



FOUNDATIONONE® CDx



Report EU *FoundationOne® CDx*

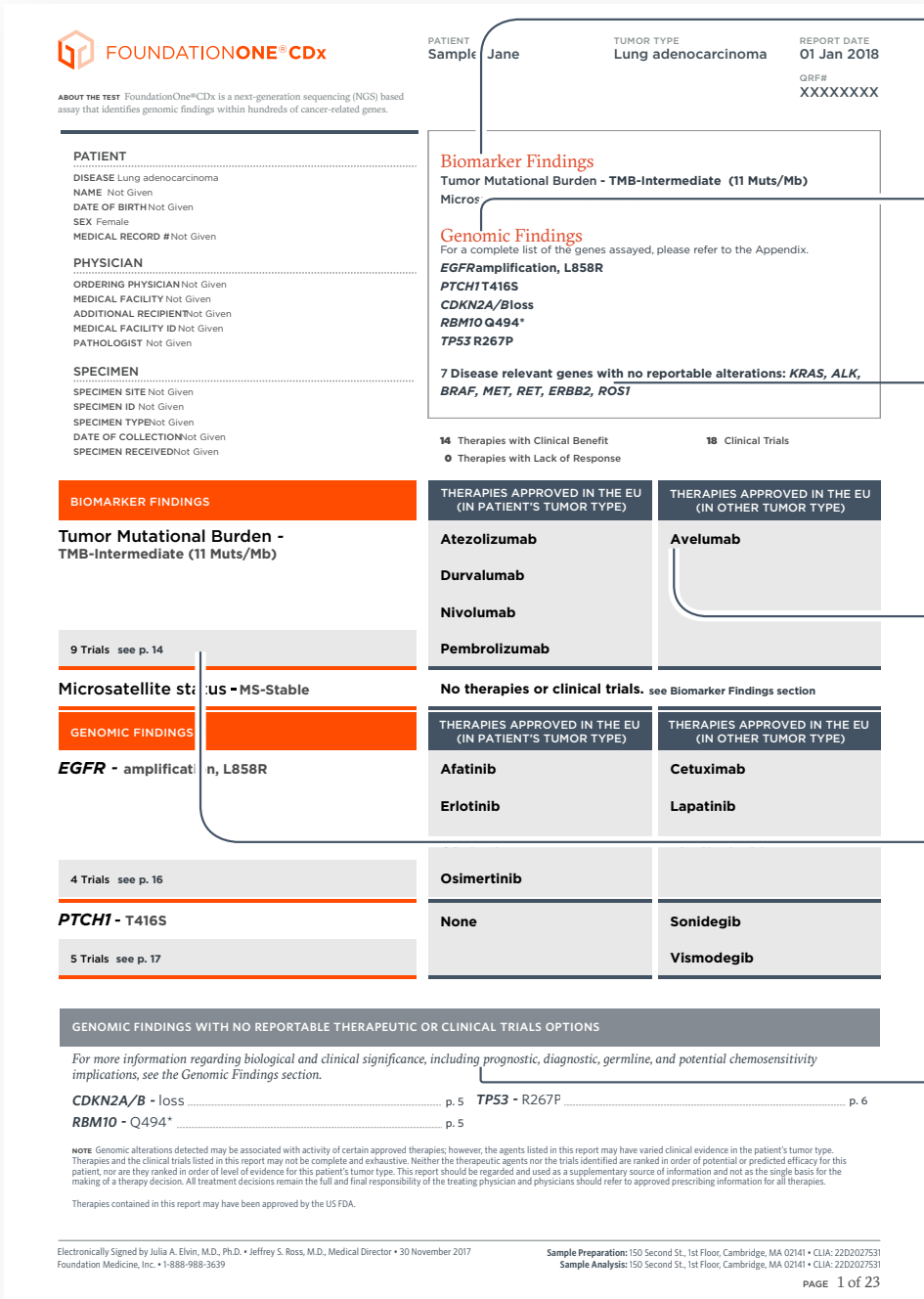


FOUNDATION
MEDICINE®



FoundationOne® CDx:

Il report EU include le terapie approvate a supporto della decisione clinica¹



FOUNDATIONONE® CDx

PATIENT Sample Jane
TUMOR TYPE Lung adenocarcinoma
REPORT DATE 01 Jan 2018
GRF# XXXXXXXX

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

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

Genomic Findings
 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, ROST

14 Therapies with Clinical Benefit
 0 Therapies with Lack of Response
18 Clinical Trials

BIOMARKER FINDINGS
Tumor Mutational Burden - TMB-Intermediate (11 Muts/Mb)
 9 Trials see p. 14

Microsatellite status: US - MS-Stable

GENOMIC FINDINGS
EGFR - amplification, L858R
 4 Trials see p. 16

PTCH1 - T416S
 5 Trials see p. 17

GENOMIC FINDINGS 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 Findings section.
CDKN2A/B - loss p. 5 **TP53 - R267P** p. 6
RBM10 - Q494* p. 5

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 by the US FDA.

