lung cancer. Atezolizumab is also available in combination with nab-paclitaxel to treat patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the Phase 3 IMpower131 study, addition of atezolizumab to first-line carboplatin and paclitaxel improved median PFS for patients with squamous NSCLC compared with chemotherapy alone (6.3 vs. 5.6 months, HR=0.71); longer PFS was observed across PD-L1 expression subgroups[312]. In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[313-315] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[314]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[313]. In IMpower132, the addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[315]. The Phase 2 B-F1RST study prospectively evaluated blood-based TMB (bTMB) as a biomarker of response to first-line atezolizumab in NSCLC, reporting improved ORR (28.6% vs. 4.4%) and a trend towards improved median PFS (4.6 vs. 3.7 months, HR=0.66, p=0.12) for patients with bTMB ≥16 Muts/Mb compared to <16 Muts/Mb; improved PFS and OS were seen with increasing bTMB cutoffs[316]. The Phase 3 OAK trial comparing atezolizumab to docetaxel for patients with previously treated non-small cell lung carcinoma (NSCLC) reported a significant increase in median OS (13.8 vs. 9.6 months) and duration of response (DOR; 16.3 vs. 6.2 months)[317], confirming previous Phase 2 trial data[318-319]. Similar benefit was observed for patients with squamous or non-squamous histology (HR=0.73 for either group); clinical benefit was observed regardless of PD-L1 status, although greater benefit was achieved with tumor PD-L1 expression >50% (HR=0.41) compared with <1% (HR=0.75)[317]. Retrospective analysis of the OAK trial revealed numerically improved ORR in patients receiving concomitant atezolizumab and metformin compared with atezolizumab alone (25% vs. 13%), but no difference in PFS or OS with the addition of metformin[320].

Sample

Crizotinib

Assay findings association

MET
S1268Y

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) whose tumors are positive for ALK either as first-line or following previous treatment. It is also available to treat patients with ROS1-positive advanced NSCLC.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[321-325] , gastric cancer[326], gastroesophageal cancer[327], glioblastoma[328], and carcinoma of unknown primary[329], as well as in patients with MET-mutated cancers, including NSCLC[70,72-75,330] , renal cell carcinoma (RCC)[69], and histiocytic sarcoma[70]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[70,72-76] . It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[331-335] , ROS1 rearrangements[336-340] , an NTRK1 fusion[341], or MET activation[72-75,321-325,330,342-348] . A patient with lung adenocarcinoma harboring K860I and L858R EGFR mutations, who acquired both EGFR T790M and MET amplification upon various treatments, experienced clinical benefit from subsequent combination treatment of osimertinib and crizotinib; this combination regimen was well tolerated[349]. A case report of a patient with chemotherapy-refractory, pulmonary sarcomatoid carcinoma with a MET exon 14 splice site alteration and amplification experienced a PR to crizotinib treatment[350]. In the Phase 2 METROS and AcSé trials and the expansion cohort of the PROFILE 1001 study, crizotinib demonstrated antitumor activity in patients with advanced MET exon 14-altered or MET-amplified NSCLC with an ORR of 27-40% and a DCR of 68-77% with a median PFS of 3.6-7.3 months and a median OS of 5.4-20.5 months[336,351-352] . Another study reported PFS of 7.36 months in patients with NSCLC and MET exon 14 alterations treated with crizotinib[76]. Several case studies have also reported response to crizotinib in NSCLC with MET exon 14 alterations, with or without concomitant MET amplification[72-75,330,344-347] . In patients with NSCLC and MET overexpression with or without gene amplification, crizotinib elicited 11 PRs and 3 SDs in 19 evaluable patients[322].

Sample

Durvalumab

Assay findings association

Tumor Mutational Burden
37 Muts/Mb

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is available in the EU to treat patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

As consolidation therapy for locally advanced, unresectable non-small cell lung cancer (NSCLC) that had not progressed on platinum-based chemoradiotherapy (CT), durvalumab significantly prolonged median PFS compared with placebo (16.8 vs. 5.6 months, HR=0.52) with manageable safety[353]; longer median OS was observed in the durvalumab cohort compared with the placebo cohort (HR=0.68)[354]. The Phase 3 MYSTIC trial for patients with treatment-naïve, EGFR/ALK-negative metastatic NSCLC reported that in comparison to CT, longer OS was observed in patients with tumor cell PD-L1 expression ≥25% following treatment with durvalumab alone, and in patients with a blood TMB (bTMB) ≥20 Muts/mb following combination treatment of durvalumab with the CTLA-4 inhibitor tremelimumab[355-356] . In Phase 2 trials for previously treated patients with advanced NSCLC, improved ORR and OS with durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity[357-358] . Patients with very high PD-L1 expression (≥90% tumor cells with PD-L1 staining) had an ORR of 31% (21/68), compared with ORRs of 16% (23/146) for patients with ≥25% of tumor cells and 7.5% (7/93) in patients with <25% of tumor cells with PD-L1 staining, respectively[358]. Patients with PD-L1 positivity in ≥25% of tumor cells or tumor and immune cells achieved OS of 15.7 months or 25.6 months, compared with OS of 7.7 to 8.4 months in PD-L1-negative patients[357]. Retreatment with durvalumab in patients with PD-L1-positive (≥25%), EGFR/ALK-negative advanced NSCLC who had progressed following previous disease control resulted in PR and SD in 25% (10/40) of patients, with a tolerable retreatment safety profile[359]. Durvalumab plus nab-paclitaxel for patients with previously treated advanced NSCLC achieved a median PFS of 4.5 months and an ORR of 27%[360]. Preliminary data from the Phase 1b TATTON study of durvalumab combined with osimertinib indicated ORRs and DCRs of 57% (12/21) and 100% (21/21), respectively, for patients previously treated with EGFR inhibitors, and 70% (7/10) and 90% (9/10) for treatment-naive patients[361]. Phase 1 studies reported ORRs of 78% to 80% (7/9 to 8/10) for durvalumab with gefitinib in TKI-naive patients with NSCLC[362] and 18.8% (40/213) for durvalumab with tremelimumab in patients with non-squamous NSCLC[363].

