FOUNDATIONONE®CDx

PATIENT
Sample, Jane

TUMOR TYPE
Lung adenocarcinoma

REPORT DATE
01 Jan 2018

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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 adenocarcinoma
NAME Not Given
DATE OF BIRTH Not Given
SEX Female
MEDICAL RECORD # Not Given

PHYSICIAN

ORDERING PHYSICIAN Not Given
MEDICAL FACILITY Not Given
ADDITIONAL RECIPIENT Not Given
MEDICAL FACILITY ID Not Given
PATHOLOGIST Not Given

SPECIMEN

SPECIMEN SITE Not Given
SPECIMEN ID Not Given
SPECIMEN TYPE Not Given
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - TMB-Intermediate (11 Muts/Mb)

Gene Alterations

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

EGFR amplification, L858R
PTCH1 T416S
CDKN2A/B loss
RBM10 Q494*
TP53 R267P

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

14 Swissmedic-Approved Therapies
0 Therapies with Lack of Response
18 Clinical Trials

GENOMIC SIGNATURES	SWISSMEDIC-APPROVED THERAPIES (IN PATIENT'S TUMOR TYPE)	SWISSMEDIC-APPROVED THERAPIES (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-Intermediate (11 Muts/Mb)	Atezolizumab	Avelumab
	Durvalumab	
	Nivolumab	
9 Trials see p. 14	Pembrolizumab	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Genomic Signatures section	

GENE ALTERATIONS	SWISSMEDIC-APPROVED THERAPIES (IN PATIENT'S TUMOR TYPE)	SWISSMEDIC-APPROVED THERAPIES (IN OTHER TUMOR TYPE)
***EGFR* -** amplification, L858R	Afatinib	Cetuximab
	Erlotinib	Lapatinib
	Gefitinib	Panitumumab
4 Trials see p. 16	Osimertinib	
***PTCH1* -** T416S	None	Sonidegib
5 Trials see p. 17		Vismodegib

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 Gene Alterations section.

NOTE Genomic alterations detected may be associated with activity of certain drugs approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities); however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. 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 includes scientific information. All treatment decisions remain the full and final responsibility of the respective treating physician. Foundation Medicine's genetic test and this genetic test report, including the information on therapies and clinical trials contained in this report, should not be used as the single basis for the therapy decision. The report should only be regarded and used as a supplementing source of information: All treatment decisions remain the full and final responsibility of the respective treating physician. For various reasons further explained below, both the therapies and the clinical trials listed in this report may not be complete and exhaustive. Please find the entire Swiss Prescribing Information on www.swissmedicinfo.ch.

GENOMIC SIGNATURE

Tumor Mutational Burden

CATEGORY

TMB-Intermediate (11 Muts/Mb)

POTENTIAL TREATMENT STRATEGIES

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-464, anti-PD- L163,71,72, and anti-PD-1 therapies57,65,73; such as ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) in patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)57. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbor elevated mutational burden reported higher overall response rates to pembrolizumab57,65,73. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses following treatment with pembrolizumab 74 or nivolumab75, a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab76, and two pediatric patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab77. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab64,78 and anti-PD-1/anti-PD-L1 treatments71. For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load [12.4 mutations (muts) per megabase (Mb)] compared to nonresponders (6.4 muts/Mb)63, and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival72.

FREQUENCY & PROGNOSIS

Intermediate TMB has been reported in 30-31% of non-small cell lung carcinomas (NSCLC), including 30% of adenocarcinomas and 41% of squamous cell carcinomas (SCC) (Spigel et al., 2016; ASCO Abstract 9017). Intermediate TMB was frequently observed in NSCLC with BRAF (31%) or KRAS (39%) mutation (Spigel et al., 2016; ASCO Abstract 9017). Although some studies have reported a lack of association between smoking and mutational burden in NSCLC (Schwartz et al., 2016; ASCO Abstract 8533)66,67, several other large studies did find a strong association with increased TMB14,68,69,70. A large study of Chinese patients with lung adenocarcinoma reported a shorter median overall survival (OS) for tumors with a higher number of mutations in a limited gene set compared with lower mutational number (48.4 vs. 61.0 months)66.

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutational 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 melanoma54,55 and cigarette smoke in lung cancer56,57, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes58,59,60,61,62, and microsatellite instability (MSI)58,61,62. The tumor seen here harbors an intermediate TMB. This level of TMB is high enough that it may be associated with sensitivity to immune checkpoint inhibitors in some tumor types, including anti-PD-1 therapy in non-small cell lung cancer57, anti-PD-L1 therapy in bladder cancer63, and anti-CTLA-4 therapy in melanoma64, potentially due to expression of immune-reactive neo-antigens in these tumors57. However, in other studies of checkpoint inhibitors, including anti-PD-1 therapy in colorectal cancer65, patients with tumors harboring intermediate TMB levels experienced lower rates of clinical benefit than those with high TMB.

GENOMIC SIGNATURE

Microsatellite status

CATEGORY

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 inhibitors139,140,141, including approved therapies nivolumab and pembrolizumab (Overman et al., 2016; ASCO Abstract 3501)65. 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) (Ayers et al., ASCO-SITC 2016; Abstract P60). Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%)65. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without (Overman et al., 2016; ASCO Abstract 3501).

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported at various frequencies in non-small cell lung cancer (NSCLC) as well as in small cell lung cancer133,134,135,136,137,138. One study observed MSI-H in 0.8% (4/480) of lung adenocarcinoma cases; the MSI-H tumors occurred in patients with smoking history, and 3/4 MSI-H cases had nonsynchronous carcinomas in other organs, although none of the patients were diagnosed with Lynch syndrome133.

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 tumor127. 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 PMS2127,128,129. The tumor seen here is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers130,131,132. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins127,129,131,132.

GENE
EGFR

ALTERATION
amplification, L858R

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations or amplification may predict sensitivity to EGFR inhibitors, including erlotinib, gefitinib, afatinib, osimertinib, cetuximab, panitumumab, and lapatinib15,16,17,18,19. Other EGFR-targeted therapies are also in clinical trials. A Phase 2 trial of the pan- ERBB inhibitor dacomitinib in patients with lung adenocarcinoma reported 98% (44/45) disease control [partial response (PR) or stable disease], including a 76% PR rate, in patients with EGFR exon 19 deletions or the L858R mutation; lower disease control and PR rates were reported in patients with other EGFR mutations, wild-type EGFR, or unknown EGFR status20. Consistent with preclinical data demonstrating that the EGFR-inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed partial responses (PRs) and 3 unconfirmed PRs (Ahn et al., 2016; ASCO Abstract 9003)21,22. Third-generation EGFR inhibitors, such as osimertinib or rociletinib, selectively target mutated EGFR, including the EGFR resistance variant T790M. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin, but it is not indicated for non-squamous NSCLC23,24. HSP90 inhibitors have been clinically evaluated for patients with EGFR-mutated NSCLC (Garon et al., 2012; ASCO Abstract 7543)25,26,27,28 and have shown activity against NSCLC with certain EGFR mutations (Piotrowska et al., 2015; ASCO Abstract 8015). The reovirus Reolysin, which targets cells that harbor activated RAS signaling due to alterations in RAS genes or upstream activators such as EGFR29,30,31, is also in clinical trials in some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for head and neck cancer32,33,34,35,36,37,38,39,40.

