CeGaT

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Name	Doe, John (*##.##.20##)
Sex	Male
Patient-ID	######
Report date	DD.MM.YYYY
Report-ID	R9999999999

CancerPrecision® - Report of Somatic Tumor Variants
Doe, John (*DD.MM.YYYY)

Indication **Glioblastoma, IDH-wildtype, WHO grade 4 (ID MM/YYYY)**

Result Overview

Tumor Tissue & Tumor Content (TC)	Germline Variants	Tumor Drivers	Fusions, Structural Variants	Pharmacogenetics
Primary tumor sample from MM/YYYY 75% diagnostically Diag-TC min 20%	No evidence for pathogenic or likely pathogenic alterations	Identified tumor drivers: *VEGFA, EGFR, CDKN2A, CCND2, TERT, TP53* Relevant genes without oncogenic alterations: *ATRX, BRAF*	EGFRvIII Detection on RNA and DNA level	Detection of a germline variant in gene *UGT1A1*

Tumor Mutational Burden (TMB)	Microsatellite Instability (MSI)	Homologous Recombination Deficiency (HRD)	Viral Infection	CHIP
1.4 Var/Mb High ≥ 10	No evidence for MSI (NGS prediction) Score 0.15 Indication of MSI ≥ 0.33	No evidence for HRD Score 2 Indication of HRD ≥ 30	No evidence for an infection with HPV/EBV/CMV/MCV in the tumor sample	No evidence for CHIP

Variants with Potential Therapeutic Relevance

Gene	Functional category	Variant	NAF	Effect on protein function	Therapeutic option for discussion in the MTB	Approved by EMA/FDA	Approved for current entity
VEGFA	overexpression	complete gene	N/A	activating	VEGF inhibitor	EMA* & FDA*	FDA*
					VEGFR inhibitor	EMA & FDA*	no
EGFR	deletion	CDS 2-7, focal (EGFR vIII)	N/A	activating	EGFR inhibitor	EMA* & FDA*	no
					EGFRvIII-targeted Immunotherapy	no	no
					Possible resistance to Immune checkpoint inhibitor	N/A	N/A
	amplification	complete gene, non focal (10 copies)	N/A	activating	EGFR inhibitor	EMA* & FDA*	no
					Possible resistance to Immune checkpoint inhibitor	N/A	N/A
	overexpression	complete gene	N/A	activating	EGFR inhibitor	EMA* & FDA*	no
					Possible resistance to Immune checkpoint inhibitor	N/A	N/A
CDKN2A	homozygous deletion	complete gene, focal	N/A	inactivating	CDK4/6 inhibitor	EMA* & FDA*	no
					Possible resistance to Immune checkpoint inhibitor	N/A	N/A
	reduced expression	complete gene	N/A	inactivating	CDK4/6 inhibitor	EMA* & FDA*	no
					Possible resistance to Immune checkpoint inhibitor	N/A	N/A
CCND2	overexpression	complete gene	N/A	activating	CDK4/6 inhibitor	EMA* & FDA*	no
TERT	upstream_gene	c.-146C>T (C250T) chr5:1295250 G>A (hg19)	0.35	activating	TERT-targeting inhibitor	EMA* & FDA*	no
					TERT-targeting immunotherapy	no	no
	overexpression	complete gene	N/A	activating	TERT-targeting inhibitor	EMA* & FDA*	no
					TERT-targeting immunotherapy	no	no
TP53	missense	c.524G>A; p.Arg175His chr17:7578406 C>T (hg19) and loss of wildtype allele	0.74	function changed	CHK1 inhibitor	no	no
					Wee inhibitor	no	no

NAF: *Novel allele frequency*, the frequency with which the mutated allele occurs in the sequencing data (1 is 100%). The observed frequencies are influenced by the tumor content as well as copy number alterations and do not directly correlate with the variant's frequency in the tumor. **CDS:** Coding DNA-sequence.
Protein function: The somatic alterations were classified with respect to their effect on protein function with the following categories: inactivating/activating/function changed, likely inactivating/activating/function changed, unknown, and benign (details in the methods section).
Approval: Only those organisations having approved the respective therapeutical option are listed here. An asterisk indicates approval restrictions (for details regarding targeted therapeutical options please refer to the appendix).
Gene expression: An altered gene expression does not necessarily lead to a (therapeutically) relevant, altered protein biosynthesis. We recommend using an independent method such as direct staining of the target structure at the protein level to support therapeutic decisions based on gene expression data only.

Please refer to the table in the appendix for more information regarding targeted approved drug therapies (EMA/FDA), including information on approval requirements and potential drug resistance.

Variants with Pharmacogenetic Relevance

Gene	Functional category	Variant	Transcript-ID	Zygosity	Effect on protein function	Therapeutic option	Phenotype
UGT1A1	5_prime_UTR	c.-41_-40dup (*28/*28) chr2:234668879 C>CAT (hg19)	NM_000463.3	homozygous	inactivating	Topoisomerase inhibitor	Poor metabolizer

The variants were classified with respect to their effect on protein function with the following categories: inactivating/activating/function changed, likely inactivating/activating/function changed, unknown, and benign (please refer to the method section for further details regarding variant classification).

Complete List of Automatically Detected Somatic Variants

The table below includes all somatic variants (single nucleotide variants and small deletions/insertions (≤ 40bp)) detected automatically within the sequenced regions (tumor panel V.8).

Gene	Functional category	Variant	Transcript-ID	NAF
GRM3	missense	c.145G>C; p.Glu49Gln chr7:86394606 G>C (hg19)	NM_000840.3	0.25
JAK1	synonymous	c.120C>T; p.= chr1:65349045 G>A (hg19)	NM_002227.4	0.31
TERT	upstream_gene	c.-146C>T (C250T) chr5:1295250 G>A (hg19)	NM_198253.3	0.35
TP53	missense	c.524G>A; p.Arg175His chr17:7578406 C>T (hg19)	NM_000546.6	0.74

NAF: *Novel allele frequency*, the frequency with which the mutated allele was detected in the sequencing data (1 is 100%). The observed frequencies are influenced by the tumor content as well as copy number alterations and do not correlate directly with the variant frequency in the tumor.