Sample

Nivolumab

Assay findings association

Tumor Mutational Burden
37 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is available in the EU as adjuvant treatment for patients with completely resected advanced melanoma and as monotherapy or in combination with the immunotherapy ipilimumab to treat patients with unresectable or metastatic melanoma. Nivolumab is also available in combination with ipilimumab to treat intermediate- or poor-risk, previously untreated advanced renal cell carcinoma (RCC) and as monotherapy to treat advanced RCC after prior therapy. Nivolumab is available as a monotherapy to treat patients with chemotherapy-refractory advanced non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (ASCT) and brentuximab vedotin treatment, head and neck squamous cell carcinoma (HNSCC) following disease progression on or after platinum-based therapy, and advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45], patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

Secondary analysis of 129 patients with NSCLC treated with nivolumab in a Phase 1 CA209-003 study reported an ORR of 17.1% and DCR of 41.9%, with a median OS (mOS) of 9.9 months, median duration of response of 19.1 months, 5-year OS rate of 15.6%, and 1/11 patients treated beyond progression achieving a response[364]. For patients with platinum-refractory non-squamous NSCLC, nivolumab improved median OS (12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel; PD-L1 expression was associated with benefit from nivolumab in this study (OS HR=0.40–0.59)[365]. As second-line therapy for advanced squamous NSCLC, nivolumab resulted in a longer mOS (9.2 vs. 6.0 months) and a higher ORR (20% vs. 9%) than docetaxel; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[366-367]. Real-world studies of nivolumab reported clinical benefit for 35% to 36% of patients[368-369]. First-line nivolumab for patients with advanced NSCLC and at least 5% PD-L1 expression did not improve PFS compared with investigator's choice of platinum-based doublet chemotherapy (PT-DC) (median PFS of 4.2 vs. 5.9 months, HR=1.15); the mOS was 14.4 months with nivolumab compared to 13.2 months with chemotherapy (HR=1.02)[8]. Exploratory subgroup analysis of TMB, however, revealed that patients with elevated TMB (approximately 13 muts/Mb or more) had experienced more benefit from nivolumab than from chemotherapy (PFS of 9.7 vs. 5.8 months, ORR of 47% vs. 28%)[8]. In the Phase 3 Checkmate 227 study, the combination of nivolumab and ipilimumab improved mOS for patients with advanced NSCLC relative to chemotherapy regardless of PD-L1 positivity or TMB status (17.1 vs. 13.9 months; HR=0.73), although a previous analysis of this trial had reported improved PFS for nivolumab plus ipilimumab relative to chemotherapy only for patients with TMB ≥10 muts/Mb but not for those with TMB <10 muts/Mb[17]. Combinations with PT-DC (gemcitabine/cisplatin, pemetrexed/cisplatin, and paclitaxel/carboplatin) resulted in ORRs of 33 to 47%, 1-year OS rates of 50 to 87%, and 2-year OS rates of 25 to 62%[370]. Nivolumab plus erlotinib for the treatment of chemotherapy-naive EGFR-mutant NSCLC achieved an ORR of 19%; additionally, 15% (3/20) PRs and 45% (9/20) SDs were reported in cases with acquired erlotinib resistance[371]. Nivolumab has shown intracranial activity, with disease control in the brain for 33% of patients[372-373]. A study of nivolumab as neoadjuvant therapy for patients with resectable NSCLC reported that major pathologic responses occurred in 45% (9/20) of patients and significantly correlated with TMB[12].

Sample

Pembrolizumab

Assay findings association

Tumor Mutational Burden
37 Muts/Mb

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is available in the EU to treat patients with unresectable or metastatic melanoma, as adjuvant treatment for completely resected advanced melanoma with lymph node involvement, classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) treatment or after BV if transplant ineligible, and for patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum chemotherapy or who are not eligible for cisplatin-containing chemotherapy and whose tumors are PD-L1-positive (combined positive score of at least 10). It is also available as first-line treatment for metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (at least 50% tumor proportion score) and without EGFR or ALK genomic alterations, as first-line treatment in combination with pemetrexed and carboplatin for metastatic non-squamous NSCLC without EGFR or ALK genomic alterations, as first-line treatment in combination with carboplatin and paclitaxel or nab-paclitaxel for metastatic squamous NSCLC, and as monotherapy for PD-L1-positive (at least 1% tumor proportion score) advanced NSCLC following prior therapy. Pembrolizumab is also available to treat patients with head and neck squamous cell carcinoma (HNSCC) whose tumors are recurrent or metastatic, express high PD-L1 and have progressed on or after platinum chemotherapy, and as a first-line treatment for patients with metastatic or unresectable recurrent PD-L1-positive (combined positive score of 1 or more) disease either as a monotherapy or in combination with platinum and 5-fluorouracil (5-FU). Pembrolizumab is also available in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In multiple clinical trials, first-line pembrolizumab improved survival for patients with EGFR/ALK wild-type advanced NSCLC expressing PD-L1 compared with control treatments, including in patients with PD-L1 expression on ≥50% of tumor cells (median OS [mOS] 20.0–35.4 vs. 12.0–19.5 months)[374-377] , and on ≥1.0% of tumor cells (mOS 10.4–12.7 vs. 8.2 months)[378]. In metastatic squamous NSCLC, the addition of pembrolizumab to first-line carboplatin plus paclitaxel or nab-paclitaxel resulted in a longer mOS (15.9 vs. 11.3 months, HR=0.64) and median PFS (mPFS; 6.4 vs. 4.8 months, HR=0.56), irrespective of PD-L1 status[379]. One study reported no difference in OS (HR=0.70) or PFS (HR=0.72) between first-line pembrolizumab plus chemotherapy versus pembrolizumab alone for patients with PD-L1 positive (≥50.0%) NSCLC, although combination therapy was associated with a higher ORR (+21.5%)[380]. A Phase 1b study of pembrolizumab for patients with advanced PD-L1-expressing NSCLC reported median OS of 22.3 and 10.5 months for treatment-naive and previously treated patients, respectively; PD-L1 expression on ≥50.0% of tumor cells was associated with an mOS and a 5-year OS rate of 35.4 months and 29.6%, respectively, for treatment-naive patients and 19.5 months and 15.7%, respectively, for previously treated patients[377]. For previously treated patients with NSCLC and PD-L1 expression on ≥1% of tumor cells, pembrolizumab extended mOS (10.4–12.7 vs. 8.2 months) when compared with docetaxel[378]. In a pooled analysis of several clinical trials for patients with NSCLC, benefit of pembrolizumab in combination with chemotherapy versus chemotherapy alone for patients with brain metastases (mPFS HR=0.44; mOS HR=0.48; DOR 11.3 vs. 6.8 months; ORR 39.0% vs. 19.7%) was similar to that for patients without brain metastases (mPFS HR=0.55; mOS HR=0.63; DOR 12.2 vs. 6.0 months; ORR 54.6% vs. 31.8%)[381]. In a pooled analysis of several clinical trials for patients with PD-L1 positive NSCLC, benefit of pembrolizumab versus chemotherapy for patients with brain metastases (mPFS HR=0.96; mOS HR=0.83; DOR NR vs. 8.3; ORR 26.1% vs. 18.1%) was also similar to that for patients without brain metastases (mPFS HR=0.91; mOS HR=0.78; DOR 30.4 vs. 8.1 months; ORR 25.8% vs. 22.2%)[382]. In a Phase 2 study, among the patients with PD-L1-positive advanced NSCLC with brain metastases, 33.3% (6/18) experienced responses to pembrolizumab in the brain lesions[383]. Clinical benefit has also been achieved with pembrolizumab in combination with chemotherapy[379-380,384] , ipilimumab[385], the HDAC inhibitor vorinostat[386], and the multikinase inhibitor lenvatinib[387].

