REPORT DATE REPORT ID PATIENT NAME CANCERPLEX[®] FP+IO Patient Example 1 PARTNER **BIRTH DATE** Full panel of 400+ genes for solid tumors-includes PATIENT ID GENDER LOGO potential response to immune checkpoint inhibitors AA000 00-00-0000 Μ ORDERING PHYSICIAN PHONE TUMOR SITE CLINICAL DIAGNOSIS Lymph node NSCLC, adenocarcinoma Oncologist COLLECTED RECEIVED KEW SPECIMEN ID REFERENCE ID PATHOLOGIST PHONE 00-00-0000 00 K0000 X000 Pathologist

RESULTS SUMMARY

The patient's tumor harbors an oncogenic EGFR Exon 19 deletion, for which EGFR TKIs are approved therapies. However, there is also an EGFR T790M mutation and amplification of MET, both of which are associated with RESISTANCE to EGFR TKIs. A possible therapeutic strategy is to treat with osimertinib, approved for NSCLC with EGFR T790M, in combination with a MET inhibitor which has demonstrated response in MET-amplified NSCLC.

	FDA-approved therapies		Therapies in clinical trials	
GENE Variants	For patient's disease	For other disease	Associated with resistance	For patient's disease
EGFR p.E746_A750del	Afatinib, Erlotinib, Gefitinib	Cetuximab, Ibrutinib, Necitumumab, Osimertinib, Panitumumab, Vandetanib	None	Cetuximab, Ibrutinib, Osimertinib, Panitumumab, Vandetanib, Afatinib, Erlotinib, Gefitinib, Investigational
EGFR T790M	Osimertinib	None	Gefitinib, Erlotinib, Afatinib,	Gefitinib, Erlotinib Afatinib, Cetuximab, Panitumumab
MET Gain	None	Crizotinib, Cabozantinib	Gefitinib, Erlotinib, Afatinib,	Crizotinib, Cabozantinib

PERTINENT NEGATIVES

No clinically significant mutations are found in KRAS, NRAS, BRAF or HER2 (ERBB2). No rearrangements are found in ALK, RET, or ROS1.

MSI-STATUS

MSS: No genomic evidence of microsatellite instability is detected (microsatellite stable).

PD-L1 IHC

Negative for PD-L1 Clone 22C3 (tumor proportion score <1%)

MUTATION BURDEN (IO)

A low tumor mutation burden is detected consistent with a non-hypermutated phenotype. Studies have demonstrated that a high mutation burden in NSCLC is associated with a hypermutated phenotype and better response to treatment with immune checkpoint inhibitors [PMID:25765070].

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Variants associated with approved therapies

EGFR	EGFR is a receptor tyrosine kinase of the ERBB family. EGFR is involved in a high proportion of GBM, NSCLC, HNSCC,
p.E746_	bladder, and GI cancers by increased expression, amplification, and/or expression of an aberrant gene. This recurrent
A750del	exon 19 in-frame deletion occurs within the kinase domain and has been reported in different tumor types, particularly in
	lung carcinoma (COSMIC). The patients harboring the mutation are sensitive to the EGFR kinase inhibitors, gefitinib,
	afatinib, and erlotinib [PMID:15118073;15118125;15329413], which are approved for metastatic NSCLC with EGFR exon 19
	deletions or exon 21 (L858R) substitution mutations.