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-35% of lung adenocarcinomas13,14, and EGFR protein expression/overexpression has been reported in up to 70% of non-small cell lung cancer (NSCLC) tumors15. In the TCGA dataset, EGFR amplification was observed in 6.5% of lung adenocarcinoma cases16. In other studies, EGFR amplification has been documented in up to 62% of non-small cell lung cancer (NSCLC) tumors2,17,18,19. EGFR mutations has been shown to predict survival advantage in patients with with resected Stage 1-3 lung adenocarcinoma20 or resected Stage 1 NSCLC21.

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases; in response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide1. EGFR L858 is located in the kinase domain and is encoded by exon 21; mutations at this position including L858R2,3,4 and L858Q5 have been characterized as activating. Patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib2,3,4, and afatinib6. Other mutations at this position are predicted to be activating. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types7,8,9.

GENE
PTCH1

ALTERATION
T416S

POTENTIAL TREATMENT STRATEGIES

Loss of PTCH1 function results in ligand-independent and constitutive activation of SMO and downstream Hh signaling, and may predict sensitivity to SMO inhibitors87,88,89 such as vismodegib and sonidegib. Significant clinical responses to vismodegib or sonidegib have been observed in patients with basal cell carcinoma or medulloblastoma with activated Hedgehog signaling90,91,92,93, including in patients harboring PTCH1 mutations91,92,93; in one study PTCH1 copy number loss was significantly associated with improved progression-free survival in patients with SHH- subtype medulloblastoma93. The transcriptional activity of the GLI transcription factors have been shown to be dependent on the bromo and extra C-terminal (BET) bromodomain protein BRD4; preclinical studies have shown that the BET inhibitor JQ1 results in downregulation of GLI transcriptional activity94. Therefore, BET inhibitors may be a relevant therapeutic approach for cancers with PTCH1 loss or inactivation. BET inhibitors are in clinical trials for multiple cancer types. However, as the alteration reported here has not been fully characterized, it is not known if these therapeutic approaches would be relevant.

FREQUENCY & PROGNOSIS

PTCH1 mutations have been reported in approximately 5% and 1% of cases analyzed in the lung adenocarcinoma and lung squamous cell carcinoma (SCC) TCGA datasets, respectively16,84. PTCH1 has been shown to be overexpressed in non-small cell lung carcinoma (NSCLC) tumors, with higher expression in SCC than in adenocarcinoma85. Loss of PTCH1 has also been observed in lung SCC, and correlated with poor prognosis86.

FINDING SUMMARY

The PTCH1 tumor suppressor gene encodes a 12-transmembrane protein that functions as an inhibitor of Smoothened (SMO) and downstream Hedgehog (Hh) signaling79. PTCH1 is a receptor for Hh ligands80 and Hh ligand binding to PTCH1 results in derepression of SMO and downstream activation GLI-family transcription factors81. Inactivating germline mutations in PTCH1 are associated with Basal Cell Nevus Syndrome (Gorlin syndrome)82,83. Patients with Gorlin syndrome develop basal cell carcinomas and are also predisposed to medulloblastoma. Somatic mutations that inactivate PTCH1 are frequently found in the sporadic forms of these cancers. This alteration has not been characterized and its effect on function is unclear; however, similar mutations have been observed in the context of cancer, which may indicate biological relevance.

GENE
CDKN2A/B

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES
Preclinical data suggest that tumors with loss of p16INK4a and p15INK4b function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib115,116,117,118. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment119,120, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents (Gopalan et al., 2014; ASCO Abstract 8077, Peguero et al., 2016; ASCO Abstract 2528, Konecny et al., 2016; ASCO Abstract 5557)121,122,123,124; 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 inhibitors125,126, the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS
CDKN2A/B loss or mutation has been reported in 19% and 4% of lung adenocarcinomas, respectively16. 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 21-43% of NSCLC samples97,108,109,110,111. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC108,112–114.

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b95,96. 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 control97,98. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition99,100. This alteration is predicted to inactivate p16INK4a101,102,103,104, p15INK4b105, and p14ARF106,107.

GENE
RBM10

ALTERATION
Q494*

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies approved or clinical trials that directly address genomic alterations in RBM10.

FREQUENCY & PROGNOSIS
Recurrent somatic mutations in RBM10 have been identified in breast, colorectal, ovarian, pancreatic, lung, and prostate cancers14,146,147,148. In breast cancer, RBM10 expression, as well as the other RBM genes on the X chromosome, RBMX and RBM3, has been shown to be correlated with expression of both caspase-3 and the pro-apoptotic gene BAX, leading the authors to hypothesize that RBM10 may play a role in apoptosis in breast cancer149,150.
asefasefeaf

FINDING SUMMARY
RBM10 encodes RNA binding motif protein 10, a nuclear RNA-binding protein involved in the regulation of alternative splicing142,143. Germline mutations in RBM10 cause TARP syndrome, an X-linked recessive disorder characterized by development of micrognathia, glossoptosis, and cleft palate144,145.

GENE
TP53

ALTERATION
R267P

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 tumor shrinkage176. 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 model178. Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer. TP53 mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)16,84,110,162,163,164,165,166. Mutations in TP53 have been associated with lymph node

WEE1 inhibitor AZD1775168,169,170,171 or p53 gene therapy and immunotherapeutics such as SGT-53172,173,174,175,176 and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease 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-type177. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and metastasis in patients with lung adenocarcinoma167. 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 study73.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers151. Any alteration that

carboplatin alone in patients with TP53-mutant ovarian cancer (Oza et al., 2015; ASCO Abstract 5506). Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel (Leijen et al., 2015; ASCO Abstract 2507). 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 two confirmed and one unconfirmed partial responses and two instances of stable disease with significant 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 tumorigenesis152,153,154. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers155,156,157,158,159,160. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000161 to 1:20,000160, and in the appropriate clinical context, germline testing of TP53 is recommended.