Sample

Avelumab

Assay findings association

Tumor Mutational Burden
37 Muts/Mb

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is available in the EU to treat patients with metastatic Merkel cell carcinoma (MCC). It is also available in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma (RCC).

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In a Phase 1b study evaluating single-agent avelumab for the treatment of patients with non-small cell lung cancer (NSCLC), the ORR was 12% (22/184) in previously treated patients and 18.7% (14/75) in the first-line setting, and the median PFS was 12 weeks for both cohorts[388-389]. In patients with NSCLC and PD-L1-positive tumor cells, first-line treatment with avelumab resulted in numerically increased ORR (20%; 7/35 vs. 0%; 0/10) and a trend toward prolonged PFS (11.6 vs. 6.0 weeks) relative to patients with fewer than 1% of tumor cells expressing PD-L1[388]; however, response rates, PFS, and OS were similar regardless of immune or tumor cell PD-L1 expression in patients who had previously received platinum-based treatment[389].

Cabozantinib

Assay findings association

MET
S1268Y

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is available in the EU to treat advanced renal cell carcinoma (RCC) as first-line therapy for patients with intermediate- or poor-risk RCC or following prior antiangiogenic therapy. It is also available to treat progressive, unresectable, advanced medullary thyroid carcinoma (MTC), and as monotherapy for the treatment of hepatocellular carcinoma (HCC) after prior treatment with sorafenib.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[72,390] , as well as by extensive preclinical data[391-397] . It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Studies of single-agent cabozantinib have reported 2 PRs and 1 SD in a series of 5 patients with RET-rearranged lung adenocarcinoma[398], a CR in a patient with lung adenocarcinoma harboring MET amplification and a mutation associated with MET exon 14 skipping[72], and intracranial activity of cabozantinib in a patient with MET-mutated NSCLC without co-occurring MET amplification who had previously progressed on crizotinib[390]. In genomically unselected patients with metastatic NSCLC, a Phase 2 randomized discontinuation trial of cabozantinib in a heavily pretreated cohort reported PRs in 10% (6/60) of patients, tumor regression in 65% (31/48) of patients, a median PFS of 4.2 months, and a safety profile similar to that of other tyrosine kinase inhibitors[399]. In patients with EGFR wild-type non-squamous NSCLC who have progressed after previous treatment, patients treated with cabozantinib alone or in combination with erlotinib experienced a longer median PFS (4.3 months and 4.7 months, respectively) compared to single agent erlotinib (1.8 months)[400].

Cemiplimab

Assay findings association

Tumor Mutational Burden
37 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is available in the EU to treat patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

A Phase 1 trial for patients with advanced NSCLC reported a 40% ORR (8/20; 1 CR and 7 PRs) and 60% DCR following treatment with cemiplimab monotherapy and an 18.2% ORR (6/33; 6 PRs) and 73% DCR for patients who received cemiplimab and radiotherapy[401].

Sample

Everolimus

Assay findings association

STK11
loss exons 1-4

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor. It is available in the EU to treat advanced renal cell carcinoma (RCC) following antiangiogenic therapy; unresectable or metastatic, well- or moderately-differentiated, progressive pancreatic neuroendocrine tumors; unresectable or metastatic, well-differentiated non-functional, progressive neuroendocrine tumors of the lung or gastrointestinal tract; and, in association with tuberous sclerosis complex (TSC), renal angiomyolipoma and subependymal giant cell astrocytoma. Everolimus is also available in combination with exemestane to treat postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer following prior therapy with a nonsteroidal aromatase inhibitor.

GENE ASSOCIATION

Increased mTOR signaling is present in LKB1-deficient tumors[113-115,117,402] ; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[113]. Everolimus elicited clinical responses lasting >6 months in 2 patients with pancreatic cancer[118,403] and 1 patient with atypical pituitary adenoma[404], all of whom harbored STK11 alterations in their tumors.

SUPPORTING DATA

A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity[405], but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population[406]. A Phase 1 study evaluated the addition of everolimus to carboplatin and paclitaxel +/- bevacizumab in advanced NSCLC and found the combinations produced 1 CR and 10 PRs (n=52), although treatments were not well tolerated[407]. A Phase 1 study in patients with advanced NSCLC of the combination of everolimus and erlotinib reported 9 objective responses and 28 patients experiencing SD (n=74), but a Phase 2 study found the combination inefficacious at tolerated doses[408-409] . A trial of combination treatment with sorafenib and everolimus reported 1 PR and 1 SD in 2 patients with lung adenocarcinoma, with both patients experiencing progression-free survival of more than 4 months[410]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[411], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[412].

Temsirolimus

Assay findings association

STK11
loss exons 1-4

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor. It is available in the EU to treat advanced renal cell carcinoma (RCC) and relapsed or refractory mantle cell lymphoma (MCL).

GENE ASSOCIATION

Increased mTOR signaling is present in LKB1-deficient tumors[113-115,117,402] ; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[113].

SUPPORTING DATA

In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), front-line temsirolimus monotherapy demonstrated some clinical benefit but failed to meet the trial's primary end point[413]. In a Phase 1 trial of temsirolimus and radiation in patients with NSCLC, of 8 evaluable patients, 3 exhibited PR and 2 exhibited SD[414].

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies listed in this report may not be complete and exhaustive and the therapeutic agents are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type.

Sample

IMPORTANT Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT

37 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors.