Based on the DNA sequencing analysis of the EDTA blood sample (normal tissue) the HLA genotype was determined to be:
HLA-A*##:##, HLA-A*##:##, HLA-B*##:##, HLA-B*##:##, HLA-C*##:##, HLA-C*##:##, HLA-DPA1*##:##, HLA-DPA1*##:##, HLA-DPB1*##:##, HLA-DPB1*##:##, HLA-DQA1*##:##, HLA-DQA1*##:##, HLA-DQB1*##:##, HLA-DQB1*##:##, HLA-DRB1*##:##, HLA-DRB1*##:##, HLA-DRB3*##:##

Copy Number Alterations

Our sequencing data provide evidence for the presence of potentially relevant copy number alterations of large genomic segments as well as single therapeutically relevant genes (see tables above and below).

Chromosomal region	Functional category	Variant	Copy number	Affected genes with potential therapeutic relevance
chr7 50344312-55273310	amplification	p-arm, partial	10	*EGFR*

The sensitivity of copy number detection depends on the sample's tumor content and the sample's overall quality. Copy numbers, as well as breakpoints, are estimated on the basis of the NGS data and should be treated as estimated values. The set of candidate genes represents a selection only and makes no claim of completeness. Please be aware that copy number variants likely cover a large number of genes. Possible interactions between these genes may impair reliable prediction of single gene effects on the analyzed tumor.

Recommendation

The detected variant *28/*28 in gene *UGT1A1* is a homozygous germline variant. Potential increased toxicity has been described for this genotype (also known as (TA)7/(TA)7, rs8175347 or rs3064744) when treated with irinotecan-based chemotherapeutic agents (Steventon, 2020, PMID: 31092094; PharmGKB Level of Evidence 1A; Whirl-Carrillo et al., 2012, PMID: 22992668; Dean, Medical Genetics Summaries, updated 2018, PMID: 28520360). In addition, when using the TROP2 inhibitor sacituzumab govitecan in patients with known reduced UGT1A1 activity, close monitoring of side effects is recommended as they may be at increased risk of neutropenia, febrile neutropenia and anemia (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761115s023lbl.pdf).
Drug dosing adjustments should exclusively be performed following consultation with the attending clinician.

The results of this report should be evaluated against this patient's current clinical status and should be reviewed by an interdisciplinary tumor board.

Please do not hesitate to contact us if you have any questions.

Medical report written by: Forename Surname

Proofread by: Forename Surname

Validated by: Forename Surname

With kind regards,

Dr. med. Dr. rer. nat. Saskia Biskup

Consultant for Human Genetics

Additional Information

Order

1. **Somatic molecular genetic analysis of a tumor tissue sample:**
Tumor panel analysis TUM01, evaluation of somatic variants of potential clinical relevance
2. **RNA fusion panel analysis STR**
3. **Gene expression analysis**

Sample material

Tumor tissue: Primary sample of the known glioblastoma
Sample collection MM/YYYY
DNA and RNA isolation from tumor in FFPE (FFPE-ID: ####/##) with estimated tumor content of 70% (HE staining)
Diagnostically estimated tumor content 75%

Normal tissue: EDTA blood

Sample receipt

DD.MM.YYYY (Normal-DNA: EDTA blood, ID P######_1)
DD.MM.YYYY (Tumor-DNA: FFPE material, ID P######_2)
DD.MM.YYYY (Tumor-RNA: FFPE material, IDs P######_3, P######_4)

Requested Regions

Somatic tumor panel (TUM01) contains interpretation of the following cancer-relevant genes:

CACNA1S, *DPYD*, *G6PD*, *NUDT15*, *RYR1*, *TPMT*, *UGT1A1* (Pharmacogenetics)