Afatinib

Assay findings associations

EGFR

amplification, L858R

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is Swissmedic approved to treat patients with advanced non-small cell lung cancer (NSCLC) positive for activating EGFR mutations (exon 19 deletions, exon 18 G719X substitutions, exon 20 S768I substitutions, or exon 21 L858R or L861Q substitutions) who have not been pretreated with EGFR tyrosine kinase inhibitors. It is also approved to treat patients with advanced squamous cell lung cancer who have progressed on or after platinum-based chemotherapy or who are ineligible for immunotherapy.

GENE ASSOCIATION

EGFR activating mutations or amplification may indicate sensitivity to afatinib. In Phase 2 studies of afatinib, patients with EGFR-amplified NSCLC achieved an objective response rate of 20% (5/25) and a disease-control rate of 64% (16/25) (Cappuzzo et al., 2015; 25514804), and 2/5 patients with EGFR amplification in other solid tumors experienced stable disease (Kwak et al., 2013; 23775486).

SUPPORTING DATA

Phase 3 clinical trials have demonstrated that treatment with afatinib, compared to chemotherapy, leads to significantly increased progression-free survival for patients with EGFR-mutant NSCLC (Sequist et al., 2013; 23816960, Wu et al., 2014; 24439929), and increased overall survival (OS) for patients with EGFR exon 19 alterations specifically (Yang et al., 2015; 25589191). A Phase 3 trial comparing afatinib with erlotinib as second-line therapies for advanced lung squamous cell carcinoma reported significantly higher OS (7.9 months vs. 6.8 months) and disease control rate (DCR) (51% vs. 40%) for patients treated with afatinib (Soria et al., 2015; 26156651). Phase 2/3 studies of afatinib treatment for patients with erlotinib- or gefitinib-resistant NSCLC have generally reported partial responses (PRs) of only 7-9% (Miller et al., 2012; 22452896, Chen et al., 2013; 23664448, Katakami et al., 2013; 23816963, Landi et al., 2014; 25242668, De Greve et al., 2015; 25682316, Yang et al., 2015; 26051236), and DCRs of more than 50% (De Greve et al., 2015; 25682316); in particular, disease control was achieved for 2/2 patients with EGFR-amplified NSCLC (De Greve et al., 2015; 25682316) and 9/14 patients with T790M-positive NSCLC (Yang et al., 2015; 26051236). The T790M mutation has been implicated in reduced response to afatinib (Wu et al., 2016; 26862733, Landi et al., 2014; 25242668, Kim et al., 2012; 22228822), with a secondary T790M mutation reported in 48% (20/42) of patients with afatinib-resistant lung adenocarcinoma (Wu et al., 2016; 26862733). The combination of afatinib with cetuximab resulted in a higher response rate (29%) for patients with erlotinib- or gefitinib-resistant disease (Janjigian et al., 2014; 25074459), including T790M-positive cases (Janjigian et al., 2014; 25074459, Ribeiro Gomes and Cruz, 2015; 26056478), although adverse reactions may be a concern with this combination (Castellanos et al., 2015; 25842367). Upon progression on afatinib, further benefit has been reported from combination treatment with afatinib and paclitaxel (Schuler et al., 2016; 26646759).

Atezolizumab

Assay findings associations

Tumor Mutational Burden

TMB-Intermediate (11 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 Swissmedic approved to treat patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) following prior chemotherapy.

GENE ASSOCIATION

On the basis of emerging clinical data (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017)57, patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutational burden (TMB) may benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling, such as atezolizumab.

SUPPORTING DATA

The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated non-small cell lung carcinoma (NSCLC) reported a significant increase in median overall survival (OS; 13.8 vs. 9.6 months) and duration of response (DOR; 16.3 vs. 6.2 months), with similar benefit for patients with squamous or non-squamous histology [hazard ratio (HR) of 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% compared with <1% (HR of 0.41 vs. 0.75)181. Similar results were reported in the Phase 2 POPLAR study (OS of 12.6 vs. 9.7 months; DOR, 18.6 vs. 7.2 months)(Smith et al., 2016; ASCO Abstract 9028)182. Patients on this study who continued on atezolizumab after experiencing progressive disease (PD) achieved responses in 11% of cases and a median OS of 11.1 months, compared with 8.3 months for patients switching to different treatment (Mazieres et al., 2016; ASCO Abstract 9032). In another study of atezolizumab in patients with NSCLC, an overall response rate (ORR) of 23% (12/53) and a median progression-free survival of 15 weeks were reported183. Atezolizumab achieved similar ORRs for patients with NSCLC who received no prior chemotherapy (24-29%), progressed on previous platinum therapy (17-19%), or had brain metastases or treated asymptomatic brain metastases (17%) (Wakelee et al., 2016; IASLC Abstract ORAL01.04, Spigel et al., 2015; ASCO Abstract 8028).

Durvalumab

Assay findings associations

Tumor Mutational Burden

TMB-Intermediate (11 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 Swissmedic approved to treat patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) that has not progressed following platinum-based chemoradiotherapy.

GENE ASSOCIATION

On the basis of emerging clinical data (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017) (Rizvi et al., 2015; 25765070), patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutational burden (TMB) may benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as durvalumab.

SUPPORTING DATA

Durvalumab as consolidation therapy for locally advanced, unresectable, non-small cell lung cancer (NSCLC) that had not progressed on platinum-based chemoradiotherapy significantly prolonged median progression-free survival (PFS) compared with placebo (16.8 vs. 5.6 months, hazard ratio of 0.52), with manageable safety (Antonia et al., 2017; 28885881). In Phase 2 trials for previously treated patients with advanced NSCLC, improved objective response rate (ORR) and overall survival (OS) with durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity (Bais et al., 2017; AACR Abstract 3720/5, Garassino et al., 2016; IASLC Abstract PLO4a.03). 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 (Garassino et al., 2016; IASLC Abstract PLO4a.03). 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 7.7–8.4 months in PD-L1-negative patients (Bais et al., 2017; AACR Abstract 3720/5). Durvalumab is also under investigation in combination with other therapies in NSCLC. Durvalumab plus nab-paclitaxel for patients with previously treated advanced NSCLC achieved a median PFS of 4.5 months and an ORR of 27% (Govindan et al., 2017; DOI: 10.1016/j.jtho.2017.09.534). Preliminary data from the Phase 1b TATTON study of durvalumab combined with osimertinib indicated ORRs and disease control rates 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 (Ahn et al., 2016; ELCC Abstract 136O). Phase 1 studies reported ORRs of 78–80% (7/9 to 8/10) for durvalumab with gefitinib in TKI-naive patients with NSCLC (Gibbons et al., 2016; ELCC Abstract 57O) and 18.8% (40/213) for durvalumab with the anti-CTLA4 antibody tremelimumab in patients with non-squamous NSCLC (Chaft et al., 2018; AACR Abstract CT113).