NCT03178552

PHASE 2/3

A Study to Evaluate Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)

TARGETS
ALK, RET, PD-L1, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Edmonton (Canada), Hospitalet de Llobregat (Spain), California, Napoli (Italy), Meldola (Italy), Aviano (Italy), Illinois, Santiago de Compostela (Spain), Roma (Italy), Bergamo (Italy), Cremona (Italy), Milano (Italy), Monza (Italy), Majadahonda (Spain), Winnipeg (Canada), CD Mexico (Mexico), Moscow (Russian Federation), Pamplona (Spain), New Hampshire, St Leonards (Australia), New York, Barrie (Canada), Brampton (Canada), London (Canada), Oshawa (Canada), Toronto (Canada), Oregon, Orbassano (TO) (Italy), Montreal (Canada), Chermside (Australia), Rio de Janeiro (Brazil), Ijui (Brazil), Porto Alegre (Brazil), San Luis Potosí (Mexico), Sao Paulo (Brazil), Saskatoon (Canada), Kurralta Park (Australia), Tennessee, Heidelberg (Australia), Buenos Aires (Argentina), Ciudad Autonoma Buenos Aires (Argentina), La Rioja (Argentina), Brussel (Belgium), Bruxelles (Belgium), Leuven (Belgium), Recoleta (Chile), San Jose (Costa Rica), Bordeaux (France), Caen (France), Lille (France), Lyon (France), Paris (France), Poitiers (France), Tours (France), Vantoux (France), Chemnitz (Germany), Essen (Germany), Esslingen (Germany), Gauting (Germany), Gerlingen (Germany), Heidelberg (Germany), Wiesbaden (Germany), Shatin (Hong Kong), Beer Sheva (Israel), Haifa (Israel), Kfar-Saba (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Chiba (Japan), Ehime (Japan), Fukuoka (Japan), Hiroshima (Japan), Ishikawa (Japan), Kanagawa (Japan), Kyoto (Japan), Miyagi (Japan), Niigata (Japan), Okayama (Japan), Osaka (Japan), Saga (Japan), Shizuoka (Japan), Tokyo (Japan), Wakayama (Japan), Yamaguchi (Japan), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of), Monterrey (Mexico), Auckland (New Zealand), Panama City (Panama), Lima (Peru), San Isidro (Peru), Gdansk (Poland), Krakow (Poland), Olsztyn (Poland), Otwock (Poland), Poznan (Poland), Warszawa (Poland), Saint-Petersburg (Russian Federation), St Petersburg (Russian Federation), Belgrade (Serbia), NIS (Serbia), Sremska Kamenica (Serbia), Singapore (Singapore), Alicante (Spain), Barcelona (Spain), Madrid (Spain), Malaga (Spain), Sevilla (Spain), Valencia (Spain), Kaohsiung (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Bangkok (Thailand), Hat Yai (Thailand), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Edirne (Turkey), Istanbul (Turkey), Karşıyaka (Turkey)

NCT03976362

PHASE 3

A Study of Pembrolizumab (MK-3475) With or Without Maintenance Olaparib in First-line Metastatic Squamous Non-small Cell Lung Cancer (NSCLC, MK-7339-008/KEYLYNK-008)

TARGETS
PD-1, PARP

LOCATIONS: Nagoya (Japan), Alabama, La Paz (Mexico), Bahia Blanca (Argentina), California, Fortaleza (Brazil), Kashiwa (Japan), Cheongju si (Korea, Republic of), Rio Cuarto (Argentina), Westcliff-on-Sea (United Kingdom), Florida, Georgia, London (United Kingdom), Goyang-si (Korea, Republic of), Suwon (Korea, Republic of), Illinois, Indiana, Kanazawa (Japan), Yokohama (Japan), Maryland, Michigan, Mississippi, Montana, Wollongong (Australia), Wellington (New Zealand), Halifax (Canada), Hamilton (Canada), Kingston (Canada), Newmarket (Canada), Hirakata (Japan), Belem (Brazil), Greenfield Park (Canada), Laval (Canada), Montreal (Canada), Trois-Rivieres (Canada), Townsville (Australia), Rio de Janeiro (Brazil), Porto Alegre (Brazil), Itajai (Brazil), Sao Paulo (Brazil), Rosario (Argentina), Sunto-gun (Japan), Texas, San Miguel de Tucuman (Argentina), Clayton (Australia), Washington, Caba (Argentina), Santa Fe (Argentina), Innsbruck (Austria), Linz (Austria), Vienna (Austria), Wels (Austria), Wien (Austria), Bento Goncalves (Brazil), Salvador - BA (Brazil), Sao Jose Rio Preto (Brazil), Angers (France), Caen (France), Chauny (France), Clermont Ferrand (France), Pau (France), Rouen (France), Vandoeuvre les Nancy (France), Vantoux (France), Essen (Germany), Hamburg (Germany), Immenhausen (Germany), Koblenz (Germany), Muenchen (Germany), Munich (Germany), Fukuoka (Japan), Niigata (Japan), Okayama (Japan), Osaka (Japan), Tokyo (Japan), Gyeonggi-do (Korea, Republic of), Jinju (Korea, Republic of), Seoul (Korea, Republic of), Konin (Poland), Krakow (Poland), Olsztyn (Poland), Poznan (Poland), Raciborz (Poland), Warszawa (Poland), Zgorzelec (Poland), Bucuresti (Romania), Cluj-Napoca (Romania), Constanta (Romania), Timisoara (Romania), Kazan (Russian Federation), Moscow (Russian Federation), Omsk (Russian Federation), Saint Petersburg (Russian Federation), Samara (Russian Federation), Barcelona (Spain), Hospitalet de Llobregat (Spain), Jaen (Spain), Madrid (Spain), Malaga (Spain), Sevilla (Spain), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Adana (Turkey), Ankara (Turkey), Istanbul (Turkey), Izmir (Turkey), Kayseri (Turkey), Samsun (Turkey), Tekirdag (Turkey), Cherkasy (Ukraine), Dnipropetrovsk (Ukraine), Ivano-Frankivsk (Ukraine), Kharkiv (Ukraine), Kropyvnytskyi (Ukraine), Kyiv (Ukraine), Odesa (Ukraine), Uzhgorod (Ukraine), Birmingham (United Kingdom), Colchester (United Kingdom)

Sample

NCT03829319

PHASE 3

Safety and Efficacy Study of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) With or Without Lenvatinib (MK-7902/E7080) as First-line Intervention in Adults With Metastatic Nonsquamous Non-small Cell Lung Cancer (MK-7902-006/E7080-G000-315/LEAP-006)