ABCB1, *ABCG2*, *ABL1*, *ABL2*, *ABRAXAS1*, *ACD*, *ACVR1*, *ACVR2A*, *ADGRA2*, *ADRB1*, *ADRB2*, *AIP*, *AIRE*, *AJUBA*, *AKT1*, *AKT2*, *AKT3*, *ALK*, *ALOX12B*, *AMER1*, *ANKRD26*, *APC*, *APLNR*, *APOBEC3A*, *APOBEC3B*, *AR*, *ARAF*, *ARFRP1*, *ARHGAP35*, *ARID1A*, *ARID1B*, *ARID2*, *ARID5B*, *ASXL1*, *ASXL2*, *ATM*, *ATR*, *ATRX*, *AURKA*, *AURKB*, *AURKC*, *AXIN1*, *AXIN2*, *AXL*, *B2M*, *B4GALNT1*, *BAP1*, *BARD1*, *BAX*, *BCHE*, *BCL10*, *BCL11A*, *BCL11B*, *BCL2*, *BCL2L1*, *BCL2L11*, *BCL3*, *BCL6*, *BCL9*, *BCOR*, *BCORL1*, *BCR*, *BIRC2*, *BIRC3*, *BIRC5*, *BLM*, *BMI1*, *BMPR1A*, *BRAF*, *BRCA1*, *BRCA2*, *BRD3*, *BRD4*, *BRD7*, *BRIP1*, *BTK*, *BTN3A1*, *BUB1B*, *CACNA1S*, *CALR*, *CARD11*, *CASP8*, *CBFB*, *CBL*, *CBLB*, *CBLC*, *CCDC6*, *CCND1*, *CCND2*, *CCND3*, *CCNE1*, *CD274*, *CD276*, *CD70*, *CD79A*, *CD79B*, *CD82*, *CDC42*, *CDC73*, *CDH1*, *CDH11*, *CDH2*, *CDH3*, *CDH5*, *CDK1*, *CDK12*, *CDK2*, *CDK4*, *CDK5*, *CDK6*, *CDK8*, *CDKN1A*, *CDKN1B*, *CDKN1C*, *CDKN2A*, *CDKN2B*, *CDKN2C*, *CEACAM5*, *CEBPA*, *CENPA*, *CEP57*, *CFTR*, *CHD1*, *CHD2*, *CHD4*, *CHEK1*, *CHEK2*, *CIC*, *CIITA*, *CLDN18*, *CNKSR1*, *COL1A1*, *COMT*, *COQ2*, *CREB1*, *CREBBP*, *CRKL*, *CRLF2*, *CRTC1*, *CSF1R*, *CSF3R*, *CSMD1*, *CSNK1A1*, *CTAG1B*, *CTCF*, *CTLA4*, *CTNNA1*, *CTNNB1*, *CTR9*, *CTRC*, *CUL3*, *CUX1*, *CXCR4*, *CYLD*, *CYP1A2*, *CYP2A7*, *CYP2B6*, *CYP2C19*, *CYP2C8*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *DAXX*, *DCC*, *DDB2*, *DDR1*, *DDR2*, *DDX11*, *DDX3X*, *DDX41*, *DHFR*, *DICER1*, *DIS3L2*, *DLL3*, *DNMT1*, *DNMT3A*, *DOT1L*, *DPYD*, *E2F3*, *EED*, *EFL1*, *EGFR*, *EGLN1*, *EGLN2*, *EIF1AX*, *ELAC2*, *ELF3*, *EME1*, *EML4*, *EMSY*, *EP300*, *EPAS1*, *EPCAM*, *EPHA2*, *EPHA3*, *EPHB4*, *EPHB6*, *ERBB2*, *ERBB3*, *ERBB4*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *ERG*, *ERRFI1*, *ESR1*, *ESR2*, *ETNK1*, *ETV1*, *ETV4*, *ETV5*, *ETV6*, *EWSR1*, *EXO1*, *EXT1*, *EXT2*, *EZH1*, *EZH2*, *EZHIP*, *F3*, *FAN1*, *FANCA*, *FANCB*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *FANCM*, *FAS*, *FAT1*, *FBXO11*, *FBXW7*, *FEN1*, *FES*, *FGF10*, *FGF14*, *FGF19*, *FGF2*, *FGF23*, *FGF3*, *FGF4*, *FGF5*, *FGF6*, *FGF9*, *FGFR1*, *FGFR2*, *FGFR3*, *FGFR4*, *FH*, *FLCN*, *FLI1*, *FLT1*, *FLT3*, *FLT4*, *FOLH1*, *FOLR1*, *FOXA1*, *FOXE1*, *FOXL2*, *FOXO1*, *FOXQ1*, *FRK*, *FRS2*, *FUS*, *FYN*, *G6PD*, *GALNT12*, *GATA1*, *GATA2*, *GATA3*, *GATA4*, *GATA6*, *GGT1*, *GLI1*, *GLI2*, *GLI3*, *GNA11*, *GNA13*, *GNAQ*, *GNAS*, *GNB3*, *GPC3*, *GPER1*, *GREM1*, *GRIN2A*, *GRM3*, *GSK3A*, *GSK3B*, *GSTP1*, *H3-3A*, *H3-3B*, *H3C1*, *H3C2*, *H3C3*, *HABP2*, *HAVCR2*, *HCK*, *HDAC1*, *HDAC2*, *HDAC6*, *HGF*, *HIF1A*, *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DRA*, *HLA-DRB1*, *HMGA2*, *HMGCR*, *HMGN1*, *HNF1A*, *HNF1B*, *HOXB13*, *HRAS*, *HSD3B1*, *HSP90AA1*, *HSP90AB1*, *HTR2A*, *ICOSLG*, *ID2*, *ID3*, *IDH1*, *IDH2*, *IDO1*, *IFNGR1*, *IFNGR2*, *IFNL3*, *IGF1*, *IGF1R*, *IGF2*, *IGF2R*, *IKBKB*, *IKBKE*, *IKZF1*, *IKZF3*, *IL1B*, *IL1RN*, *IL7R*, *INPP4A*, *INPP4B*, *INPPL1*, *INSR*, *IRF1*, *IRF2*, *IRS1*, *IRS2*, *IRS4*, *ITPA*, *JAK1*, *JAK2*, *JAK3*, *JUN*, *KAT6A*, *KDM5A*, *KDM5C*, *KDM6A*, *KDR*, *KEAP1*, *KIAA1549*, *KIF1B*, *KIT*, *KLF2*, *KLF4*, *KLHL6*, *KLLN*, *KMT2A*, *KMT2B*, *KMT2C*, *KMT2D*, *KRAS*, *KSR1*, *LAG3*, *LAMP1*, *LATS1*, *LATS2*, *LCK*, *LIG4*, *LIMK2*, *LRP1B*, *LRRK2*, *LTK*, *LYN*, *LZTR1*, *MAD2L2*, *MAF*, *MAGEA1*, *MAGEA12*, *MAGEA3*, *MAGEA4*, *MAGEA8*, *MAGI1*, *MAGI2*, *MAML1*, *MAP2K1*, *MAP2K2*, *MAP2K3*, *MAP2K4*, *MAP2K5*, *MAP2K6*, *MAP2K7*, *MAP3K1*, *MAP3K13*, *MAP3K14*, *MAP3K3*, *MAP3K4*, *MAP3K6*, *MAP3K8*, *MAPK1*, *MAPK11*, *MAPK12*, *MAPK14*, *MAPK3*, *MAX*, *MBD4*, *MC1R*, *MCL1*, *MDC1*, *MDH2*, *MDM2*, *MDM4*, *MECOM*, *MED12*, *MEF2B*, *MEN1*, *MERTK*, *MET*, *MGA*, *MGMT*, *MITF*, *MLH1*, *MLH3*, *MLLT10*, *MLLT3*, *MMP2*, *MMS22L*, *MN1*, *MPL*, *MRE11*, *MS4A1*, *MSH2*, *MSH3*, *MSH4*, *MSH5*, *MSH6*, *MSLN*, *MSR1*, *MST1R*, *MT-RNR1*, *MTAP*, *MTHFR*, *MTOR*, *MTRR*, *MUC1*, *MUTYH*, *MXI1*, *MYB*, *MYC*, *MYCL*, *MYCN*, *MYD88*, *MYH11*, *MYH9*, *MYOD1*, *NAT2*, *NBN*, *NCOA1*, *NCOA3*, *NCOR1*, *NF1*, *NF2*, *NFE2L2*, *NFKB1*, *NFKB2*, *NFKBIA*, *NFKBIE*, *NIN*, *NKX2-1*, *NLRC5*, *NOTCH1*, *NOTCH2*, *NOTCH3*, *NOTCH4*, *NPM1*, *NQO1*, *NR1I3*, *NRAS*, *NRG1*, *NSD1*, *NSD2*, *NSD3*, *NT5C2*, *NTHL1*, *NTRK1*, *NTRK2*, *NTRK3*, *NUDT15*, *NUMA1*, *NUP98*, *NUTM1*, *OBSCN*, *OPRM1*, *PAK1*, *PAK3*, *PAK4*, *PAK5*, *PALB2*, *PALLD*, *PARP1*, *PARP2*, *PARP4*, *PAX3*, *PAX5*, *PAX7*, *PBK*, *PBRM1*, *PBX1*, *PDCD1*, *PDCD1LG2*, *PDGFA*, *PDGFB*, *PDGFC*, *PDGFD*,