Variants associated with therapies in clinical trials

EGFR p.E746_ A750del	EGFR is a receptor tyrosine kinase of the ERBB family. EGFR is involved in a high proportion of GBM, NSCLC, HNSCC, bladder, and GI cancers by increased expression, amplification, and/or expression of an aberrant gene. This recurrent exon 19 in-frame deletion occurs within the kinase domain and has been reported in different tumor types, particularly in lung carcinoma (COSMIC). The patients harboring the mutation are sensitive to the EGFR kinase inhibitors, gefitinib, afatinib, and erlotinib [PMID:15118073;15118125;15329413], which are approved for metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. These drugs and several others are also in clinical evaluation, either as monotherapy or in combination, for advanced cancers with activating EGFR mutations.
EGFR T790M	EGFR is a receptor tyrosine kinase of the ERBB family. EGFR is involved in a high proportion of GBM, NSCLC, HNSCC, bladder, and GI cancers by increased expression, amplification, and/or expression of an aberrant gene. This recurrent gate-keeper mutation, in exon 20, is mainly associated with lung carcinoma (COSMIC) and contributes to the acquired resistance of targeted therapies [PMID:19096299;18413800]. This mutation is also detected in the absence of drug selection with a modest effect on EGFR function, however, it enhanced the oncogenic activity of other activating EGFR mutations [PMID:17671201]. Along with an EGFR exon 19 deletion mutation detected in this tumor, this T790M alteration is likely tumorigenic. Osimertinib is approved for patients with EGFR T790M mutation-positive metastatic NSCLC.
MET Gain	MET is a transmembrane tyrosine kinase and the high-affinity receptor for hepatocyte growth factor (HGF). MET amplification is an oncogenic driver in a number of different tumor types [PMID:25055117]. The MET amplification in this tumor is considered an oncogenic event. In patients with non-small cell lung cancer, MET amplification is associated with shorter survival [PMID:20107422]. It is a cause of acquired resistance to EGFR-targeted therapies in NSCLC [PMID:17463250]. Studies have shown that MET-amplified lung cancer cells were more sensitive to MET inhibition with the kinase inhibitor crizotinib than cells without MET amplification [PMID:21716144]. MET inhibitors are being studied in patients with advanced cancers.

Clinical trials

NCT#	Title of trial	Therapy	Phase
NCT02161770	Study to Assess the Blood Levels and Safety of AZD9291 in Patients With Advanced Solid Tumours and Normal Liver Function or Mild or Moderate Liver Impairment	AZD9291 tablet dosing	1
NCT02099058	A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors	ABBV-399; Erlotinib; Cetuximab; Bevacizumab; Nivolumab; ABBV-399	1
NCT02451553	Afatinib Dimaleate and Capecitabine in Treating Patients With Advanced Refractory Solid Tumors, Pancreatic Cancer or Biliary Cancer	Afatinib Dimaleate; Capecitabine	1
NCT01973868	Safety and Pharmacokinetics of Regorafenib and Cetuximab in Combination	Regorafenib (Stivarga, BAY73-4506); Cetuximab (ERBITUX)	1

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NCT#	Title of trial	Therapy	Phase
NCT02091141	My Pathway: A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, Erivedge, Alecensa, and Tecentriq Treatment Targeted Against Certain Molecular Alterations in Participants With Advanced Solid Tumors	Trastuzumab; Pertuzumab; Erlotinib; Vemurafenib; Cobimetinib; Vismodegib; Alectinib; Atezolizumab; All	2
NCT02693535	TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer	Erlotinib; Axitinib; Bosutinib; Crizotinib; Palbociclib; Sunitinib; Temsirolimus; Trastuzumab and Pertuzumab; Vemurafenib and Cobimetinib; Vismodegib; Cetuximab; Dasatinib; Regorafenib; Olaparib; Pembrolizumab	2
NCT01061788	A Trial of AMG 479, Everolimus (RAD001) and Panitumumab in Patients With Advanced Cancer - QUILT-3.007	AMG 479; Everolimus; Panitumumab	1
NCT02095054	Regorafenib and Cetuximab in Patients With Advanced Malignancy	Regorafenib; Cetuximab	1
NCT02327169	A Phase 1B Study of MLN2480 in Combination With MLN0128 or Alisertib, or Paclitaxel, or Cetuximab, or Irinotecan in Adult Patients With Advanced Nonhematologic Malignancies	MLN2480; MLN0128; Alisertib; Paclitaxel; Cetuximab; Irinotecan	1
NCT01582191	A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer	Vandetanib; Everolimus	1
NCT02465060	NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma	Afatinib; Akt inhibitor AZD5363; Binimetinib; Crizotinib; Dabrafenib; Dasatinib; Defactinib; FGFR Inhibitor AZD4547; Larotrectinib; Osimertinib; Palbociclib; PI3K-beta Inhibitor GSK2636771; Sapanisertib; Sunitinib Malate; Taselisib; Trametinib; Trastuzumab-MCC-DM1 Immunoconjugate; Vismodegib; WEE1 Inhibitor AZD1775	2
NCT02759835	Local Ablative Therapy for Treatment of Oligoprogressive, EGFR-Mutated, Non-Small Cell Lung Cancer After Treatment With Osimertinib	Osimertinib	2
NCT01553942	Afatinib With CT and RT for EGFR-Mutant NSCLC	Afatinib; Cisplatin; Pemetrexed	2
NCT02954523	Dasatinib and Osimertinib (AZD9291) in Advanced Non-Small Cell Lung Cancer With EGFR Mutations	Dasatinib; Osimertinib	1; 2