Erlotinib

Assay findings associations

EGFR

amplification, L858R

AREAS OF THERAPEUTIC USE

Erlotinib is an EGFR tyrosine kinase inhibitor and is Swissmedic approved to treat advanced non-small cell lung cancer as first-line and maintenance therapy for patients with EGFR activating mutations and as second-line therapy for patients who have progressed on prior chemotherapy.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival [hazard ratio (HR)=0.44] (Cappuzzo et al., 2005; 15870435). Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved overall survival (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11) (Zhang et al., 2017; 27664271, Dahabreh et al., 2011; 20826716, Dahabreh et al., 2010; 20028749).

SUPPORTING DATA

The initial approval of erlotinib in NSCLC was[120] based on the BR.21 Phase 3 randomized trial demonstrating prolonged overall survival for unselected patients with NSCLC treated with erlotinib compared with standard chemotherapy (Shepherd et al., 2005; 16014882). Furthermore, several randomized Phase 3 trials have shown a significant improvement in response and progression-free survival for erlotinib compared with combination chemotherapy in patients with known EGFR mutations. This includes the EURTAC trial of erlotinib versus platinum-based chemotherapy as first-line treatments (Rosell et al., 2011; 22285168) and the SATURN trial of erlotinib as maintenance therapy following first-line platinum-based chemotherapy (Cappuzzo et al., 2010; 20493771). On the other hand, the efficacy of erlotinib for patients lacking the common EGFR activating alterations (exon 19 deletion or L858R mutation) may be regimen-dependent. For patients with NSCLC and wild-type EGFR, chemotherapy was found to be more effective than erlotinib as first-, second-, or third-line treatment (Garassino et al., 2013; 23883922, Kawaguchi et al., 2014; 24841974, Liu et al., 2016; 26206590). However, as maintenance therapy, erlotinib reduced risk for progression compared with placebo by 19% (hazard ratio = 0.81) (Liu et al., 2016; 26206590). The single-arm, Phase IV TRUST trial for genomically unselected patients with advanced NSCLC who failed on, or were unsuitable for, chemotherapy or who were ineligible for erlotinib clinical trials reported a disease control rate of 69% (Reck et al., 2010; 20736854).

Gefitinib

Assay findings associations

EGFR

amplification, L858R

AREAS OF THERAPEUTIC USE

Gefitinib is an EGFR tyrosine kinase inhibitor and is Swissmedic approved to treat advanced non-small cell lung cancer with EGFR activating mutations.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy (Han et al., 2012; 22370314, Maemondo et al., 2010; 20573926, Mitsudomi et al., 2010; 20022809, Mok et al., 2009; 19692680, Petrelli et al., 2011; 22056888, Qi et al., 2015; 25329826, Zhao et al., 2015; 25546556).

SUPPORTING DATA

Gefitinib achieved an objective response rate of 69.8% and an overall survival of 19.2 months as first-line treatment of Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations, which were mostly EGFR exon 19 deletions and EGFR L858R (Douillard et al., 2014; 24263064). In the retrospective analysis of a Phase 3 study in East Asia, gefitinib increased progression-free survival (PFS) in a subgroup of patients with EGFR mutation-positive NSCLC as compared with carboplatin/paclitaxel doublet chemotherapy (hazard ratio for progression = 0.48) (Fukuoka et al., 2011; 21670455, Mok et al., 2009; 19692680). In a Phase 2 study, addition of pemetrexed to gefitinib improved median PFS (15.8 months) compared to treatment with gefitinib alone (10.9 months) in East Asian patients with treatment-naïve, advanced non-squamous NSCLC and activating EGFR mutations (Cheng et al., 2016; 27507876). A retrospective analysis of patients with advanced NSCLC of Asian descent receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced longer median PFS (10.9 months) compared to patients with EGFR mutations in exons 18 (7.9 months), 20 (1.2 months), 21 (7.7 months), or double mutations (5.7 months); however, no differences in overall survival were seen between EGFR mutations (Sutiman et al., 2017; 27908825). In a Phase 1 study for treatment-naïve patients with NSCLC, best objective response rates of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination subsequent to gefitinib monotherapy (Gibbons et al., 2016; 27198414).

Nivolumab

Assay findings associations

Tumor Mutational Burden
TMB-Intermediate (11 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 Swissmedic approved as adjuvant treatment for completely resected advanced melanoma as a single agent and as treatment for unresectable or metastatic melanoma as both a single agent and in combination with the immunotherapy ipilimumab. Nivolumab is also approved in combination with ipilimumab to treat previously untreated intermediate- or poor-risk advanced renal cell carcinoma (RCC) and as monotherapy to treat advanced RCC after prior antiangiogenic therapy. Nivolumab is also approved to treat advanced non-small cell lung cancer (NSCLC) after prior chemotherapy, advanced renal cell carcinoma following antiangiogenic therapy, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after prior platinum-based therapy, non-resectable or metastatic urothelial carcinoma after prior platinum-based chemotherapy, advanced or recurrent stomach or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on two or more lines of therapy, and classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation and brentuximab vedotin treatment. Furthermore, nivolumab is approved to treat mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) after fluoropyrimidine-based therapy in combination with irinotecan or oxaliplatin.

GENE ASSOCIATION

On the basis of emerging clinical data (Spigel et al., 2016; ASCO Abstract 9017) 57,184, patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutational burden (TMB) may show greater benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling, such as nivolumab.

SUPPORTING DATA

For patients with platinum-refractory non-squamous NSCLC, nivolumab improved median overall survival (OS; 12.2 vs. 9.4 months) and the objective response rate (ORR; 19% vs. 12%) compared with docetaxel; PD-L1 expression was associated with benefit from nivolumab in this study [OS hazard ration (HR) of 0.40-0.59]185. As second-line therapy for advanced squamous NSCLC, nivolumab resulted in longer median OS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy 186,187. Real- world studies of nivolumab reported clinical benefit for 35-36% of patients (Crino et al., 2016; ASCO Abstract 3067, Corny et al., 2016; ASCO Abstract e20633). First-line nivolumab for patients with advanced NSCLC and at least 5% PD-L1 expression did not improve progression-free survival (PFS) compared with investigator's choice of platinum-based doublet chemotherapy (PT-DC) (median PFS of 4.2 vs. 5.9 months, HR of 1.15); the median OS was 14.4 months with nivolumab compared to 13.2 months with chemotherapy (HR of 1.02)184. Exploratory subgroup analysis of tumor mutational burden (TMB), however, revealed that patients with elevated TMB (approximately 5 muts/Mb or more) experienced more benefit from nivolumab than from chemotherapy (PFS of 9.7 vs. 5.8 months, ORR of 47% vs. 28%)184. A Phase 1 study of first-line nivolumab alone or combined with ipilimumab every 6 or 12 weeks, respectively, reported ORRs of 23% (12/53), 38% (15/39) and 47% (18/38) and median PFS of 3.6, 3.9, and 8.1 months in unselected patients188,189; the 1-year OS rate with either ipilimumab combination was 87% for patients with at least 1% PD-L1 expression and 53% for those with less than 1% PD-L1 (Goldman et al., 2017; ASCO Abstract 9093). Combinations with PT-DC (gemcitabine/cisplatin, pemetrexed/cisplatin, and paclitaxel/carboplatin) resulted in ORRs of 33-47%, 1-year OS rates of 50-87%, and 2-year OS rates of 25-62%190. Nivolumab plus erlotinib for the treatment of chemotherapy-naive EGFR-mutant NSCLC achieved an ORR of 19%; additionally, 15% (3/20) partial responses (PRs) and 45% (9/20) stable diseases were reported in cases with acquired erlotinib resistance (Rizvi et al., 2014; ASCO Abstract 8022). Nivolumab has shown intracranial activity, with disease control in the brain for 33% of patients (Goldman et al., 2016; ASCO Abstract 9038)191. A study of 3 patients with resectable NSCLC reported 1 complete response and 1 PR with nivolumab as neoadjuvant therapy (Forde et al., 2016; ASCO Abstract e20005).