TARGETS
PD-1, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Nagoya (Japan), Toyoake (Japan), Berazategui (Argentina), Mar del Plata (Argentina), California, Kashiwa (Japan), Cheongju si (Korea, Republic of), Connecticut, Florida, Las Palmas de Gran Canaria (Spain), Guangzhou (China), Goyang-si (Korea, Republic of), Harbin (China), Shanghai (China), Kanazawa (Japan), Changchun (China), Istanbul (Turkey), Kentucky, Michigan, Missouri, Moncton (Canada), Blacktown (Australia), Port Macquarie (Australia), Sydney (Australia), New York, North Dakota, Nottingham (United Kingdom), Oklahoma, Hamilton (Canada), Kingston (Canada), Oshawa (Canada), Sault Ste Marie (Canada), Oregon, Habikino (Japan), Hirakata (Japan), Pennsylvania, Laval (Canada), Montreal (Canada), Trois-Rivieres (Canada), Cairns (Australia), Chermside (Australia), Homburg (Germany), Rosario (Argentina), Tennessee, Texas, Utah, West Virginia, Bebington (United Kingdom), Urumuqi (China), Wen Zhou (China), Hangzhou (China), Buenos Aires (Argentina), Cordoba (Argentina), San Juan (Argentina), Ballarat (Australia), Quebec (Canada), Antofagasta (Chile), Santiago (Chile), Talca (Chile), Temuco (Chile), Vina del Mar (Chile), Beijing (China), Tian Jin (China), Bron (France), Montpellier (France), Nantes cedex 1 (France), Paris (France), Suresnes (France), Vantoux (France), Aachen (Germany), Frankfurt (Germany), Grosshansdorf (Germany), Halle (Germany), Hamburg (Germany), Beer Sheva (Israel), Haifa (Israel), Kfar-Saba (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Niigata (Japan), Tokyo (Japan), Wakayama (Japan), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of), Auckland (New Zealand), Tauranga (New Zealand), Bydgoszcz (Poland), Koszalin (Poland), Lodz (Poland), Poznan (Poland), Warszawa (Poland), Kazan (Russian Federation), Moscow (Russian Federation), Omsk (Russian Federation), Saint Petersburg (Russian Federation), A Coruna (Spain), Alicante (Spain), Barcelona (Spain), Hospitalet de Llobregat (Spain), Madrid (Spain), Malaga (Spain), Valencia (Spain), Zaragoza (Spain), Adana (Turkey), Ankara (Turkey), Izmir (Turkey), Malatya (Turkey), Aberdeen (United Kingdom), Leeds (United Kingdom), Leicester (United Kingdom), London (United Kingdom), Manchester (United Kingdom)

NCT03976323

PHASE 3

Study of Pembrolizumab With Maintenance Olaparib or Maintenance Pemetrexed in First-line (1L) Metastatic Nonsquamous Non-Small-Cell Lung Cancer (NSCLC) (MK-7339-006, KEYLYNK-006)

TARGETS
PARP, PD-1

LOCATIONS: Nagoya (Japan), Alabama, Medellin (Colombia), Barranquilla (Colombia), Salvador (Brazil), North Vancouver (Canada), Victoria (Canada), Bahia Blanca (Argentina), California, Fortaleza (Brazil), Kashiwa (Japan), Cheongju si (Korea, Republic of), Rio Cuarto (Argentina), Florida, Georgia, London (United Kingdom), Goyang-si (Korea, Republic of), Suwon (Korea, Republic of), Illinois, Indiana, Kanazawa (Japan), Yokohama (Japan), Pozuelo de Alarcon (Spain), Maryland, Michigan, Mississippi, Montana, Wollongong (Australia), Wellington (New Zealand), Halifax (Canada), Newmarket (Canada), Sudbury (Canada), Hirakata (Japan), Belem (Brazil), Greenfield Park (Canada), Montreal (Canada), Rimouski (Canada), Sherbrooke (Canada), Townsville (Australia), Rio de Janeiro (Brazil), Porto Alegre (Brazil), Santa Cruz do Sul (Brazil), Itajai (Brazil), Sao Paulo (Brazil), Florianopolis (Brazil), Joinville (Brazil), Rosario (Argentina), Sunto-gun (Japan), Tennessee, Texas, San Miguel de Tucuman (Argentina), Clayton (Australia), Washington, Buenos Aires (Argentina), Caba (Argentina), Santa Fe (Argentina), Innsbruck (Austria), Linz (Austria), Vienna (Austria), Wels (Austria), Wien (Austria), Bento Goncalves (Brazil), Sao Jose Rio Preto (Brazil), Bogota (Colombia), Angers (France), Caen (France), Chauny (France), Clermont Ferrand (France), Pau (France), Rouen (France), Vandoeuvre les Nancy (France), Vantoux (France), Aschaffenburg (Germany), Essen (Germany), Hamburg (Germany), Immenhausen (Germany), Koblenz (Germany), Muenchen (Germany), Munich (Germany), Fukuoka (Japan), Niigata (Japan), Okayama (Japan), Osaka (Japan), Tokyo (Japan), Jinju (Korea, Republic of), Seoul (Korea, Republic of), Konin (Poland), Krakow (Poland), Olsztyn (Poland), Poznan (Poland), Raciborz (Poland), Warszawa (Poland), Zgorzelec (Poland), Bucuresti (Romania), Constanta (Romania), Timisoara (Romania), Kazan (Russian Federation), Moscow (Russian Federation), Omsk (Russian Federation), Saint Petersburg (Russian Federation), Samara (Russian Federation), Barcelona (Spain), Sevilla (Spain), Valencia (Spain), Zaragoza (Spain), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Adana (Turkey), Ankara (Turkey), Istanbul (Turkey), Izmir (Turkey), Kayseri (Turkey), Samsun (Turkey), Tekirdag (Turkey), Cherkasy (Ukraine), Dnipropetrovsk (Ukraine), Ivano-Frankivsk (Ukraine), Kharkiv (Ukraine), Kropyvnitskiy (Ukraine), Kyiv (Ukraine), Odesa (Ukraine), Uzhgorod (Ukraine), Birmingham (United Kingdom)

NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

TARGETS
FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Medellin (Colombia), California, Cheongju si (Korea, Republic of), Florida, Seongnam-si (Korea, Republic of), Yokohama (Japan), Kentucky, Pozuelo de Alarcon (Spain), Maryland, Massachusetts, Sendai (Japan), Montana, New Jersey, Blacktown (Australia), Port Macquarie (Australia), Westmead (Australia), Wollongong (Australia), New York, Nottingham (United Kingdom), Kingston (Canada), London (Canada), Oregon, Hirakata (Japan), Pennsylvania, Torokbalint (Hungary), Woolloongabba (Australia), Cali (Colombia), Bogota (Colombia), Monteria (Colombia), Valledupar (Colombia), Angers (France), Avignon (France), Beuvry (France), Caen (France), Clamart (France), Le Mans (France), Paris (France), Farkasgyepu (Hungary), Beer Sheva (Israel), Haifa (Israel), Kfar-Saba (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Avellino (Italy), Bari (Italy), Catania (Italy), Milano (Italy), Monza (Italy), Orbassano (Italy), Palermo (Italy), Perugia (Italy), Rome (Italy), Tokyo (Japan), Seoul (Korea, Republic of), Moscow (Russian Federation), Omsk (Russian Federation), Saint Petersburg (Russian Federation), Saint-Petersburg (Russian Federation), Barcelona (Spain), Jaen (Spain), Las Palmas de Gran Canaria (Spain), Madrid (Spain), Majadahonda (Spain), Mataro (Spain), Oviedo (Spain), Santander (Spain), Valencia (Spain), Aberdeen (United Kingdom), Birmingham (United Kingdom), Cottingham (United Kingdom), Coventry (United Kingdom), Leeds (United Kingdom), Leicester (United Kingdom), London (United Kingdom), Northwood (United Kingdom)