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NCT02321540	A Phase I/II Study of Ibrutinib in Previously Treated Epidermal Growth Factor Receptor (EGFR) Mutant Non-Small Cell Lung Cancer	Ibrutinib	1; 2
NCT02342353	Pacritinib in Patients With Endothelial Growth Factor (EGFR) Mutant Non-small Cell Lung Cancer (NSCLC) After EGFR Tyrosine Kinase Inhibitor (TKI)	Pacritinib; Erlotinib	1; 2
NCT02424617	A Study of BGB324 in Combination With Erlotinib in Patients With Non-Small Cell Lung Cancer	Erlotinib; BGB324	1; 2
NCT01248247	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	Erlotinib; AZD6244; Sorafenib; Erlotinib	2
NCT01306045	Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	AZD6244; MK-2206; Lapatinib; Erlotinib; Sunitinib	2
NCT01455389	FUS1-nanoparticles and Erlotinib in Stage IV Lung Cancer	DOTAP:Chol-fus1; Erlotinib; Dexamethasone; Diphenhydramine	1; 2
NCT02795156	Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations	Afatinib; Regorafenib	2
NCT01573702	Stereotactic Radiosurgery or Other Local Ablation Then Erlotinib in Epidermal Growth Factor Receptor (EGFR)	Erlotinib	2
NCT02803203	Osimertinib and Bevacizumab as Treatment for EGFR-mutant Lung Cancers	Osimertinib; Bevacizumab	1; 2
NCT02403271	A Multi-Center Study of Ibrutinib in Combination With MEDI4736 in Subjects With Relapsed or Refractory Solid Tumors	lbrutinib; Durvalumab (MEDI4736)	1; 2
NCT02039674	A Study of Pembrolizumab (MK-3475) in Combination With Chemotherapy or Immunotherapy in Participants With Lung Cancer (MK-3475-021/KEYNOTE-021)	Paclitaxel; Carboplatin; Pemetrexed; Erlotinib; Gefitinib	1; 2
NCT02574078	A Study of Nivolumab in Advanced Non-Small Cell Lung Cancer (NSCLC)	Nivolumab; Bevacizumab; Pemetrexed; nab- Paclitaxel; Paclitaxel; Docetaxel; Gemcitabine; Erlotinib; Crizotinib; Carboplatin	1; 2
NCT02108964	A Phase I/II, Multicenter, Open-label Study of EGFRmut-TKI EGF816, Administered Orally in Adult Patients With EGFRmut Solid Malignancies	EGF816	1; 2
NCT02538627	Phase 1 Combination Study of MM-151 and MM-121	MM-151; MM-121	1
NCT02917993	An Open-Label Phase 1/2 Study of INCB039110 in Combination With Osimertinib in Subjects With Non-Small Cell Lung Cancer	INCB039110; Osimertinib	1; 2
NCT02438722	S1403, Afatinib Dimaleate With or Without Cetuximab in Treating Patients With Newly Diagnosed Stage IV or Recurrent, EGFR Mutation Positive Non-small Cell Lung Cancer	Afatinib Dimaleate	2; 3
NCT02411448	A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Participants With EGFR Mutation-Positive Metastatic NSCLC	Ramucirumab; Placebo; Erlotinib	3