Osimertinib

Assay findings associations

EGFR

L858R

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI) that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is Swissmedic approved to treat patients with advanced EGFR T790M-positive non-small cell lung cancer (NSCLC) and disease progression on or after EGFR TKI therapy.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations and/or the EGFR T790M mutation may predict sensitivity to osimertinib22,179. T790M-positive patients showed higher response rates than T790M- negative cases in a Phase 1 study for patients with acquired EGFR TKI resistance (61% vs. 21%)22. Although tumors with EGFR amplification may not be sensitive to osimertinib, which selectively targets mutated EGFR, preclinical data indicate sensitivity[179] of various activating EGFR alterations to osimertinib.

SUPPORTING DATA

Osimertinib has been studied primarily for the treatment of EGFR-mutated NSCLC. In Phase 3 study for patients with EGFR T790M-positive advanced NSCLC who had progressed on EGFR TKI therapy, osimertinib compared with combination platinum therapy led to longer median progression-free survival (PFS) (10.1 months vs. 4.4 months), including for patients with metastases to the central nervous system (8.5 months vs. 4.2 months). An objective response rate (ORR) of 71% was achieved with osimertinib compared to 31% with combination platinum therapy (Mok et al., 2016; DOI: 10.1056/NEJMoa1612674). A Phase 2 study of osimertinib reported an ORR of 70% with a median duration of response of 11.4 months and a median PFS of 9.9 months for T790M-positive NSCLC patients with disease progression after previous EGFR TKI therapy180. A Phase 1 trial demonstrated similar outcomes for T790M-positive patients (Yang et al., 2016; ELCC Abstract LBA2_PR), but reported an ORR of 21% and median PFS of 2.8 months for T790M-negative cases with acquired EGFR TKI resistance22. Treatment-naïve patients with EGFR-mutated NSCLC achieved an ORR of 77% (46/60 overall, 20/30 with 80 mg, 26/30 with 160 mg), a stable disease rate of 20% (12/60), and a median PFS of 19.3 months (Ramalingam et al., 2016; ELCC Abstract LBA1_PR).
A Phase 1b study combined osimertinib with the investigational immunotherapy durvalumab, MEK inhibitor selumetinib, or MET inhibitor savolitinib, and observed partial responses (PR) for each of the combinations (9/14 PR with durvalumab, 9/23 PR with selumetinib, 6/11 PR with savolitinib) (Ramalingam et al., 2015; ASCO Abstract 2509). Osimertinib is being compared with erlotinib or gefitinib as first-line treatment for EGFR-mutant NSCLC (NCT02296125).

Pembrolizumab

Assay findings associations

Tumor Mutational Burden
TMB-Intermediate (11 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 Swissmedic approved to treat unresectable or metastatic melanoma, classical Hodgkin lymphoma that is refractory or following relapse after three or more prior lines of therapy, and advanced urothelial carcinoma after treatment with platinum-based chemotherapy. Pembrolizumab is also approved 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 well as for the treatment of patients with PD-L1-positive (at least 1% tumor proportion score) metastatic NSCLC following prior therapy. In patients with metastatic NSCLC whose tumors harbor EGFR or ALK alterations, pembrolizumab is available following prior treatments approved for these alterations.

GENE ASSOCIATION

On the basis of emerging clinical data (Spigel et al., 2016; ASCO Abstract 9017)57, patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutational burden (TMB) may benefit from treatment with immune checkpoint inhibitors targeting PD- 1/PD-L1 signaling, such as pembrolizumab.

SUPPORTING DATA

As first-line therapy for patients with EGFR/ALK wild-type advanced NSCLC and PD- L1 expression on at least 50% of tumor cells, pembrolizumab significantly improved median progression-free survival (PFS; 10.3 vs. 6.0 months) and 6-month overall survival (OS; 80.2% vs. 72.4%) and increasedthe objective response rate (ORR; 44.8% vs. 27.8%) compared with investigator's choice platinum-based chemotherapy192. First-line treatment of patients with EGFR/ALK wild-type advanced, nonsquamous NSCLC with pembrolizumab plus carboplatin and pemetrexed increased the ORR [55% (33/60) vs. 29% (18/63)] and PFS (13.0 vs. 8.9 months) compared with carboplatin and pemetrexed alone; 54% (21/39) of patients with PD-L1 expression on at least 1% of tumor cells and 57% (12/21) of patients with less than 1% expression responded193. In the same setting, pembrolizumab plus carboplatin and paclitaxel resulted in a ORR of 52% (13/25) for patients with NSCLC of any histology (Gadgeel et al., 2016; ASCO Abstract 9016). In a Phase 2/3 study for previously treated NSCLC with PD-L1 expression on at least 1% of tumor cells, pembrolizumab extended median OS (10.4-12.7 vs. 8.2 months) when compared with docetaxel194. A Phase 1 study of pembrolizumab in NSCLC reported an ORR of 19% and median OS of 10.6 months and 22.1 months for previously treated and treatment naive patients, respectively (Hui et al., 2016; ASCO Abstract 9026)195. In both studies, pembrolizumab demonstrated greater efficacy in patients with PD-L1 expression on at least 50% of tumor cells, with ORRs (29-45%)194,195, median OS (14.9-17.3 months)194, and median PFS (5.0-6.3 months)194,195 being increased for these patient populations. In a Phase 2 study of pembrolizumab for advanced PD-L1-positive NSCLC with brain metastases, 33% (6/18) patients experienced brain metastases responses196. Studies combining brain metastases, 33% (6/18) patients experienced brain metastases responses196. Studies combining pembrolizumab with the immunotherapy ipilimumab for patients with recurrent advanced NSCLC with at least 1 previous treatment reported an ORR of 24% with 40% (18/45) stable disease, and median PFS and OS of 6 and 17 months, respectively (Gubens et al., 2016; ASCO Abstract 9027). A Phase 1 study of pembrolizumab in combination with the 4-1BB agonist utomilumab for the treatment of advanced solid tumors reported 1 partial response out of 6 patients with NSCLC (Tolcher et al., 2016; ASCO Abstract 3002).

