diagnostics

MDPI

Supplementary Material

Cytogenetic and Biochemical Genetic Techniques for Personalized Drug Therapy in Europe

Tatjana Huebner *, Catharina Scholl and Michael Steffens

[1] Research Division, Federal Institute for Drugs and Medical Devices, 53175 Bonn, North Rhine-Westphalia, Germany; Catharina.Scholl@bfarm-research.de (C.S.); Michael.Steffens@bfarm-research.de (M.S.)

* Correspondence: Tatjana.Huebner@bfarm-research.de

Supplementary Material 1. GTR-registered tests of the category "Cytogenetics" screened by biomarker (testing required or recommended prior to prescription of the respective drug)

Drug	Disease	Gene/Biomarker	Cytogenetics
Abacavir	HIV infection	HLA-B*5701	-
Abemaciclib	Breast cancer	Hormone receptor positive (PGR, ESR1, ESR2), HER2 negative (ERBB2)	ERBB2: Fluorescence in situ hybridization
Afatinib	Lung cancer	EGFR	Fluorescence in situ hybridization
Alectinib	Lung cancer	Anaplastic Lymphoma Kinase (ALK)	Fluorescence In Situ Hybridization, RT-PCR with gel analysis (Cytogenetics)+ Molecular genetics: Allele-specific primer extension (ASPE) (Applied Biosystems™ 7900HT Sequence Detection System) (Molecular genetics), Fluorescence In Situ Hybridization Molecular genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)
Arsenic trioxide	Acute promyelocytic leukaemia	t(15;17) translocation, PML/RAR-alpha (PML (15q24.1), RARA (17q21.2)	t(15;17) translocation: G-banding PML/RAR-alpha: Fluorescence in situ hybridization (FISH)
Atazanavir	HIV infection	CYP2C19 *2,*3 or other star alleles related to decreased enzyme function	-
Atezolizumab	Urothelial cancer, lung cancer, triple-negative breast cancer	PD-L1	Fluorescence in situ hybridization (FISH)
Binimetinib	Melanoma	BRAF-V600 Mutation	-
Bosutinib	Chronic myelogenous leukaemia	Philadelphia-Chromosome	Fluorescence in situ hybridization (FISH), FISH (M)+G-banding, G-banding
Brentuximab vedotin	Hodgkin lymphoma and anaplastic large cell lymphoma	TNFRSF8	-
Brigatinib	Lung cancer	ALK	Fluorescence In Situ Hybridization, RT-PCR with gel analysis (Cytogenetics)+ Molecular genetics:

			Allele-specific primer extension (ASPE) (Applied Biosystems 7900HT Sequence Detection System), Fluorescence In Situ Hybridization+Molecular genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)
Capecitabine	Colorectal Neoplasms	DPYD (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants)	-
Carglumic acid	Hyperammonaemia	NAGS	-
Ceritinib	Lung cancer	Anaplastic Lymphoma Kinase	Fluorescence In Situ Hybridization, RT-PCR with gel analysis (Cytogenetics)+ Allele-specific primer extension (ASPE) (Applied Biosystems 7900™HT Sequence Detection System) (Molecular genetics), Fluorescence In Situ Hybridization ((Cytogenetics)+Next-Generation (NGS)/Massively parallel sequencing (MPS) (Molecular genetics)
Cerliponase alfa	Neuronal ceroid lipofuscinosis type 2 (CLN2) disease	TPP1	-
Cetuximab	Gastric cancer	Kras, Nras	Comparative Genomic Hybridization+ Molecular Genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)
Cholic acid	Inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7α-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults	CYP27A1, AMACR and CYP7A1, HSD3B7,AKR1D1	-
Cobimetinib	Melanoma	BRAF V600	-
Crizotinib	Lung cancer	ALK, ROS	Fluorescence In Situ Hybridization, RT-PCR with gel analysis (Cytogenetics) + Molecular Genetics: Allele-specific primer extension (ASPE)