Electronically Signed by Julia A. Elvin, M.D., Ph.D. • Jeffrey S. Ross, M.D., Medical Director • 30 November 2017
 Foundation Medicine, Inc. • 1-888-988-3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531
 Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531

PAGE 1 of 23

- 1. Genomic signatures**
Evidenza TMB e MSI, biomarker potenzialmente predittivi per la risposta all'immunoterapia
- 2. Gene alterations**
Alterazioni clinicamente rilevanti in 324 geni associati al tumore
- 3. Risultati negativi**
Segnala che le alterazioni rilevanti per la patologia non sono state identificate (ad es. ALK negativo per il NSCLC)
- 4. Terapie con benefici clinici**
Le terapie autorizzate in EU per il paziente che presenta genomic signatures e gene alterations
- 5. Studi clinici**
Studi clinici per i quali il paziente potrebbe essere eleggibile, in base al profilo genomico e alla posizione geografica
- 6. Alterazioni genomiche senza opzioni riportabili**
Per aiutare ad escludere i parametri incerti e determinare la strategia più appropriata

PRF# XXXXXXXX

GENOMIC SIGNATURES

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-1^{163,71,72}, and anti-PD-1 therapies^{57,65,73}; 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 pembrolizumab^{57,65,73}. 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 pembrolizumab⁷⁴ 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 ipilimumab^{64,78} 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 (mut) 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

TMB^{14,68,69,70}. 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 melanoma^{54,55} and cigarette smoke in lung cancer^{56,57}, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes^{58,59,60,61,62}, 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 inhibitors^{139,140,141}, 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 cancer^{133,134,135,136,137,138}. 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 PMS2^{127,128,129}. 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 markers^{130,131,132}. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{127,129,131,132}.

Fornisce la **genomic signatures e gene alterations** nei pazienti con tumore, in particolare fornisce le evidenze alla base delle potenziali strategie terapeutiche associate.

PRF# XXXXXXXX

THERAPIES APPROVED IN THE EU

IN PATIENT'S TUMOR TYPE

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 available in the EU to treat patients with advanced squamous non-small cell lung cancer following progression on prior therapy or with advanced non-small cell lung cancer (NSCLC) positive for activating EGFR mutations.

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 available in the EU to treat patients with advanced urothelial carcinoma following platinum-based chemotherapy or who are not eligible for cisplatin-containing chemotherapy. It is also available as monotherapy to treat patients with metastatic non-small cell lung cancer (NSCLC) following chemotherapy; patients whose tumors harbor EGFR or ALK alterations should also have received targeted therapy for these alterations.

GENE ASSOCIATION

On the basis of emerging clinical data (Kowanetz et al., 2016; ESMO Abstract 77P, Spigel et al., 2016; ASCO Abstract 901757, 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)¹⁸²(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).

Fornisce informazioni basate su
 potenzialmente attivi e compatibili co
 e le **caratteristiche specifich**

PRF# XXXXXXXX

THERAPIES APPROVED IN THE EU

IN OTHER TUMOR TYPE

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 to enhance antitumor immune responses. It is available in the EU to treat patients with metastatic Merkel cell carcinoma (MCC).

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 available in the EU to treat EGFR-expressing RAS wild-type metastatic colorectal cancer (CRC) as monotherapy or combined with chemotherapy. Cetuximab is also available to treat advanced head and neck squamous cell carcinoma (HNSCC) 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.

PRF# XXXXXXXX

CLINICAL TRIALS

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

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", "MEDL4736", "avelumab", "MSB0010718C", "BMS-936559", "pidilizumab", "CT-011", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

NCT01714739
PHASE 1 / PHASE 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-Naive Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

TARGETS
 CTLA-4, PD-1

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

Descrivere **gli studi clinici in corso** per i quali il paziente potrebbe essere eleggibile, indicandone il numero NCT (National Clinical Trial), la fase, il titolo e il luogo dove viene effettuato.

PRF# XXXXXXXX

APPENDIX

Variants of Unknown Significance

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

E132D

EP300

S12L, S24L, and S26F

IRS2

M543L and R1286Q

LRP1B

C1199F

Elenca le **varianti di significato sconosciuto (VUS)**, nell'eventualità diventino clinicamente significative in futuro.

PRF# XXXXXXXX

APPENDIX

Genes assayed in FoundationOne®CDx

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 28 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	ATRX	AMER1 (FAM123B)
APC	AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	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	ERRF1	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	MKKN1	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	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	WHSC1L1	WT1	XPO1
XRCC2	ZNF217	ZNF703						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	KIT	EGFR
ETV4	ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSPO2	SDC4	SLC34A2	TERC*	TERT**	TPRSS2

*TERC is a ncRNA

**The promoter region of TERT interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite status (MS)

Tumor Mutational Burden (TMB)

Bibliografia

1. FoundationOne® CDx esempio di report, 2018. Disponibile su: [HYPERLINK "http://www.rochefoundationmedicine.com/reporting"](http://www.rochefoundationmedicine.com/reporting)
www.rochefoundationmedicine.com/reporting.