Avelumab

Assay findings associations

Tumor Mutational Burden
TMB-Intermediate (11 Muts/Mb)

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is Swissmedic approved to treat patients with metastatic Merkel cell carcinoma who have progressed following chemotherapy.

GENE ASSOCIATION

On the basis of emerging clinical data (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 9017)57, patients with non-small cell lung cancer whose tumors harbor intermediate or higher levels of tumor mutational burden (TMB) may benefit from treatment with immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as avelumab.

SUPPORTING DATA

In a Phase 1b study evaluating single-agent avelumab for the treatment of patients with non-small cell lung cancer (NSCLC), the overall response rate (ORR) was 12% (22/184) in previously treated patients and 18.7% (14/75) in the first-line setting, and the median progression- free survival (PFS) was 12 weeks for both cohorts (Verschraegen et al., 2016; ASCO Abstract 9036)221. 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 (Verschraegen et al., 2016; ASCO Abstract 9036); 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 treatment221.

Cetuximab

Assay findings associations

EGFR
amplification, L858R

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is Swissmedic approved to treat EGFR-expressing RAS wild-type metastatic colorectal carcinoma (CRC) as monotherapy or combined with chemotherapy. Cetuximab is also approved to treat advanced head and neck squamous cell carcinoma in combination with other therapies.

GENE ASSOCIATION

EGFR activating mutations or amplifications may indicate sensitivity to EGFR inhibitory antibodies such as cetuximab. For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved overall survival (hazard ratio = 0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies214. In HNSCC, however, EGFR copy number did not associate with the efficacy of cetuximab plus chemotherapy.

SUPPORTING DATA

In previously untreated patients with non-small cell lung cancer (NSCLC), the FLEX study demonstrated that in NSCLC tumors with high expression of EGFR, treatment with cetuximab plus chemotherapy results in longer overall survival compared to chemotherapy alone26. There was no clear association between cetuximab response and EGFR mutations in the FLEX trial26. In a Phase 2 study of 31 patients with Stage 3 NSCLC, addition of cetuximab to radiotherapy and chemotherapy produced an overall response rate of 67%; EGFR gene copy number was not predictive of efficacy outcome216. A Phase 3 study of 938 patients with progressive non-small cell lung cancer after platinum- based therapy concluded that, in unselected patients, the addition of cetuximab to chemotherapy was not recommended in this second-line setting217. Cetuximab is also being studied as part of a therapeutic regimen for patients with EGFR mutations who develop secondary resistance to erlotinib or gefitinib. A Phase 1b study combining afatinib and the anti-EGFR antibody cetuximab in patients with advanced EGFR-mutant lung cancer with acquired resistance to erlotinib/gefitinib observed an overall objective response rate of 29%, and comparable response rates in both T790M-positive and T790M-negative tumors (32% vs. 25%)33. A Phase 1 study of combination erlotinib and cetuximab treatment in patients with NSCLC, including those with squamous tumors, inhibitor-resistant EGFR mutations, and wild-type EGFR, as well as those who had progressed on prior erlotinib treatment, reported partial responses in two of 20 patients and stable disease lasting at least 6 months in three of 20 patients.

Lapatinib

Assay findings associations

EGFR
amplification, L858R

AREAS OF THERAPEUTIC USE
Lapatinib inhibits the tyrosine kinases EGFR and ERBB2 (HER2) and is Swissmedic approved in combination with capecitabine for HER2-positive advanced breast cancer after progression on prior therapy with trastuzumab in the metastatic setting.

GENE ASSOCIATION
EGFR amplification or activation may confer sensitivity to EGFR/multi-tyrosine kinase inhibitors, such as lapatinib. However, a Phase 2 study of lapatinib in non-small cell lung cancer did not observe any responses for five patients with EGFR amplification (Ross et al., 2010; 20215545).

SUPPORTING DATA
Investigations into the efficacy of lapatinib have primarily been in the context of breast cancer. In preclinical assays, lapatinib reduced cell proliferation in vitro and reduced the number and size of tumors in mouse xenograft models of EGFR- and ERBB2-amplified non-small cell lung cancer (NSCLC) cells (Diaz et al., 2010; 20459769). A Phase 1 study of single-agent lapatinib included 9 unselected patients with lung cancer and reported 1 case of prolonged stable disease (Burris et al., 2009; 19825948). In a Phase 2 trial in patients with advanced or metastatic NSCLC, lapatinib monotherapy did not result in significant tumor reduction, but further investigation of lapatinib in combination with other therapies may be warranted (Ross et al., 2010; 20215545).

Panitumumab

Assay findings associations

EGFR
amplification, L858R

AREAS OF THERAPEUTIC USE
Panitumumab is a monoclonal antibody that targets EGFR. It is Swissmedic approved to treat RAS wild-type metastatic colorectal carcinoma (CRC) combined with chemotherapy as first- or second-line therapy, or as monotherapy for patients who have progressed on prior chemotherapy.

GENE ASSOCIATION
EGFR activating mutations or amplifications may indicate sensitivity to EGFR inhibitory antibodies such as panitumumab. For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved overall survival (hazard ratio = 0.62) in a meta-analysis, although increased survival was not seen in populations[214] that received first-line treatment with EGFR antibodies.

SUPPORTING DATA
In a Phase 2 trial, the addition of panitumumab to paclitaxel/carboplatin did not result in improved clinical benefit in patients with advanced NSCLC219, and subsequent studies investigating the addition of panitumumab to pemetrexed/cisplatin reported no benefit for patients with wild-type KRAS lung adenocarcinoma220. The combination of afatinib and panitumumab has been explored for 2 patients with EGFR T790M NSCLC, with 1 partial response reported.

Sonidegib

Assay findings associations

PTCH1
T416S

AREAS OF THERAPEUTIC USE
Sonidegib is a small-molecule inhibitor of the protein Smoothened (SMO), a member of the Hedgehog signaling pathway. Sonidegib is Swissmedic approved to treat advanced basal cell carcinoma (BCC) that cannot be treated with curative surgery or radiotherapy.