			(Applied Biosystems™ 7900HT Sequence Detection System), Fluorescence In Situ Hybridization + Molecular Genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)
Dabrafenib	Melanoma	BRAF V600	-
Dacomitinib	Lung cancer	EGFR (ErbB-1)	Fluorescence in situ hybridization (FISH)
Dasatinib	Acute lymphatic leukemia	Philadelphia-chromosome	Fluorescence in situ hybridization (FISH)(M,I), FISH (M)+G-banding, G-banding
Eliglustat	Gaucher's disease	CYP2D6	-
Elosulfase alfa	Mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA)	GALNS	-
Encorafenib	Unresectable or metastatic melanoma	BRAF V600	-
Erlotinib	Lung cancer	EGFR (ErbB-1)	Fluorescence in situ hybridization (FISH) (F,I),
Everolimus	Breast cancer	ERBB2	Fluorescence In Situ Hybridization (F, T)
Fulvestrant	Breast cancer	PGR gene residing on chromosome 11q22, ESR1 (6q25.1), ESR2 (14q23.2)	-
Gefitinib	Lung cancer	EGFR (ErbB-1)	Fluorescence in situ hybridization (FISH) (F,I),
Ibrutinib	Chronic lymphocytic leukemia	17p deletion or TP53 mutation	17p deletion: Digital / Virtual karyotyping (M)+G-banding+ Molecular genetics: Microarray, G-banding, Fluorescence in situ hybridization +Microarray (e.g., Affymetrix® Cytoscan® HD Array) TP53: Comparative Genomic Hybridization + Molecular Genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS), Fluorescence in situ hybridization (FISH)(F)+G-banding, Fluorescence in situ hybridization (FISH) (I,M,F) (e.g., Affymetrix® GeneChip® Scanner 3000 7G Whole-Genome Association System)
Imatinib	Acute lymphatic and chronic myeloid leukemia	Philadelphia-chromosome	Fluorescence in situ hybridization (FISH)(M,I), FISH (M)+G-banding, G-banding
Ivacaftor	Mucoviscidosis	CFTR mutations	G-banding+ Molecular Genetics:

			Allele-specific PCR+PCR with allele specific hybridization, G-banding+ Molecular Genetics: PCR+Next-Generation (NGS)/Massively parallel sequencing (MPS)+ Bi-directional Sanger Sequence Analysis
Lapatinib	Breast cancer	HER2 overexpression, ERBB2	Fluorescence In Situ Hybridization
Lomitapid	Increased cholesterol or fat levels	LDLR, APOB and PCSK9	-
Lorlatinib	Non-small cell lung cancer	ALK	Fluorescence In Situ Hybridization (T,I), RT-PCR with gel analysis (Cytogenetics)+ Molecular Genetics: Allele-specific primer extension (ASPE) (Applied Biosystems™ 7900HT Sequence Detection System), Fluorescence In Situ Hybridization + Molecular Genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)
Lumacaftor / Ivacaftor	Cystic fibrosis	F508del mutation in the CFTR gene	-
Midostaurin	Acute myeloid leukaemia	FLT3	Comparative Genomic Hybridization)+ Molecular Genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)
Migalastat	Fabry disease	GLA	-
Neratinib	Breast cancer	HER2/ERBB2	Fluorescence In Situ Hybridization
Nilotinib	Chronic myeloid leukaemia	Philadelphia-chromosome	Fluorescence in situ hybridization (FISH)(M,I), FISH (M)+G-banding, G-banding
Olaparib	Ovarian Cancer	BRCA1/2	-
Osimertinib	Non-small cell lung cancer (NSCLC)	EGFR (ErbB-1) T790M	Fluorescence in situ hybridization (FISH)
Palbociclib	HR-positive, HER2-negative locally advanced or metastatic breast cancer	PGR, ESR1, ESR2, ERBB2	ERBB2: Fluorescent in situ hybridization
Panitumumab	Colon Cancer	RAS	-
Pembrolizumab	Non-small cell lung carcinoma (NSCLC) Head and neck squamous cell carcinoma (HNSCC) Urothelial carcinoma	PD-L1	Fluorescence in situ hybridization (FISH) (F,T)
Pertuzumab	Breast cancer	ERBB2	Fluorescent in situ hybridization (I, T, F)
Ponatinib	Chronic myeloid leukaemia (CML)	Philadelphia chromosome	Fluorescence in situ hybridization (FISH)(M,I), FISH (M)+G-banding, G-banding
Ribociclib	Breast cancer,	PGR, ESR1, ESR2, ERBB2	ERBB2: Fluorescent in situ