PDGFRA, *PDGFRB*, *PDK1*, *PDPK1*, *PGR*, *PHF6*, *PHOX2B*, *PIAS4*, *PIGA*, *PIK3C2A*, *PIK3C2B*, *PIK3C2G*, *PIK3CA*, *PIK3CB*, *PIK3CD*, *PIK3CG*, *PIK3R1*, *PIK3R2*, *PIK3R3*, *PIM1*, *PLCG1*, *PLCG2*, *PLK1*, *PMEL*, *PML*, *PMS1*, *PMS2*, *POLB*, *POLD1*, *POLE*, *POLH*, *POLQ*, *POR*, *POT1*, *PPARG*, *PPM1D*, *PPP2R1A*, *PPP2R2A*, *PRAME*, *PREX2*, *PRKAR1A*, *PRKCA*, *PRKCI*, *PRKDC*, *PRKN*, *PRMT5*, *PRR4*, *PSMB1*, *PSMB10*, *PSMB2*, *PSMB5*, *PSMB8*, *PSMB9*, *PSMC3IP*, *PSME1*, *PSME2*, *PSME3*, *PTCH1*, *PTCH2*, *PTEN*, *PTGS2*, *PTK2*, *PTK7*, *PTPN11*, *PTPN12*, *PTPRC*, *PTPRD*, *PTPRS*, *PTPRT*, *RABL3*, *RAC1*, *RAC2*, *RAD21*, *RAD50*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54B*, *RAD54L*, *RAF1*, *RALGDS*, *RARA*, *RASA1*, *RASAL1*, *RB1*, *RBM10*, *RECQL4*, *REST*, *RET*, *RFWD3*, *RFX5*, *RFXANK*, *RFXAP*, *RHBDF2*, *RHEB*, *RHOA*, *RICTOR*, *RIF1*, *RINT1*, *RIPK1*, *RIT1*, *RNASEL*, *RNF43*, *ROS1*, *RPS20*, *RPS6KB1*, *RPS6KB2*, *RPTOR*, *RSF1*, *RSPO1*, *RSPO2*, *RSPO3*, *RSPO4*, *RUNX1*, *RYR1*, *SAMHD1*, *SAV1*, *SBDS*, *SCG5*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SEC23B*, *SERPINB9*, *SETBP1*, *SETD2*, *SETDB1*, *SF3B1*, *SGK1*, *SH2B3*, *SHH*, *SHLD2*, *SIK2*, *SKP2*, *SLC19A1*, *SLC26A3*, *SLC45A2*, *SLCO1B1*, *SLFN11*, *SLIT2*, *SLX4*, *SMAD3*, *SMAD4*, *SMARCA2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SMC1A*, *SMC3*, *SMO*, *SOCS1*, *SOS1*, *SOX11*, *SOX2*, *SOX9*, *SPEN*, *SPINK1*, *SPOP*, *SPRED1*, *SRC*, *SRD5A2*, *SRGAP1*, *SRSF2*, *SSTR2*, *SSX1*, *STAG2*, *STAT1*, *STAT3*, *STAT5A*, *STAT5B*, *STK11*, *SUCLG2*, *SUFU*, *SUZ12*, *SYK*, *TACSTD2*, *TAF1*, *TAF15*, *TAP1*, *TAP2*, *TAPBP*, *TBK1*, *TBX3*, *TCF3*, *TCF4*, *TCL1A*, *TEK*, *TERC*, *TERF2IP*, *TERT*, *TET1*, *TET2*, *TFE3*, *TGFB1*, *TGFBR2*, *TMEM127*, *TMPRSS2*, *TNFAIP3*, *TNFRSF13B*, *TNFRSF14*, *TNFRSF8*, *TNFSF11*, *TOP1*, *TOP2A*, *TP53*, *TP53BP1*, *TP63*, *TPMT*, *TPX2*, *TRAF2*, *TRAF3*, *TRAF5*, *TRAF7*, *TRIM28*, *TRRAP*, *TSC1*, *TSC2*, *TSHR*, *TTK*, *TYMS*, *U2AF1*, *UBE2T*, *UBR5*, *UGT1A1*, *UGT2B15*, *UGT2B7*, *UIMC1*, *USP9X*, *VEGFA*, *VEGFB*, *VHL*, *VKORC1*, *VTCN1*, *WRN*, *WT1*, *XIAP*, *XPA*, *XPC*, *XPO1*, *XRCC1*, *XRCC2*, *XRCC3*, *XRCC5*, *XRCC6*, *YAP1*, *YES1*, *ZFHX3*, *ZNF217*, *ZNF703*, *ZNRF3*, *ZRSR2* (somatic tumor panel version 8)

Methods

DNA and RNA isolation: The isolation of tumor and normal DNA as well as tumor RNA was performed at CeGaT GmbH. Macrodissection prior to tumor and normal DNA as well as tumor RNA isolation was performed, if necessary. The tumor material was assessed by a pathology specialist.

The pathological services (confirmation of the histological diagnosis and determination of the tumor content) were carried out on our behalf by a specialist in pathology. Pathology services are not within the scope of the ISO 15189 accreditation.

Sample quality: The suitability of a sample for molecular genetic analysis depends on the tumor content as well as on the overall material quality (e.g. impairment of quality by chemical or physical stress due to fixation, Arreaza et al., 2016 PMID: 27657050; Einaga et al., 2017, PMID: 28498833; Jones et al., 2019, PMID: 31061401). In cases with low material quality the detection of aberrations (variant calling, copy number variation, structural variants) as well as mutational burden (TMB), microsatellite instability (MSI), viral infection in the tumor, gene expression and HRD-score determination may be impaired or even impossible.

NGS-laboratory DNA: Protein-coding regions, as well as flanking intronic regions and additional disease-relevant non-coding regions, were enriched using in-solution hybridization technology, and were sequenced using the Illumina NovaSeq 6000/NovaSeq X Plus system.

NGS-laboratory RNA (STR): RNA from tumor tissue was sequenced. Fusion transcripts were enriched using in-solution hybridization technology. For fusion transcripts with known breakpoints, breakpoint spanning probes were used. For genes with unknown breakpoints or a large number of possible fusion partners, the coding sequence was used for enrichment. Sequencing was performed on Illumina NovaSeq 6000/NovaSeq X Plus systems.

NGS-laboratory RNA (transcriptome): Library preparation was performed using the TruSeq Total RNA (RiboZero rRNA removal Kit) or- SMARTer Stranded Total RNA Library Kit and subsequently analyzed using high-throughput sequencing on the HiSeq/NovaSeq system (Illumina).