GENE ASSOCIATION
Alterations that inactivate PTCH1 may predict sensitivity to SMO inhibitors such as sonidegib, which has shown significant clinical activity in patients with Hh pathway activated basal cell carcinoma or medulloblastoma 90,223,224. However, as the alteration reported here has not been characterized, it is not known if this therapeutic approach would be relevant.

SUPPORTING DATA
Studies of sonidegib have largely focused on BCC and medulloblastoma, twodiseases associated with activated Hedgehog pathway (Hh) signaling. The BOLT Phase 2 trial demonstrated objective response rates (ORR) of 47% (31/66) for patients with locally advanced BCC [3% complete responses (CR), 44% partial responses (PR)] and 15% (2/13) for patients with metastatic BCC; similar results were obtained with higher dose (800mg) sonidegib (35% and 17% ORR, respectively)224. In three Phase 1 studies, 4/6 adults and 2/3 pediatric patients with medulloblastoma and a high Hh gene signature experienced a response to sonidegib, whereas 0/7 adults and 0/34 pediatric patients with a non-Hh gene signature responded90. A Phase 1 clinical trial of sonidegib for solid tumors reported stable disease (SD) for 23% of patients (24/99), lasting > 6 months for some patients with lung adenocarcinoma,[35] spindle cell sarcoma, and BCC; ORRs of 38% (6/16) in BCC and 33% (3/9) in medulloblastoma were reported in this study223.

Vismodegib

Assay findings associations

PTCH1

T416S

AREAS OF THERAPEUTIC USE

Vismodegib is a small molecule inhibitor of the protein Smoothened (SMO), a member of the Hedgehog signaling pathway. Vismodegib is Swissmedic approved to treat advanced basal cell carcinoma (BCC) that cannot be treated with surgery or radiotherapy.

GENE ASSOCIATION

Based on strong clinical evidence in basal cell carcinoma91 and medulloblastoma90,92,93, alterations that inactivate PTCH1 may predict sensitivity to vismodegib. In one study of patients with medulloblastoma treated with vismodegib, PTCH1 copy number loss was significantly associated with improved progression-free survival93. However, as the alteration reported here has not been characterized, it is not known if this therapeutic approach would be relevant.

SUPPORTING DATA

Studies of vismodegib have largely focused on BCC and medulloblastoma, which are disease types associated with activated Hedgehog pathway signaling. In the ERIVANCE BCC Phase 2 study, 43% of patients with locally advanced BCC experienced a partial or complete response, whereas 21% of patients with metastatic BCC experienced a complete response225. In two Phase 2 studies of vismodegib for recurrent or refractory medulloblastoma, 8 of 26 (31%) patients with SHH- subtype medulloblastoma (SHH-MB) had a response to vismodegib, whereas 0 of 9 patients with non-SHH-MB had a response; vismodegib also resulted in significantly improved progression-free survival for patients with SHH-MB compared to patients with non-SHH-MB93. Significant responses to vismodegib in patients with medulloblastoma have also been reported in other studies92,226,227, including responses in patients with SHH-MB227 or in patients harboring a PTCH1 mutation92. A Phase 1 clinical trial of vismodegib in patients with solid tumors reported tumor response in 29% (20/68, including 19 patients with BCC and one with medulloblastoma), stable disease in 20% (14/68), and tumor progression in 41% (28/68) of patients226. Another Phase 1 clinical trial of vismodegib in patients with solid tumors was unable to achieve the unbound plasma concentrations that have been associated with efficacy in basal cell carcinoma and medulloblastoma228. Vismodegib has recently been reported to alter calcium homeostasis and inhibit cell growth in lung adenocarcinoma and small cell carcinoma cell lines229,230.

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. The clinical trials to consider listed in this report may not be complete and exhaustive or may include trials in which the patient cannot participate. Please keep in mind that the information available in the public domain is continually updated and should be investigated by the physician or research staff. There may also be compassionate use programs where patients could be included, and these programs are not listed in this report. The clinical trial information may not be up to date or may not be accurate. In addition, search errors when searching the clinical trials cannot be ruled out completely.

GENOMIC SIGNATURE

Tumor Mutational Burden

CATEGORY

TMB-Intermediate (11 Muts/Mb)

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "PD-L1", "B7-H1", "PD-1", "pembrolizumab", "nivolumab", "atezolizumab", "MPDL3280A", "durvalumab", "MEDI4736", "avelumab", "MSB0010718C", "BMS-936559", "pidilizumab", "CT-011", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

NCT01714739

PHASE 1 / 2

A Phase 1/2 Study of the Combination of Lirilumab (Anti-KIR) Plus Nivolumab (Anti-PD-1) or Lirilumab Plus Nivolumab and Ipilimumab in Advanced Refractory Solid Tumors

TARGETS
CTLA-4, KIR, PD-1

LOCATIONS: Madrid (Spain), Paris (France), Barcelona (Spain), New York, Toronto (Canada), Illinois, Oregon, Pennsylvania, Ohio, Tennessee, Lyon Cedex 08 (France)

NCT02486718

PHASE 3

A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: Pennsylvania, Kansas, South Carolina, New York, Tennessee, New Mexico

NCT02657434

PHASE 3

A Phase III, Open-Label, Randomized Study of Atezolizumab (MPDL3280A, Anti-Pd-L1 Antibody) in Combination With Carboplatin or Cisplatin + Pemetrexed Compared With Carboplatin or Cisplatin + Pemetrexed in Patients Who Are Chemotherapy-Naive and Have Stage IV Non-Squamous Non-Small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: California, Connecticut, Florida, Georgia, Illinois, Indiana, Kentucky, Michigan, Minnesota

NCT02713867

PHASE 3

A Dose Frequency Optimization, Phase IIIB/IV Trial of Nivolumab 240 mg Every 2 Weeks vs Nivolumab 480 mg Every 4 Weeks in Subjects With Advanced or Metastatic Non-small Cell Lung Cancer Who Received up to 12 Months of Nivolumab at 3 mg/kg or 240 mg Every 2 Weeks

TARGETS
PD-1

LOCATIONS: New Jersey, North Carolina, Pennsylvania, Kansas, New York, Tennessee, New Mexico

NCT01473095

PHASE 3

An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum Doublet Chemotherapy Versus Platinum Doublet Chemotherapy in Subjects With Chemotherapy- Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

TARGETS
CTLA-4, PD-1

LOCATIONS: North Carolina, Pennsylvania, Kansas, South Carolina, New York

NCT01915576

PHASE 2

A Study of Nivolumab in Combination With Ipilimumab (Part 1); and Nivolumab Plus Ipilimumab in Combination With Chemotherapy vs. Chemotherapy Alone (Part 2) as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC)

TARGETS
CTLA-4, PD-1

LOCATIONS: California, New Jersey, North Carolina, Pennsylvania, Kansas, South Carolina, New York, Tennessee, New Mexico

