FOUNDATIONONE® CDx

REPORT
EU

Report EU
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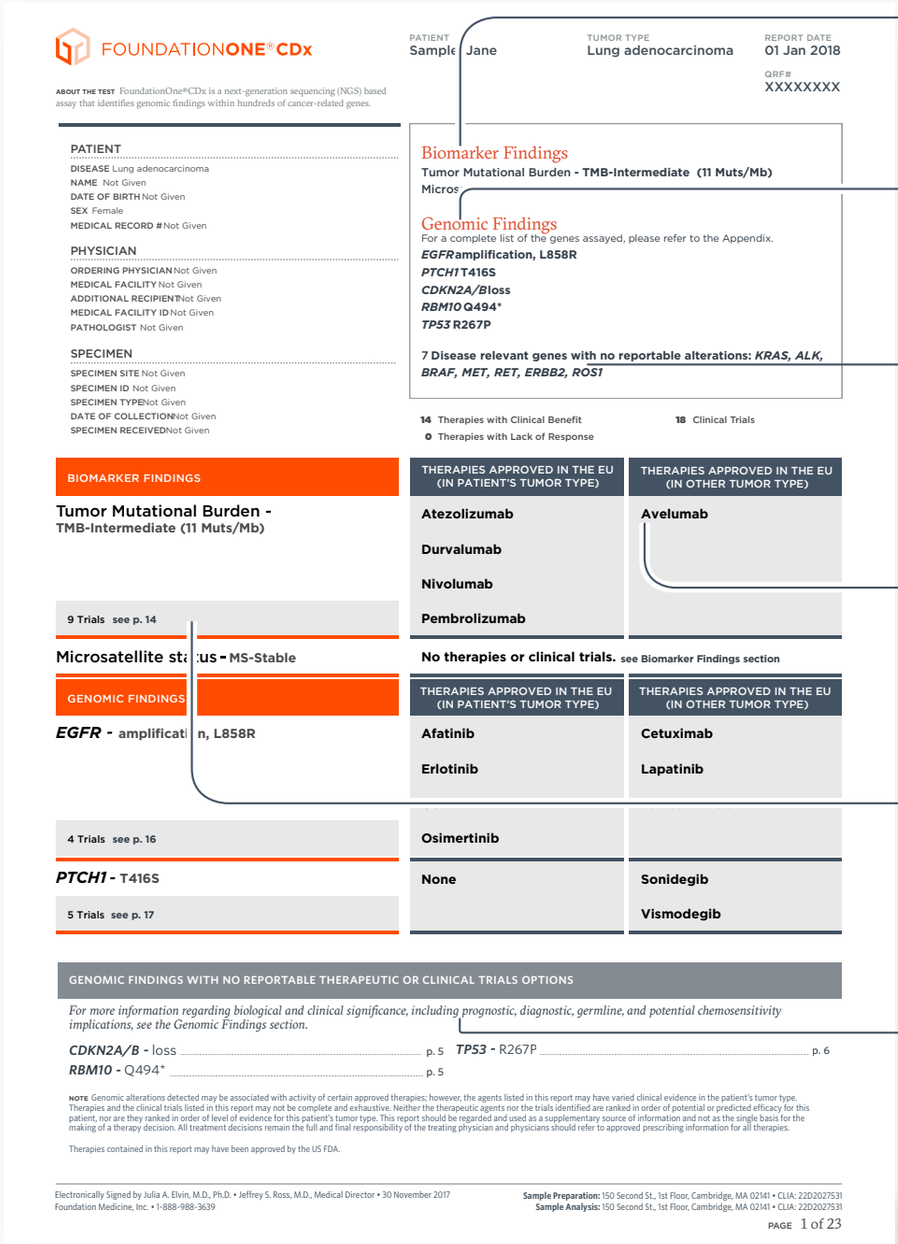
Il report EU include le terapie approvate a supporto della decisione clinica[1]



FOUNDATIONONE®CDx

PATIENT Sample Jane | TUMOR TYPE Lung adenocarcinoma | REPORT DATE 01 Jan 2018 | QRF# 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)
Microsatellite status - MS-Stable

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, ROS1*

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

BIOMARKER FINDINGS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-Intermediate (11 Muts/Mb)	Atezolizumab Durvalumab Nivolumab Pembrolizumab	Avelumab
9 Trials see p. 14		
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)**	**THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)**
EGFR - amplification, L858R	Afatinib Erlotinib	Cetuximab Lapatinib
4 Trials see p. 16	Osimertinib	
PTCH1 - T416S	None	Sonidegib Vismodegib
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
RBM10 - Q494* ..... p. 5
TP53 - R267P ..... p. 6

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

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1. **Genomic signatures**
   Evidenzia 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

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-4[64], anti-PD- L1[63,71,72], 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 pembrolizumab 74 or nivolumab[75], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab[76], and two pediatric patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[77]. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[64,78] and anti-PD-1/anti-PD-L1 treatments[71]. 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 survival[72].

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 cancer[57], anti-PD-L1 therapy in bladder cancer[63], and anti-CTLA-4 therapy in melanoma[64], potentially due to expression of immune-reactive neo-antigens in these tumors[57]. However, in other studies of checkpoint inhibitors, including anti-PD-1 therapy in colorectal cancer[65], 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 syndrome[133].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[127]. 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].

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 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).

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.

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", "MEDI4736", "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- 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

Descrive **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.

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*	*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*	*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***	*TMPRSS2*

*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" www.rochefoundationmedicine.com/reporting.