	HR-positive, HER2-negative		hybridization (I,F)
Rituximab	CD20-positive diffuse large V cell non-Hodgkin's lymphoma	MS4A1	-
Rucaparib	Relapsed or progressive epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC)	BRCA	-
Talazoparib	Breast cancer	BRCA1/2, HER2	ERBB2: Fluorescent in situ hybridization
Tezacaftor / Ivacaftor	Cystic fibrosis	F508del, CTFR	-
Trametinib	Melanoma, Non-small cell lung cancer (NSCLC)	BRAF V600	-
Trastuzumab	Breast and gastric cancer	HER2/ERBB2	Fluorescence In Situ Hybridization (I,F)
Trastuzumab emtansin	Breast cancer	HER2/ERBB2	Fluorescence In Situ Hybridization (I,F)
Vandetanib	Medullary thyroid cancer (MTC)	RET	Fluorescence In Situ Hybridization, Fluorescence in situ hybridization (FISH)+ Molecular Genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)+ Biochemical Genetics: Protein Expression (PD-L1) (e.g., NeoTYPE® Discovery Profile for Solid Tumors)
Velaglucerase alfa	Type 1 Gaucher disease	GBA	-
Vemurafenib	Melanoma	BRAF V600	-

M: Metaphase, I: Interphase, F: Fluorescence In Situ Hybridization, T: Targeted variant analysis.

Supplementary Material 2. GTR-registered tests of the category "Cytogenetics" and "Biochemical Genetics" by biomarker (drugs with annotations on actionable pharmacogenomics in the drug label provided by the respective EPAR).

Drug	Disease	Gene/Biomarker	Cytogenetics	Biochemical Genetics
Amifampridine Phosphate	Lambert–Eaton myasthenic syndrome	NAT2	-	-
Aripiprazole	Schizophrenia	CYP2D6	-	-
Brexpiprazole	Schizophrenia	CYP2D6	-	-
Brivaracetam	Epilepsy	CYP2C19 (poor metabolism)	-	-
Clopidogrel	Secondary prevention of atherothrombotic events, Prevention of atherothrombotic and thromboembolic events in atrial fibrillation	CYP2C19 intermediate or poor metabolism	-	-
Darifenacin (hydrobromide)	Urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with overactive bladder syndrome	CYP2D6 (poor metabolism)	-	-
Dolutegravir	HIV infection	UGT1A1 (poor dolutegravir metabolism)	-	-
Duloxetine	Treatment of major depressive disorder. Treatment of diabetic peripheral neuropathic pain. Treatment of generalised anxiety disorder.	CYP2D6	-	-
Efavirenz	HIV infection	Homozygous G516T genetic variant of the CYP2B6 isoenzyme	-	-
Efavirenz / Emtricitabine / Eenofovir Disoproxil	HIV infection	Homozygous G516T genetic variant of the CYP2B6 isoenzyme	-	-
Eltrombopag	Chronic immune (idiopathic) thrombocytopenic purpura (ITP)	Factor V Leiden (F5 gene) and ATIII deficiency (SERPINC1 gene)	-	F5: Electromagnetic Clot Detection/Quantitative Enzymatic (Analyte)+ Molecular Genetics: Polymerase Chain Reaction/Fluorescence Monitoring, Clotting (A)+ Molecular Genetics: Polymerase Chain Reaction/Fluorescence Monitoring
Erlotinib	Non-small-cell lung cancer (NSCLC)	UGT1A1	-	-

Ethinyl estradiol / norelgestromin	Female contraception	Predisposition for venous thromboembolism (including F5), antithrombin-III deficiency (SERPINC1), protein C deficiency (PROC) and protein S deficiency (PROS))	-	-
Fesoterodine	Treatment of the symptoms that may occur with overactive bladder syndrome.	CYP2D6 (poor metabolisers)	-	-
Gefitinib	Advanced or metastatic non-small cell lung cancer	CYP2D6 (poor metabolism)	-	-
Glibenclamide	Neonatal diabetes mellitus	G6PD (deficiency)	-	-
Glimepiride	Type 2 diabetes mellitus	G6PD (deficiency)	-	-
Irinotecan	Metastatic adenocarcinoma of the pancreas	Homozygozity for UGT1A1*28 allele	-	-
Lapatinib	Breast cancer, whose tumours overexpress HER2 (ErbB2)	HLA-DQA1*02:01 and HLA-DRB1*07:01	-	-
Lesinurad	Hyperuricaemia in gout patients	CYP2C9 (poor metabolism)	-	-
Lidocaine / Prilocaine	Primary premature ejaculation	G6PD	-	-
Mercaptopurine	Acute lymphoblastic leukaemia (ALL)	TPMT, NUDT15	-	-
Methylene blue	Medicinal and chemical products-induced methaemoglobinaemia	G6PD, NADPH deficiency	-	-
Pazopanib	Advanced renal cell carcinoma	HLA-B	-	-
Pioglitazone	Type 2 diabetes mellitus	G6PD	-	-
Pioglitazone	Stable angina pectoris	CYP2D6	-	-
Ranolazine	Stable angina pectoris	CYP2D6 (poor metabolism)	-	-
Rasburicase	Acute hyperuricaemia	G6PD	-	-
Regorafenib	Metastatic colorectal cancer	KRAS	-	-
Ticagrelor	Prevention of atherothrombotic events	CYP2C19 (loss of function allele)	-	-
Toremifen	Hormone-dependent metastatic breast cancer	ESR1 and ESR2	-	-
Vortioxetine	Major depressive episodes	CYP2D6 (poor metabolism, ultra-rapid metabolism)	-	-