NCT02383212

PHASE 1

A First-in-Human Study of Repeat Dosing With REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death - 1 (PD-1), as Single Therapy and in Combination With Other Anti-Cancer Therapies in Patients With Advanced Malignancies

TARGETS
PD-1

LOCATIONS: Arizona, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Illinois, Indiana, Kansas

NCT02118337

PHASE 1 / 2

A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination With MEDI4736 and MEDI0680 Monotherapy in Subjects With Select Advanced Malignancies

TARGETS
PD-L1

LOCATIONS: Oklahoma, Oregon, South Carolina, Kansas, Kentucky, Minnesota, New Jersey, Pennsylvania, Washington

NCT02646748

PHASE 1

A Phase 1b Study of LY2835219 in Combination With Multiple Single Agent Options for Patients With Stage IV NSCLC A Platform Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Pembrolizumab + INCB Combinations in Advanced Solid Tumors

TARGETS
JAK1, PD-1, PI3K-delta

LOCATIONS: California, New York, District of Columbia, Florida, North Carolina, Pennsylvania

GENE
EGFR

ALTERATION
amplification, L858R

RATIONALE
Activating mutations in EGFR have been shown to confer sensitivity to EGFR inhibitors. Other agents, including irreversible EGFR inhibitors and HSP90 inhibitors, also may be relevant. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrails.gov using keyword terms such as "EGFR", "afatinib", " BIBW 2992 MA2", "cetuximab", "IMC-C225", "C225", "erlotinib", "CP-358,774", "OSI-774", "gefitinib", "ZD 1839", "lapatinib", "GSK572016", "osimertinib", "AZD9291", "mereletinib", "panitumumab", "ABX-EGF", "dacomitinib", "PF-00299804", "ASP8273", "HSP90", "ASP8273", "reolysin", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

NCT02486718

PHASE 1 / 2

A Phase I/II, Multicenter, Open-label Study of EGFRmut-TKI EGF816, Administered Orally in Adult Patients With EGFRmut Solid Malignancies

TARGETS
EGFR

LOCATIONS: New York, Aichi (Japan), Amsterdam (Netherlands), Berlin (Germany), Catalunya (Spain), Fukuoka (Japan), Korea (Korea, Republic of), MI (Italy), Madrid (Spain), Nordrhein-Westfalen (Germany)

NCT02276027

PHASE 2

A Phase II, Open Label, Multiple Arm Study of Single Agent AUY922, BYL719, INC280, LDK378 and MEK162 in Chinese Patients With Advanced Non-small Cell Lung Cancer (NSCLC)

TARGETS
ALK, MEK, MET, PI3K- alpha, ROS1

LOCATIONS: New York, Aichi (Japan), Amsterdam (Netherlands), Berlin (Germany), Catalunya (Spain), Fukuoka (Japan), Korea (Korea, Republic of), MI (Italy), Madrid (Spain), Nordrhein-Westfalen (Germany)

NCT02143466

PHASE 1

A Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Combination With Ascending Doses of Novel Therapeutics in Patients With EGFRm+ Advanced NSCLC Who Have Progressed Following Therapy With an EGFR TKI

TARGETS
EGFR

LOCATIONS: Georgia, New York, Tennessee, Cheongju-si (Korea, Republic of), Chuo-ku (Japan), Goyang-si (Korea, Republic of), Habikino-shi (Japan), Hirakata-shi (Japan), Kashiwa-shi (Japan), Nagoya- shi (Japan)

NCT02486718

PHASE 3

Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients With Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy With an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

TARGETS
EGFR

LOCATIONS: Beijing (China), Buenos Aires (Argentina), Caba (Argentina), Changchun (China), Changsha (China), Chengdu (China), ChongQing (China), Chongqin (China), Chongqing (China), Dalian (China)

GENE
PTCH1

ALTERATION
T416S

RATIONALE

Loss or inactivation of the tumor suppressor PTCH1 upregulates the activity of the Hedgehog pathway member Smoothened (SMO), which may contribute to excessive cell proliferation. Inhibitors of SMO or BET-domain containing transcription factors may be relevant in a tumor with a loss or inactivation of PTCH1. However, because the functional effect of the mutation reported here is unclear, it is not known whether this therapeutic strategy would be relevant. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "SMO", "BMS-833923", "vismodegib", "GDC-0449", "itraconazole", "sonidegib", "LDE225", "BET", "CPI-0610", "I-BET762", "GSK525762", "GSK1324726A", "TEN-010", "RVX-208", "OTX015", "lung", "NSCLC", "solid tumor", and/or "advanced cancer".

NCT02419417

PHASE 1 / 2

A Phase I/IIa Trial With BMS-986158, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects With Selected Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: California, Melbourne (Australia), Ottawa (Canada), Villejuif (France), South Carolina

NCT02276027

PHASE 1

A Phase I/II Open-Label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects With NUT Midline Carcinoma (NMC) and Other Cancers

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Texas, Maryland, Tennessee, Clayton (Australia), Lyon Cedex 08 (France), Paris Cedex 5 (France), Seoul (Korea, Republic of), Madrid (Spain), Málaga (Spain)

NCT02693535

PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
VEGFRs, BCR- ABL, SRC, LYN, ALK, MET, ROS1, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB2, BRAF, MEK, SMO, ABL, DDR2, FGFR1, FGFR2, NTRK1, RAF1, PARP, PD-1

LOCATIONS: Arizona, Georgia, Illinois, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, South Dakota

NCT02091141

PHASE 2

My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

TARGETS
SMO, BRAF, EGFR, ERBB2

LOCATIONS: Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, Missouri

NCT02276027

PHASE 1

A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABBV-075 in Subjects With Advanced Cancer

TARGETS
BCL2, BRD2, BRD3, BRD4, BRDT

LOCATIONS: Arizona, California, Illinois, Indiana, North Carolina, Texas

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.

AKT3	***EP300***	***IRS2***	***LRP1B***
E132D	S12L, S24L, and S26F	M543L and R1286Q	C1199F

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 (PD1)*	*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

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

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) and tumor mutational burden (TMB) 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 PRINCIPLE

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 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

Appear at the top of the report, but are not ranked higher than Gene Alterations.

Gene Alterations

Therapies approved in Switzerland (In Patient's Tumor Type) → Therapies approved in Switzerland (In Other Tumor Type) → Clinical Trial Options → No Known Options (If multiple findings exist within any of these categories, the results are listed alphabetically by gene name.)

Therapies

Sensitizing therapies → Resistant therapies. (If multiple therapies exist within any of these categories, they are listed alphabetically by therapy name.)

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

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.
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.

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

The median exon coverage for this sample is 733X

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