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NCT#	Title of trial	Therapy	Phase
NCT02535338	Erlotinib Hydrochloride and Onalespib Lactate in Treating Patients With Recurrent or Metastatic EGFR-Mutant Non-small Cell Lung Cancer	Erlotinib Hydrochloride; Onalespib Lactate	1; 2
NCT02335944	Study of Safety and Efficacy of EGFR-TKI EGF816 in Combination With cMET Inhibitor INC280 in Non-small Cell Lung Cancer Patients With EGFR Mutation.	INC280; EGF816	1; 2
NCT02365662	A Study Evaluating Safety and Pharmacokinetics of ABBV-221 in Subjects With Advanced Solid Tumor Types Likely to Exhibit Elevated Levels of Epidermal Growth Factor Receptor	ABBV-221	1
NCT01748825	AZD1775 for Advanced Solid Tumors	AZD1775	1
NCT02610075	Phase Ib Study to Determine MTD of AZD1775 Monotherapy in Patients With Locally Advanced or Metastatic Solid Tumours.	AZD1775	1
NCT02617277	Safety, Tolerability and Pharmacokinetics of AZD1775 Plus MEDI4736 in Patients With Advanced Solid Tumours	AZD1775; MEDI4736	1
NCT01588821	Cabozantinib in Advanced Solid Malignancies	Cabozantinib	2
NCT01827384	Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors	Carboplatin; Everolimus; Temozolomide; Trametinib; Veliparib; WEE1 Inhibitor AZD1775	2
NCT01470209	A Phase I Study of BKM120 and Everolimus in Advanced Solid Malignancies	BKM120; Everolimus	1

References

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Methodology

This test is performed on DNA extracted from tumor tissue. Prior to testing, a histopathological review is performed to determine tissue adequacy. Extended coding regions of 435 genes are sequenced using a next-generation sequencing technology. The hybrid-capture target enrichment workflow is deeply optimized for "real-life" clinical samples in order to sequence full coding regions of all genes in the panel. This library is sequenced using Illumina's fast sequencers, then data is compared to reference genome GRCh37/hg19. Variant calls are generated by a proprietary data analysis pipeline. MSI status is determined using a set of molecular markers including but not limited to Bethesda panel. Predictive markers of response to immune checkpoint inhibitor therapy are distilled including burden of somatic mutations. Analytic sensitivity for SNP calls is 99.2% (98.9%-100% at 95% confidence interval), specificity is >99.9%; for insertions or deletions sensitivity is 100% (99.8%-100% at 95% confidence interval), specificity is >99.9%; for insertions or deletions and the additional 16 genes is 100% at tumor purity as low as 20%; specificity is 100%. Detection of copy-number variants is 100% sensitive for amplifications over 2.5-fold and homozygous deletions. Variants are annotated, sorted, and prioritized. Clinical significance is curated by a team of MD and PhD experts. The complete variant record, which may include variants of unknown significance, is available upon request.