Sample

CLINICAL TRIALS

NCT02903914

PHASE 1/2

Arginase Inhibitor CB-1158 in Patients With Solid Tumors

TARGETS
PD-1, Arginase

LOCATIONS: Alabama, Arizona, District of Columbia, Maryland, Massachusetts, Michigan, Tennessee, Texas, Milan (Italy), Siena (Italy), Amsterdam (Netherlands), Nijmegen (Netherlands), Barcelona (Spain), Madrid (Spain)

NCT03631706

PHASE 2

M7824 Versus Pembrolizumab as a First-line (1L) Treatment in Participants With Programmed Death-ligand 1 (PD-L1) Expressing Advanced Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-1, PD-L1, TGF-beta

LOCATIONS: Nagoya-shi (Japan), Alabama, California, Cheongju-si (Korea, Republic of), Colorado, Connecticut, Florida, Seongnam-si (Korea, Republic of), Sapporo-shi (Japan), Illinois, Kentucky, Michigan, Missouri, Nebraska, St. John (Canada), New Jersey, New York, Ohio, Pennsylvania, Tennessee, Texas, Virginia, Washington, Berazategui (Argentina), Ciudad Autonoma Buenos Aires (Argentina), Cordoba (Argentina), Rio Cuarto (Argentina), Rosario (Argentina), San Miguel de Tucuman (Argentina), Bruxelles (Belgium), Hasselt (Belgium), Pellenberg (Belgium), Yvoir (Belgium), Barretos (Brazil), Fortaleza (Brazil), Porto Alegre (Brazil), Rio de Janeiro (Brazil), Salvador (Brazil), Santo Andre (Brazil), Alberta (Canada), Ontario (Canada), Beijing (China), Guangzhou (China), Shanghai (China), Berlin (Germany), Gauting (Germany), Grosshansdorf (Germany), Hannover (Germany), Luebeck (Germany), Regensburg (Germany), Athens (Greece), Heraklion (Greece), Thessaloniki (Greece), Hong Kong (Hong Kong), Shatin (Hong Kong), Avellino (Italy), Aviano (Italy), Bologna (Italy), Catania (Italy), Catanzaro (Italy), Milano (Italy), Napoli (Italy), Chuo-ku (Japan), Hidaka-shi (Japan), Kitaadachigun (Japan), Koto-ku (Japan), Kurume-shi (Japan), Osaka-shi (Japan), Osakasayama-sh (Japan), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Amsterdam (Netherlands), Groningen (Netherlands), Maastricht (Netherlands), Rotterdam (Netherlands), Tilburg (Netherlands), Barcelona (Spain), L'Hospitalet de Llobregat (Spain), Madrid (Spain), Málaga (Spain), Sevilla (Spain), Valencia (Spain), Taichung (Taiwan), Taipei (Taiwan), Adana (Turkey), Ankara (Turkey), Edirne (Turkey), Kocaeli (Turkey), Dnipro (Ukraine), Ivano-Frankivsk (Ukraine), Kharkiv (Ukraine), Lutsk (Ukraine), Uzhgorod (Ukraine), Zaporizhzhia (Ukraine)

NCT02829723

PHASE 1/2

Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors

TARGETS
PD-1, CSF1R

LOCATIONS: Nagoya (Japan), Hospitalet de LLobregat (Spain), Rozzano (Italy), Tennessee, Texas, Tel Aviv (Israel), Singapore (Singapore), Taipei (Taiwan)

NCT03013491

PHASE 1/2

PROCLAIM-072: A Trial to Find Safe and Active Doses of an Investigational Drug CX-072 for Patients With Solid Tumors or Lymphomas

TARGETS
CTLA-4, PD-L1, BRAF

LOCATIONS: California, Connecticut, Illinois, Indiana, Massachusetts, Michigan, Pamplona (Spain), New York, Oregon, Tennessee, Texas, Virginia, Wisconsin, Amsterdam (Netherlands), Groningen (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Madrid (Spain), Valencia (Spain), Dnepropetrovsk (Ukraine), Glasgow (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle upon Tyne (United Kingdom)

NCT03647488

PHASE 2

Phase II, Randomized Two-arm Study of Capmatinib and Spartalizumab Combination Therapy vs Docetaxel in Non-small Cell Lung Cancer

TARGETS
PD-1, MET

LOCATIONS: Arkansas, Barcelona (Spain), Florida, Athens (Greece), Nijmegen (Netherlands), North Carolina, Sunto Gun (Japan), Leuven (Belgium), Grenoble (France), LILLE Cédex (France), Koeln (Germany), Tel Aviv (Israel), Madrid (Spain)

Sample

GENE
ERBB3

ALTERATION
G582W

RATIONALE
Clinical and preclinical data support sensitivity of ERBB3 activating mutations to HER2-targeting TKIs, including afatinib and lapatinib. ERBB3 amplification or activating mutations may confer sensitivity to therapies targeting ERBB3. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Brussels (Belgium), Gent (Belgium), Liège (Belgium)

NCT02795156

PHASE 2

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

TARGETS
BRAF, KIT, PDGFRs, RAF1, RET, VEGFRs, EGFR, ERBB2, ERBB4, MET, ROS1

LOCATIONS: Colorado, Florida, Missouri, Tennessee, Wisconsin

Sample

GENE
KEAP1

RATIONALE
KEAP1 inactivation may predict sensitivity to glutaminase inhibitors.