Computational analysis DNA: Illumina bcl2fastq2 was used to demultiplex sequencing reads. Adapter removal was performed with Skewer. The trimmed reads were mapped to the human reference genome (hg19) using the Burrows Wheeler Aligner. Reads mapping to more than one location with identical mapping score were discarded. Read duplicates that likely result from PCR amplification were removed. The remaining high-quality sequences were used to determine sequence variants (single nucleotide changes and small insertions/deletions). The variants were annotated based on several internal as well as external databases. Typing of HLA class I/II was performed using sequencing data from patient's normal tissue using OptiType (Szolek et al., 2014, PMID: 25143287).

Computational analysis RNA: Sequencing data was demultiplexed using bcl2fastq2. Adapter sequences were removed using Skewer and the resulting reads were mapped to the human reference genome hg19 using STAR aligner. Fusions were detected using the software STAR-Fusion (Haas et al., 2017). Additional intragene structural events in genes *EGFR* and *MET* were extracted from STAR output. Gene expression analysis (counting of aligned reads per gene, calculation of normalized read counts and calculation of FPKM values) was done with DESeq2 (Love et al., 2014, PMID: 25516281) in R (R Core Team 2015)).

Genetic data evaluation DNA: Only variants (SNVs/small indels) with a novel allele frequency (NAF) of ≥ 5% in the tumor sample within the coding regions and their adjacent intronic regions (-/+ 8 base pairs) were evaluated. Known hotspot variants may also be reported up to a NAF of ≥ 2%. The clinical interpretation of variants is based on different external and internal databases and on information from scientific literature. The sensitivity of the test is dependent on the tumor content of the analyzed material, the sample quality, and the sequencing depth. In this case, 99.14% of the targeted regions were covered by a minimum of 70 high-quality sequencing reads per base. The diagnostic tumor content (expert estimate) was 75%. A theoretical sensitivity of >99% can be obtained for variants with a NAF ≥37.5% when a coverage of 30 reads per base is achieved. Variants are named according to the HGVS recommendations without any information regarding the cis or trans configuration.

Genetic data evaluation RNA (STR): The sensitivity of the test is dependent on the tumor content of the analyzed material, the sample quality, and the amount of transcripts sequenced. In this case, an amount of 12.06 gigabases RNA was sequenced. Therefore, this analysis is appropriate to detect structural variants on RNA level.

Variant classification: The somatic alterations were assessed with respect to their possible impact on protein function based upon the available data (i.e. cBioPortal, My Cancer Genome, Clinical Interpretations of Variants in Cancer (CIVIC), MD Anderson Personalized Medicine Center Database, *TP53* database (tp53.cancer.gov/), CKB, OncoKB, PubMed research) and/or using *in silico* predictions (MetaLR, PrimateAI, and SpliceAI). The functional categories assigned are: inactivating, activating, function altered, likely inactivating/activating/function altered, unknown or benign. "Inactivating": known inactivating variants as well as frameshift, nonsense and essential splice site variants, unless they are described as activating or benign. "Activating" and "function altered": known activating/function changing variants. The functional evidence of variants classified as inactivating, activating and function altered is highly reliable (i.e. ClinVar/ClinGen data with a review status of at least two stars, databases of specific consortia and/or *in vivo/in vitro* analyses). "Likely inactivating/activating/function altered": an impact of the variant on protein function is considered as likely with respect to the affected amino acid position (e.g. known hot spot, pathogenic variant in the same codon, high conservation, *in silico* predictions), but there are insufficient functional data available. "Unknown": based upon the available data, we are not able to conclusively confirm or exclude a possible functional relevance of the variant. "Benign": the variant is described as benign and does not impair protein function.

A variant is classified as a driver mutation if it represents a disease-causing germline variant, or a somatic mutation known to define a specific cancer entity. Additionally, recurring and well described somatic mutations known to "drive" tumor development/progression in the analyzed tumor entity, or across multiple cancer entities, are classified as driver mutations.

The relevance of germline variants in genes belonging to our pharmacogenetic subpanel (PGX-01) were assessed using the PharmGKB and CPIC databases and guidelines.

In the context of the pharmacogenetic evaluation (PGX-01), not all detected variants in a gene are taken into account; only variants with therapeutic relevance, variants for which "dosing guidelines" are published, or variants which have an evident influence on drug administration.

Copy Number Analysis: Copy number variations (CNV) were computed on uniquely mapping, non-duplicate, high-quality reads using an internally developed method based on sequencing coverage depth (only applicable for nuclear encoded genes). Briefly, we used reference samples to create a model of the expected coverage that represents wet-lab biases as well as inter-sample variation. CNV calling was performed by computing the sample's normalized coverage profile and its deviation from the expected coverage. Genomic regions are called as variant if they deviate significantly from the expected coverage. Aberrations on the Y chromosome and in the pseudoautosomal region (PAR) cannot be detected with high accuracy. The integration site of duplications cannot be determined by NGS based CNV-Calling.

Please note that next generation sequencing based detection of copy number variations has lower sensitivity/specificity than a direct quantification method, e.g. MLPA. The absence of reported CNVs therefore does not ultimately guarantee the absence of CNVs.

Copy number variants as well as breakpoints were estimated on the basis of the NGS data and should be treated as estimated values. CNVs are assigned to be therapeutically relevant when both 1: a focal or cluster amplification of 4 or more copies or a homozygous deletion is detected, containing known druggable genes, and 2: the detected gain or loss of DNA is consistent with the underlying pathomechanism of the affected druggable gene (e.g. amplification of oncogenes and deletion of tumor suppressor genes).

The list of genes additionally reported in the copy number alterations table represents a selection of therapeutically relevant genes potentially affected by CNVs and makes no claim of completeness. A loss of one allele does not necessarily result in reduced protein expression and likewise, low grade amplification does not necessarily lead to an increase of protein expression. Therefore, only strong amplifications (≥ 5 copies) and homozygous deletions are reported. Gross deletions and amplifications likely cover a large number of

genes. The evaluation of CNV effects on relevant oncogenes or tumor suppressor genes may therefore remain speculative.

Prediction of structural variants detected in DNA: Genomic regions known to be involved in translocation, gene fusion or large insertion/deletion events are additionally enriched during the sequencing process. The alignment data is bioinformatically analyzed for potential structural variants by identifying discordant read pairs and split reads (Chen et al., 2016, PMID: 26647377). Regions of interest are visually reviewed and possible structural variants are manually annotated. Please note that targets evaluated for the occurrence of relevant structural variants only represent a selection of hot spots frequently mutated. The absence of reported structural variants therefore does not ultimately guarantee the absence of structural variants.