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Genes analyzed: ABL1, ABL2, ACVR1B, ACVR2A, ADGRA2, AKT1, AKT2, AKT3, ALK, AMER1 (FAM123B), APC, AR, ARAF, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ATM, ATR, ATRX, AURKA, AURKB, AURKC, AXIN1, AXIN2, AXL, BAP1, BARD1, BCL11A, BCL11B, BCL2, BCL2L1, BCL6, BCL9, BCOR, BCORL1, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTK, BUB1B, CARD11, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CCR4, CD274, CD276, CD40, CD79A, CD79B, CD80, CD86, CDC73, CDH1, CDH11, CDH2, CDH5, CDK1, CDK12, CDK2, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD2, CHD4, CHEK1, CHEK2, CIC, CREBBP, CRKL, CRTC1, CSF1R, CTCF, CTLA4, CTNNA1, CTNNA2, CTNNB1, CUL3, CUX1, CYLD, DAXX, DCLRE1C, DDR1, DDR2, DDX5, DICER1, DNMT3A, DOT1L, EGFR, EML4, EMSY (C11orf30), EP300, EPCAM, EPHA2, EPHA3, EPHA5, EPHA7, EPHB1, EPHB6, ERBB2 (HER2), ERBB3 (HER3), ERBB4 (HER4), ERG, ERRF11, ESR1, ETS1, ETV1, ETV4, ETV5, ETV6, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, FAT1, FBXW7 (BAF250), FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FL11, FLT1 (VEGFR1), FLT3 (STK1), FLT4 (VEGFR3), FOXA1 (HNF3A), FOXO1, FOXP1, FRS2, GATA2, GATA3, GATA4, GATA6, GLI1, GNA11, GNA13, GNAQ, GNAS, GRIN2A, GRM3, GSK3B, HDAC1, HDAC2, HGF, HIF1A, HNF1A, HNF4A, HRAS, HSP90AA1, HSP90AB1, ICK, IDH1, IDH2, IGF1R, IGF2, IGF2R, IKBKB (IKKKB), IKBKE, IKZF1 (IKAROS), IL2RG, IL4R, INHBA, INPP4B, IRF2, IRF4, IRS2, JAK1, JAK2, JUN, KDM5A (JARID1A), KDM5C, KDM6A, KDR (VEGFR2), KEAP1, KIAA1804 (MLK4), KISS1R, KIT, KLF5, KLF6, KLHL6, KMT2A, KMT2C, KMT2D, KRAS, LIG3, LMO1, LPP, LYN, LZTR1, MAGI2, MAGI3, MALT1, MAML2, MAP2K1 (MEK1), MAP2K2 (MEK2), MAP2K4 (MEK4), MAP3K1 (MEKK1), MAP3K7 (TGF1A), MAPK1 (ERK2), MAPK3 (ERK1), MAPK4, MAPK6, MAPK7, MAPK8 (JNK1), MBD1, MCL1, MDM2, MDM4, MED12, MEF2B, MEN1, MET, MITF, MLH1, MN1, MRE11A, MSH2, MSH6, MST1R (RON), MTOR, MTR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOA1, NCOA2, NF1, NF2, NFE2L2, NFKB1, NFKB2, NFKBIA, NKX2-1 (TTF1), NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NRG1, NSD1, NTRK1, NTRK2, NTRK3, NUP214, PAK3, PALB2, PARK2, PARP1, PAX3, PAX7, PAX8, PBRM1, PBX1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDK1, PGAP3, PIK3C2A, PIK3C2B. PIK3C2G. PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3CG, PIK3R1, PIK3R2, PIK3R3, PLAG1, PLCG1, PLCG2, PLK1, PMS1, PMS2, POLD1, POLE, POLE4, POLR2A, PPARG, PPP2R1A, PPP6C, PRDM1, PREX2, PRKAR1A, PRKCI, PRKDC, PRSS1, PTCH1, PTEN, PTGS2, PTK2, PTPN11, PTPRD, PTPRT, PXDNL, QKI, RAC1, RAD17, RAD50, RAD51, RAD51C, RAD51D, RAF1, RALGDS, RASA1, RB1, RBM10, REL, RET, RHEB, RHOA, RICTOR, RNASEL, RNF2, RNF43, ROS1, RPS6, RPS6KA2, RPS6KB1, RPTOR, RUNX1, RUNX1T1, RYR1, SCN8A, SDHA, SDHB, SDHC, SDHD, SETD2, SETDB1, SF3B1, SGK1, SH2D1A, SLIT2, SLIT3, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMO, SOS1, SOX10, SOX11, SOX2, SOX9, SPEN, SPOP, SRC, SSTR1, SSTR2, SSTR3, SSTR5, STAG2, STAT3, STAT4, STK11 (LKB1), STK36 (FU), SUFU, TAF1, TCF7L1, TCF7L2, TEK, TERT*, TET2, TFE3, TGFB2, TGFB2, TMPRSS2, TNFAIP3, TNFRSF14, TNFRSF14, TNK2, TOP1, TOP2A, TP53, TP63, TPR, TPX2, TRIM33, TRRAP, TSC1, TSC2, TSHR, TYMS, U2AF1, UBR5, USP9X, VHL, VTCN1, WEE1, WISP3, WRN, WT1, XPC, XPO1, XRCC2, XRCC5, XRCC6, ZFHX3, ZNF217, ZNF384, ZNF521 (EVI3), **ZNF703**

Viral genomic detection is performed for: Human papillomavirus (HPV) 16/18 and Epstein-Barr virus (EBV).

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