ALTERATION
loss

NCT03872427

PHASE 2

Testing Whether Cancers With Specific Mutations Respond Better to Glutaminase Inhibitor, CB-839 HCl, Anti-Cancer Treatment, BeGIN Study

TARGETS
GLS

LOCATIONS: Kentucky, New York, Ohio, Pennsylvania, Texas

NCT03875313

PHASE 1/2

Study of CB-839 (Telaglenastat) in Combination With Talazoparib in Patients With Solid Tumors

TARGETS
GLS, PARP

LOCATIONS: Alabama, Georgia, Iowa, Massachusetts, New York, Texas, Utah, Wisconsin

NCT02861300

PHASE 1/2

CB-839 + Capecitabine in Solid Tumors and Fluoropyrimidine Resistant PIK3CA Mutant Colorectal Cancer

TARGETS
GLS

LOCATIONS: Ohio

NCT03965845

PHASE 1/2

A Study of Telaglenastat (CB-839) in Combination With Palbociclib in Patients With Solid Tumors

TARGETS
CDK4, CDK6, GLS

LOCATIONS: Georgia, Texas

Sample

GENE
MET

ALTERATION
S1268Y

RATIONALE
Activation of MET may lead to increased MET expression and activation and may therefore confer sensitivity to MET inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03647488

PHASE 2

Phase II, Randomized Two-arm Study of Capmatinib and Spartalizumab Combination Therapy vs Docetaxel in Non-small Cell Lung Cancer

TARGETS
PD-1, MET

LOCATIONS: Arkansas, Barcelona (Spain), Florida, Athens (Greece), Nijmegen (Netherlands), North Carolina, Sunto Gun (Japan), Leuven (Belgium), Grenoble (France), LILLE Cédex (France), Koeln (Germany), Tel Aviv (Israel), Madrid (Spain)

NCT03170960

PHASE 1/2

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-L1, MET, RET, ROS1, VEGFRs

LOCATIONS: Arizona, California, Villejuif (France), Colorado, Connecticut, District of Columbia, Florida, Nijmegen (Netherlands), Illinois, Kansas, Kentucky, Louisiana, Massachusetts, Michigan, Rozzano (Italy), Minnesota, Missouri, Nebraska, New Jersey, New York, Düsseldorf (Germany), Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Utah, Virginia, Gent (Belgium), Leuven (Belgium), Paris (France), Tübingen (Germany), Milano (Italy), Barcelona (Spain), Madrid (Spain), London (United Kingdom)

NCT03539536

PHASE 2

Study of Telisotuzumab Vedotin (ABBV-399) in Subjects With Previously Treated c-Met+ Non-Small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Santiago de Compostela (Spain), Alabama, Edmonton (Canada), Hefei (China), Miskolc (Hungary), Marseille (France), California, Colorado, Dublin 8 (Ireland), Meldola (Italy), Fuzhou (China), Fukuoka-shi (Japan), Goyang (Korea, Republic of), Seongnam (Korea, Republic of), Be'er Sheva (Israel), Paris CEDEX 05 (France), Illinois, Changchun (China), Kansas, Kentucky, Rome (Italy), Massachusetts, Michigan, Missouri, Montana, New Hampshire, Darlinghurst (Australia), Lambton Heights (Australia), Tweed Heads (Australia), Novosibirsk (Russian Federation), Ottawa (Canada), Toronto (Canada), Oregon, Budapest (Hungary), Lyon CEDEX 08 (France), Sunto-gun (Japan), Tainan City (Taiwan), Taipei City (Taiwan), Kazan (Russian Federation), Petakh Tikva (Israel), Tennessee, Chuo-ku (Japan), Villejuif (France), Valencia (Spain), Virginia, Volgograd (Russian Federation), Washington, Wisconsin, Hangzhou (China), Beijing (China), Chengdu (China), Shanghai (China), Zhengzhou, Henan (China), Lille (France), Berlin (Germany), Gauting (Germany), Hamm (Germany), Kassel (Germany), Farkasgyepu (Hungary), Kékesteto (Hungary), Cork (Ireland), Haifa (Israel), Kfar Saba (Israel), Ramat Gan (Israel), Avellino (Italy), Orbassano (Italy), Parma (Italy), Osaka (Japan), Yokohama (Japan), Cheongju (Korea, Republic of), Jeonnam (Korea, Republic of), Seoul (Korea, Republic of), San Juan (Puerto Rico), Moscow (Russian Federation), Pushkin (Russian Federation), Saint Petersburg (Russian Federation), Sankt-Peterburg (Russian Federation), Barcelona (Spain), Madrid (Spain), Dalin Township (Taiwan), Taichung City (Taiwan), Taoyuan City (Taiwan), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Edirne, Istanbul (Turkey), Birmingham (United Kingdom), Oxford (United Kingdom)

Sample

NCT02414139

PHASE 2

Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Avellino (Italy), Nagoya (Japan), Nagoya City (Japan), Nice Cedex 2 (France), Sevilla (Spain), Arkansas, Oviedo (Spain), Bologna (Italy), Brescia (Italy), Heidelberg (Germany), Gauting (Germany), Marseille cedex 20 (France), Caba (Argentina), Catania (Italy), Catanzaro (Italy), Buenos Aires (Argentina), California, Barcelona (Spain), Putzu City (Taiwan), Kashiwa-City (Japan), Connecticut, Dijon Cedex (France), Huixquilucan (Mexico), District of Columbia, Mexico (Mexico), Meldola (Italy), Firenze (Italy), Florida, Minami-Ku (Japan), La Coruna (Spain), Georgia, Bundang Gu (Korea, Republic of), Akashi-city (Japan), Illinois, Iowa, Gyeonggi do (Korea, Republic of), Seoul (Korea, Republic of), Lecce (Italy), Las Palmas De Gran Canarias (Spain), Monza (Italy), Macerata (Italy), Taormina (Italy), Milano (Italy), Modena (Italy), Massachusetts, Otwock (Poland), Michigan, Minnesota, Missouri, Sendai-city (Japan), Nebraska, New Hampshire, New York, Koeln (Germany), North Carolina, Halifax (Canada), Okayama-city (Japan), Ottawa (Canada), Oregon, OsakaSayama-city (Japan), Pennsylvania, Rio De Janiero (Brazil), Roma (Italy), Ljui (Brazil), Barretos (Brazil), Sao Jose do Rio Preto (Brazil), Sao Paulo (Brazil), South Carolina, Tennessee, Texas, Chuo-ku (Japan), Koto ku (Japan), Utah, Verona (Italy), Virginia, Ube-city (Japan), La Rioja (Argentina), Wien (Austria), Leuven (Belgium), Clermont-Ferrand (France), LILLE Cédex (France), La Tronche (France), Marseille (France), Paris (France), Pierre Benite (France), Rennes (France), Strasbourg Cedex (France), Berlin (Germany), Frankfurt (Germany), Freiburg (Germany), Gottingen (Germany), Halle (Saale) (Germany), Hamburg (Germany), Hannover (Germany), Homburg (Germany), Muenchen (Germany), Nuernberg (Germany), Ravensburg (Germany), Tübingen (Germany), Ulm (Germany), Haifa (Israel), Kfar Saba (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Napoli (Italy), Ashrafieh (Lebanon), Beirut (Lebanon), Saida (Lebanon), Amsterdam (Netherlands), Groningen (Netherlands), Maastricht (Netherlands), Rotterdam (Netherlands), Oslo (Norway), Gdansk (Poland), Poznan (Poland), Moscow (Russian Federation), Saint Petersburg (Russian Federation), St.-Petersburg (Russian Federation), Tambov (Russian Federation), Singapore (Singapore), Madrid (Spain), Zaragoza (Spain), Stockholm (Sweden), Uppsala (Sweden), Basel (Switzerland), Kaohsiung (Taiwan), Taichung (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Ankara (Turkey), Fatih / Istanbul (Turkey), Birmingham (United Kingdom), London (United Kingdom)