Structural variants potentially affecting the following genes are being assessed:
ALK, *BCL2*, *BCR*, *BRAF*, *BRD4*, *EGFR*, *ERG*, *ETV4*, *ETV6*, *EWSR1*, *FGFR1*, *FGFR2*, *FGFR3*, *FUS*, *MET*, *MYB*, *MYC*, *NOTCH2*, *NTRK1*, *PAX3*, *PDGFB*, *RAF1*, *RARA*, *RET*, *ROS1*, *SSX1*, *SUZ12*, *TAF15*, *TCF3*, *TFE3*, *TMPRSS2*

Prediction of structural variants detected in RNA: RNA fusions panel (STR) contains interpretation of translocations/fusions of the following cancer-relevant genes:

ABL1, *ACTB*, *ADGRG7*, *AFAP1*, *AGK*, *AKAP12*, *AKAP4*, *AKAP9*, *AKT1*, *AKT2*, *AKT3*, *ALK*, *ARHGAP26*, *ARHGAP6*, *ASPSCR1*, *ATF1*, *ATP1B1*, *ATRX*, *AVIL*, *AXL*, *BAG4*, *BCL2*, *BCOR*, *BCORL1*, *BCR*, *BEND2*, *BICC1*, *BRAF*, *BRD3*, *BRD4*, *CAMTA1*, *CCAR2*, *CCDC170*, *CCDC6*, *CCDC88A*, *CCNB3*, *CCND1*, *CD44*, *CD74*, *CEP85L*, *CIC*, *CLDN18*, *CLIP1*, *CLTC*, *CNTRL*, *COL1A1*, *CREB1*, *CREB3L1*, *CREB3L2*, *CRTC1*, *CTNNB1*, *DDIT3*, *DNAJB1*, *EGFR*, *EML4*, *EPC1*, *EPCAM*, *ERBB2*, *ERBB4*, *ERG*, *ESR1*, *ESRRA*, *ETV1*, *ETV4*, *ETV5*, *ETV6*, *EWSR1*, *EZR*, *FEV*, *FGFR1*, *FGFR2*, *FGFR3*, *FLI1*, *FN1*, *FOXO1*, *FOXO4*, *FOXR2*, *FUS*, *GLI1*, *GOPC*, *HEY1*, *HMGA2*, *HTRA1*, *IGF1R*, *INSR*, *JAK2*, *JAZF1*, *KIAA1549*, *KIF5B*, *KIT*, *LEUTX*, *LMNA*, *LPP*, *LTK*, *MAGI3*, *MAML1*, *MAML2*, *MAML3*, *MAMLD1*, *MAP3K8*, *MARS1*, *MAST1*, *MAST2*, *MEAF6*, *MET*, *MGA*, *MGMT*, *MITF*, *MN1*, *MRTFB*, *MSH2*, *MYB*, *MYBL1*, *MYC*, *NAB2*, *NCOA1*, *NCOA2*, *NCOA3*, *NCOA4*, *NFATC2*, *NFIB*, *NOTCH2*, *NPM1*, *NR4A3*, *NRG1*, *NRG2*, *NSD3*, *NTRK1*, *NTRK2*, *NTRK3*, *NUTM1*, *PAX3*, *PAX7*, *PAX8*, *PBX1*, *PDGFB*, *PDGFD*, *PDGFRA*, *PDGFRB*, *PHF1*, *PIK3CA*, *PLAG1*, *PML*, *POU5F1*, *PPARG*, *PPARGC1A*, *PPP1CB*, *PRKACA*, *PRKAR1A*, *PRKCA*, *PRKCB*, *PRKD1*, *PRKD2*, *PRKD3*, *PTPRZ1*, *QKI*, *RAD51B*, *RAF1*, *RANBP2*, *RARA*, *RELA*, *RELCH*, *RET*, *ROS1*, *RPS6KB1*, *RREB1*, *RSPO2*, *RSPO3*, *SDC1*, *SDC4*, *SH3PXD2A*, *SHTN1*, *SLC1A2*, *SLC34A2*, *SLC44A1*, *SLC45A3*, *SND1*, *SQSTM1*, *SS18*, *SSX1*, *SSX2*, *SSX4*, *STAT6*, *STRN*, *SUZ12*, *TACC1*, *TACC2*, *TACC3*, *TAF15*, *TCF12*, *TCF3*, *TERT*, *TFE3*, *TFEB*, *TFG*, *THADA*, *TMPRSS2*, *TPM3*, *TPR*, *TRIM24*, *TRIM33*, *TRIO*, *TTYH1*, *VGLL2*, *VGLL3*, *VMP1*, *WT1*, *WWTR1*, *YAP1*, *YWHAE*, *ZC3H7B*, *ZFTA*, *ZMYM2*, *ZNF703* (Structural Variants Panel version 8)

Selected break points within the mentioned fusion genes:

TRIM24-BRAF, KIAA1549-BRAF, SND1-BRAF, EML4-ALK, CLTC-ALK, NPM1-ALK, TPM3-ALK, KIF5B-ALK, ETV6-NTRK3, EWSR1-ERG, EWSR1-FLI1, FGFR3-TACC3, FGFR2-BICC1, FGFR2-TACC3, FGFR1-TACC1, TMPRSS2-ERG, TPM3-NTRK1, TPR-NTRK1, TRIM24-NTRK2, AFAP1-NTRK2, QKI-NTRK2, ETV6-NTRK2, KIF5B-RET, CCDC6-RET, NCOA4-RET, PRKAR1A-RET, TRIM33-RET, CD74-ROS1, EZR-ROS1, SLC34A2-ROS1, TPM3-ROS1, SDC4-ROS1, BRD4-NUTM1, BRD3-NUTM1, MGA-NUTM1, NSD3-NUTM1, NAB2-STAT6, CD74-NRG1, SDC4-NRG1, ATP1B1-NRG1, BCOR-CCNB3, DNAJB1-PRKACA, EGFR-PPARGC1A, CCDC88A-ALK, PPP1CB-ALK, PAX3-FOXO1, PAX7-FOXO1, SS18-SSX1, SS18-SSX2, EWSR1-WT1, EWSR1-ATF1, TRIO-TERT

Specific transcript variants:

EGFR del ex2-3, *EGFR* del ex2-4, *EGFR* del ex2-14, *EGFR* del ex2-22 (mLEEK), *EGFR* del ex5-6, *EGFR* del ex6-7, *EGFR* del ex9, *EGFR* del ex9-10, *EGFR* del ex10, *EGFR* del ex12, *EGFR* del ex25-26, *EGFR* del ex25-27, *EGFR* del ex26-27, *EGFR* VII, *EGFR* VIII, *MET* ex14 skipping

Tumor mutational burden (TMB): Tumor mutational burden is defined as the number of somatic SNV-, InDel- and essential splice site variants (NAF ≥ 0.1) per megabase of coding DNA. On exome level it is extrapolated, taking the results of panel data analysis as a basis. Truncating variants in tumor suppressor genes and known driver mutations as well as somatic variants with an inhouse frequency of ≥ 1% are not accounted. Tumor mutational burden is classified as high, when ≥ 10 Mut/Mb are present in the tumor (Hellmann et al., 2018, PMID: 29658845; Reck et al., 2019, PMID: 31195357).