Supplementary Material 3. GTR-registered tests of the category "Biochemical Genetics" screened by biomarker (testing required or recommended prior to prescription of the respective drug)

Drug	Disease	Gene/Biomarker	Biochemical Genetics
Alectinib	Lung cancer	ALK	Immunohistochemistry for ALK and ROS fusion proteins(I)+ Molecular Genetics: Pyrosequencing
Atezolizumab	Urothelial cancer, lung cancer, triple-negative breast cancer	PD-L1	Immunohistochemistry
Brigatinib	Lung cancer	ALK	Immunohistochemistry for ALK and ROS fusion proteins(I)+ Molecular Genetics: Pyrosequencing
Capecitabine	Colorectal Neoplasms	DPYD (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants)	Gas chromatography–mass spectrometry (GC-MS) (Analyte analysis) (A), Metabolite analysis (A) + Enzyme diagnostics(E) + Molecular Genetics: Bi-directional Sanger Sequence Analysis
Carglumic acid	Hyperammonaemia	NAGS	Metabolite levels (A) + Bi-directional Sanger Sequence Analysis(C) (Molecular Genetics), Enzymatic levels (E)+ Molecular Genetics: Multiplex Ligation-dependent Probe Amplification (MLPA) + Trinucleotide repeat by PCR or Southern Blot +Bi-directional Sanger Sequence Analysis+ Next-Generation (NGS)/Massively parallel sequencing (MPS) (C)
Ceritinib	Lung cancer	Anaplastic Lymphoma Kinase	Immunohistochemistry for ALK and ROS fusion proteins(I)+Pyrosequencing
Cerliponase alfa	Neuronal ceroid lipofuscinosis type 2 (CLN2) disease	TPP1	Enzyme activity(E)+ Molecular Genetics: Bi-directional Sanger Sequence Analysis(C) Fluorometry (E)
Ivacaftor	Mucoviscidosis (cystic fibrosis)	CFTR mutations	Enzyme activity+Molecular genetics: PCR with allele specific hybridization, Enzymatic levels+Molecular genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS),Enzymatic levels+Molecular genetics: Next-Generation (NGS)/Massively parallel sequencing (MPS)+Trinucleotide repeat by PCR or Southern Blot
Lorlatinib	Non-small cell lung cancer	ALK	Immunohistochemistry for ALK and ROS fusion proteins(I) + Molecular Genetics: Pyrosequencing
Migalastat	Fabry disease	GLA	Enzyme activity (E), Enzyme activity (E) + Molecular Genetics: Bi-directional Sanger Sequence Analysis (e.g., Applied Biosystems™ 3500xL capillary sequencing instrument)
Pembrolizumab	Non-small cell lung carcinoma (NSCLC) Head and neck squamous	PD-L1	Immunohistochemistry (I), Protein expression (I) Antibodies, conjugates, and chromogens (I)

	cell carcinoma (HNSCC) Urothelial carcinoma		
Velaglucerase alfa	Type 1 Gaucher disease	GBA	Enzyme activity Fluorometry (Enzymes:beta-Glucosidase) (E)+ Molecular Genetics: Bi-directional Sanger Sequence Analysis +PCR / RFLP, Enzymatic levels (E), Fluorometry (E)+Bi-directional Sanger Sequence Analysis+PCR / RFLP (Molecular Genetics) Enzyme activity (E)+Bi-directional Sanger Sequence Analysis (Molecular Genetics)

I: Immunohistochemistry, A: Analyte, E: Enzyme assay, A: Analyte analysis, C: Sequence analysis of the entire coding region.