NCT02323126

PHASE 2

Study of Efficacy and Safety of Nivolumab in Combination With EGF816 and of Nivolumab in Combination With INC280 in Patients With Previously Treated Non-small Cell Lung Cancer

TARGETS
EGFR, PD-1, MET

LOCATIONS: Camperdown (Australia), Chermside (Australia), Adelaide (Australia), Texas, Caen Cedex (France), La Tronche (France), Amsterdam (Netherlands), Singapore (Singapore)

NCT02099058

PHASE 1

A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors

TARGETS
MET, EGFR, PD-1

LOCATIONS: California, Colorado, Villejuif (France), Illinois, Massachusetts, Michigan, North Carolina, Marseille CEDEX 05 (France), Tainan City (Taiwan), Taipei City (Taiwan), Tennessee, Texas, Virginia

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Belfast (United Kingdom), Birmingham (United Kingdom), Bristol (United Kingdom), Cambridge (United Kingdom), Cardiff (United Kingdom), Colchester (United Kingdom), Exeter (United Kingdom), Glasgow (United Kingdom), Leeds (United Kingdom), Leicester (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle (United Kingdom), Oxford (United Kingdom), Sheffield (United Kingdom), Southampton (United Kingdom)

Sample

NCT03906071

PHASE 3

Phase 3 Study of Sitravatinib Plus Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC

TARGETS
PD-1, AXL, DDR2, FLT3, KIT, MET, PDGFRA, RET, TRKA, TRKB, VEGFRs

LOCATIONS: Alabama, Arizona, Arkansas, California, Connecticut, Florida, Georgia, Hawaii, Illinois, Indiana, Kentucky, Maine, Maryland, Michigan, Minnesota, Missouri, Nebraska, Nevada, New Jersey, New York, Ohio, Tennessee, Texas, Virginia, Washington, Wisconsin

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, RAF1, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Alabama, Arizona, California, Florida, Georgia, Hawaii, Illinois, Indiana, Massachusetts, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington

NCT01639508

PHASE 2

Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity

TARGETS
MET, RET, ROS1, VEGFRs

LOCATIONS: New Jersey, New York

Sample

GENE
STK11

ALTERATION
loss exons 1-4

RATIONALE
Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations. In addition, analysis in lung tumors indicate that loss of LKB1 function may result in SRC activation, suggesting inhibitors of the SRC kinases may be clinically beneficial when LKB1 is inactive.

NCT02890069

PHASE 1

A Study of PDR001 in Combination With LCL161, Everolimus or Panobinostat

TARGETS
mTOR, PD-1, CXCR2, HDAC, MDM2, IAPs

LOCATIONS: California, Barcelona (Spain), Seoul (Korea, Republic of), Maryland, Massachusetts, Michigan, Pamplona (Spain), Sutton (United Kingdom), Texas, Utah, Washington, Jena (Germany), Ulm (Germany), Wuerzburg (Germany), Amsterdam (Netherlands), Leiden (Netherlands), Rotterdam (Netherlands), Utrecht (Netherlands), Madrid (Spain), Taipei (Taiwan), Manchester (United Kingdom)

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Edmonton (Canada), California, Maryland, Massachusetts, Missouri, New York, Brampton (Canada), Ottawa (Canada), Toronto (Canada), Pennsylvania, Montreal (Canada), Tennessee, Texas, Innsbruck (Austria), Salzburg (Austria), Wien (Austria), Bordeaux (France), Nantes Cedex 1 (France), Paris (France), Villejuif (France), Haifa (Israel), Kfar Saba (Israel), Petach-Tikva (Israel), Ramat Gan (Israel), Seoul (Korea, Republic of)

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Belfast (United Kingdom), Birmingham (United Kingdom), Bristol (United Kingdom), Cambridge (United Kingdom), Cardiff (United Kingdom), Colchester (United Kingdom), Exeter (United Kingdom), Glasgow (United Kingdom), Leeds (United Kingdom), Leicester (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Newcastle (United Kingdom), Oxford (United Kingdom), Sheffield (United Kingdom), Southampton (United Kingdom)

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, Massachusetts, New Jersey, New York

NCT01827384

PHASE 2

Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, mTOR, MEK, WEE1

LOCATIONS: Colorado, Kentucky, Maryland, Missouri, New Jersey, Pennsylvania, Texas

Sample

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, PDGFRs, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, BRAF, MEK, SMO

LOCATIONS: Vancouver (Canada), Kingston (Canada), London (Canada), Ottawa (Canada), Toronto (Canada), Montreal (Canada), Regina (Canada), Saskatoon (Canada)

NCT03023319

PHASE 1

Bosutinib in Combination With Pemetrexed in Patients With Selected Metastatic Solid Tumors

TARGETS
ABL, SRC

LOCATIONS: Georgia

NCT02719691

PHASE 1

Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer

TARGETS
Aurora kinase A, mTORC1, mTORC2

LOCATIONS: Colorado

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

Sample

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ATR
S1508N

BCL6
A407T

BRCA2
G2576E

C11ORF30 (EMSY)
Q877*

CARD11
E1028* and V659L

CDK12
R1407S

CEBPA
amplification

CUL4A
Q183L

EGFR
A722S

ERBB4
C1106F

GNA11
loss

GRM3
A172T

IRF4
G388V and Q369K

IRS2
R301W

JUN
A224S

KDR
E540K

MAP3K1
S939C

MEF2B
R64L

MTOR
R1080C

PPP2R1A
E241D

RAD51
amplification

RAD51B
L87F

SPEN
P3655S

Sample

The content provided as a professional service by Foundation Medicine, Inc., has not been reviewed or approved by the FDA.

Electronically signed by J. Keith Killian, M.D. | Julia Elvin, M.D., Ph.D., Laboratory Director | |
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europe.foundationmedicine@roche.com

Sample Preparation: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany
Sample Analysis: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

Sample

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Alterations and Therapies

Genomic Signatures and Gene Alterations

Therapies are ranked based on the following criteria: Therapies approved in the EU in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies approved in the EU in another tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NCCN Categorization

Genomic signatures and gene alterations detected may be associated with certain National Comprehensive Cancer Network (NCCN) Compendium drugs or biologics (www.nccn.org). The NCCN categories indicated reflect the highest possible category for a given therapy in association with each genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH.

sample

Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

Sample

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

PDF Service version: 2.6.0

Sample

The median exon coverage for this sample is 1,062x

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Sample

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