Microsatellite instability (MSI): A probable MSI status is predicted from sequencing data (step-wise difference (DIF); threshold 0.33; Kautto et al., 2017, PMID: 27980218). Please be aware that bioinformatics MSI prediction cannot replace a validated diagnostic test for MSI.

Viral Infection (RNA and DNA): Viral coding sequences are enriched using probes specifically designed for the genomes of EBV (Epstein-Barr virus), CMV (Cytomegalovirus), MCV (Merkel cell polyomavirus) and HPV (human papilloma virus) types 6, 11, 16, 18, 26, 31, 33, 35, 39, 42, 44, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73

and 82. Reads that cannot be mapped to the human genome are compared with these genomes and hits are counted.

Therapeutic options: The placement of drugs into different drug classes is done by cross referencing information from FDA, EMA, and PubChem. Approval status and limitations are taken from drugs.com (FDA) and ema.europa.eu (EMA).

In case of evidence (NCCN and/or ESMO guidelines) of a respective biomarker causing non-response, decreased response, or resistance to the specified medication class in the given entity, or in case of evidence in current literature suggesting non-response, decreased response, or resistance, the affected drugs will be marked with a warning sign in appendix.

Clonal hematopoiesis of indeterminate potential (CHIP): CHIP is defined by low frequency (~10%) somatic mutations found in peripheral blood in the absence of hematopoietic dysplasia. Such variants are considered to be of uncertain disease relevance with a low risk (0.5-1% per year) of transformation into myeloid or lymphoid neoplasms (Heuser et al., 2016, PMID: 27215596). As CHIP variants can have allele frequencies <5%, the diagnosis in our reports is considered to be an incidental finding.

The sample fulfilled our quality criteria upon arrival and during/after each processing step in the laboratory.

The procedure described above was developed and validated in-house (Laboratory developed test; LDT). A minimal tumor content of 20% was taken as a basis.

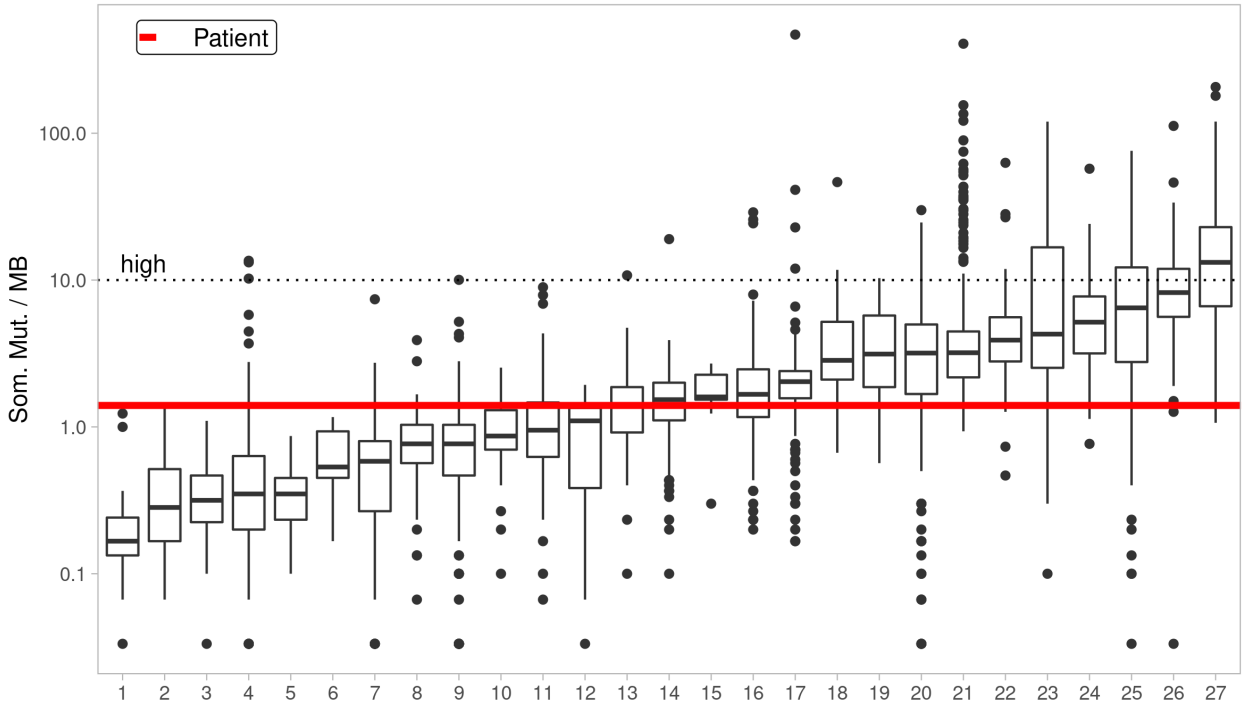
Genetic Counseling

Please be aware that this somatic report cannot replace conventional germline diagnostics. A lack of evidence for therapy relevant or likely disease causing germline variants does not exclude the presence of disease relevant germline mutations. In cases where a relevant germline mutation has been detected, genetic counseling should be considered. Variants were classified and reported based on ACMG/ACGS-2020v4.01 guidelines (Richards et al., 2015, PMID: 25741868, Ellard et al., 2020, Association for Clinical Genomic Science).

Communication, dissemination and usage of this report for scientific purposes is only permitted in accordance with the German Genetic Diagnostics Legislation.

Supplement - Tumor Mutational Burden

The figure shows the approximated tumor mutational burden (TMB) of the previously described tumor sample (red bar) in relation to TMB published for different tumor entities (Lawrence et al., 2013, PMID: 23770567). TMB on exome level is extrapolated, taking the results of panel data analysis as a basis. A high TMB has been associated with a superior response to immune therapy approaches in different tumor entities (Johnson et al., 2016, PMID: 27671167; Rizvi et al., 2015, PMID: 25765070; Snyder et al., 2014, PMID: 25409260; Le et al., 2015, PMID: 26028255; Bouffet et al., 2016, PMID: 27001570; Hellmann et al., 2018, PMID: 29658845; Reck et al., 2019, PMID: 31195357).

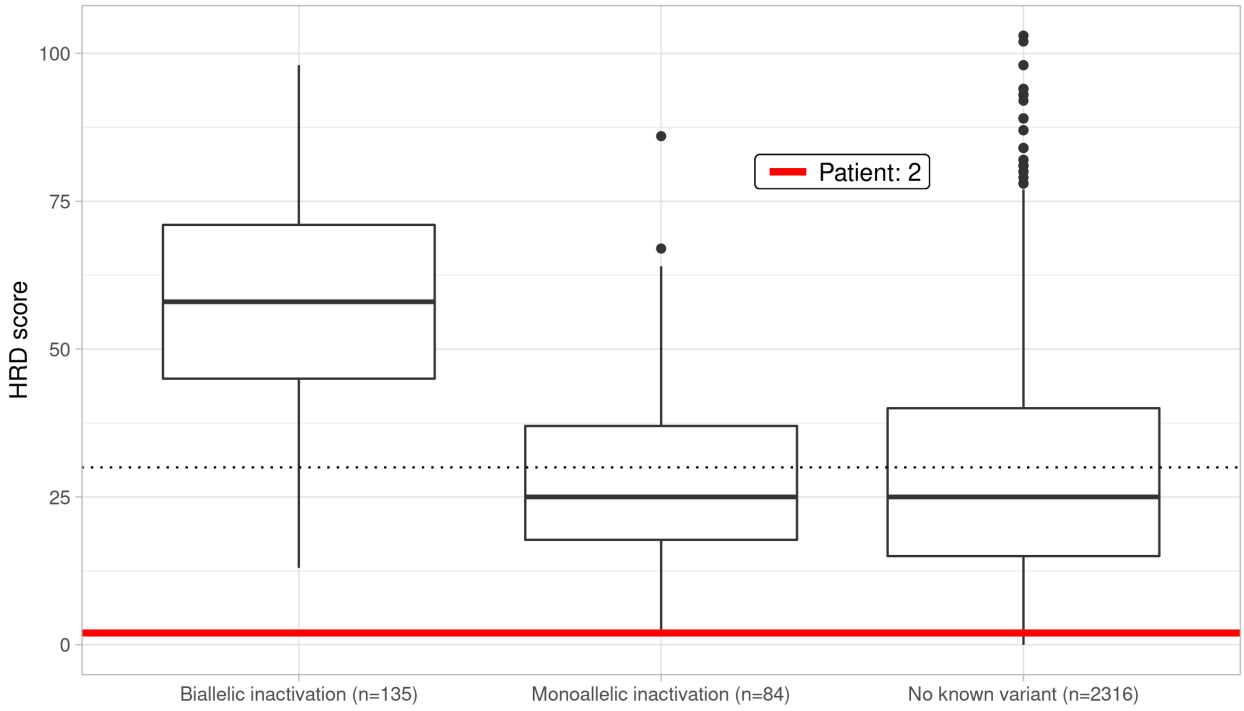


Distribution of tumor mutational burden in 27 tumor entities

The distribution of tumor mutational burden (somatic variants per megabase of coding DNA) is shown for 27 different tumor entities (n=3083). Boxplots show the range containing 50% of all values (interquartile range, IQR, between percentile 75 and 25) as boxes, medians as solid horizontal lines. Outliers (circles) are shown for values deviating by more than 1.5 times the IQR (indicated by vertical lines). Tumor mutational burden of 1.4 mut/Mbp determined for the current case is shown for comparison (solid red line). Y-axis is log scaled. A high mutational burden (≥ 10 Mut/Mb) is indicated with a dashed line.

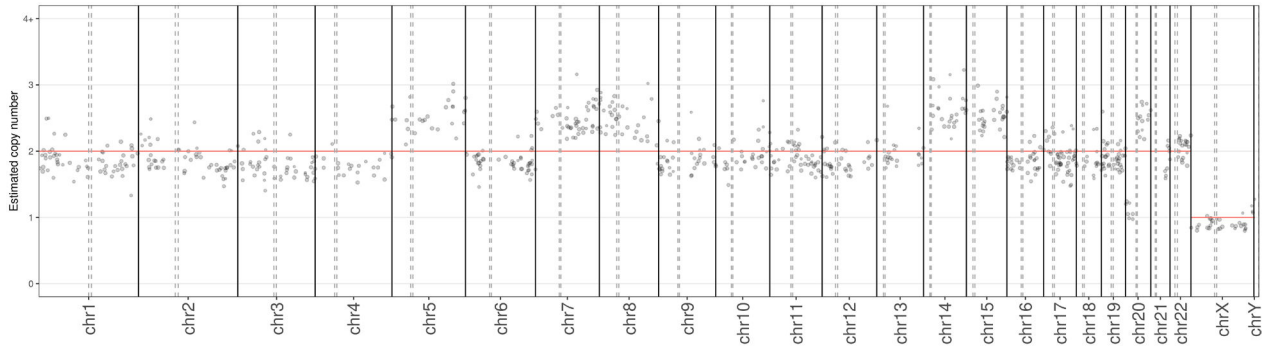
Entities are: (1) Rhabdoid tumor, (2) Ewing Sarcoma, (4) Acute myeloid leukemia, (5) Medulloblastoma, (6) Carcinoid, (7) Neuroblastoma, (8) Prostate cancer, (9) Chronic lymphocytic leukemia, (10) Low-grade glioma, (11) Breast cancer, (12) Pancreatic cancer, (13) Multiple myeloma, (14) Kidney clear cell, (15) Kidney papillary cell, (16) Ovarian cancer, **(17) Glioblastoma multiforme**, (18) Cervical cancer, (19) Diffuse large B-cell lymphoma, (20) Head and neck carcinoma, (21) Colorectal cancer, (22) Esophageal adenocarcinoma, (23) Gastric cancer, (24) Bladder carcinoma, (25) Lung adenocarcinoma, (26) Lung squamous cell carcinoma, (27) Melanoma (Figure modified referring to Lawrence et al., 2013, PMID: 23770567).

Supplement - Homologous Recombination Deficiency (HRD)



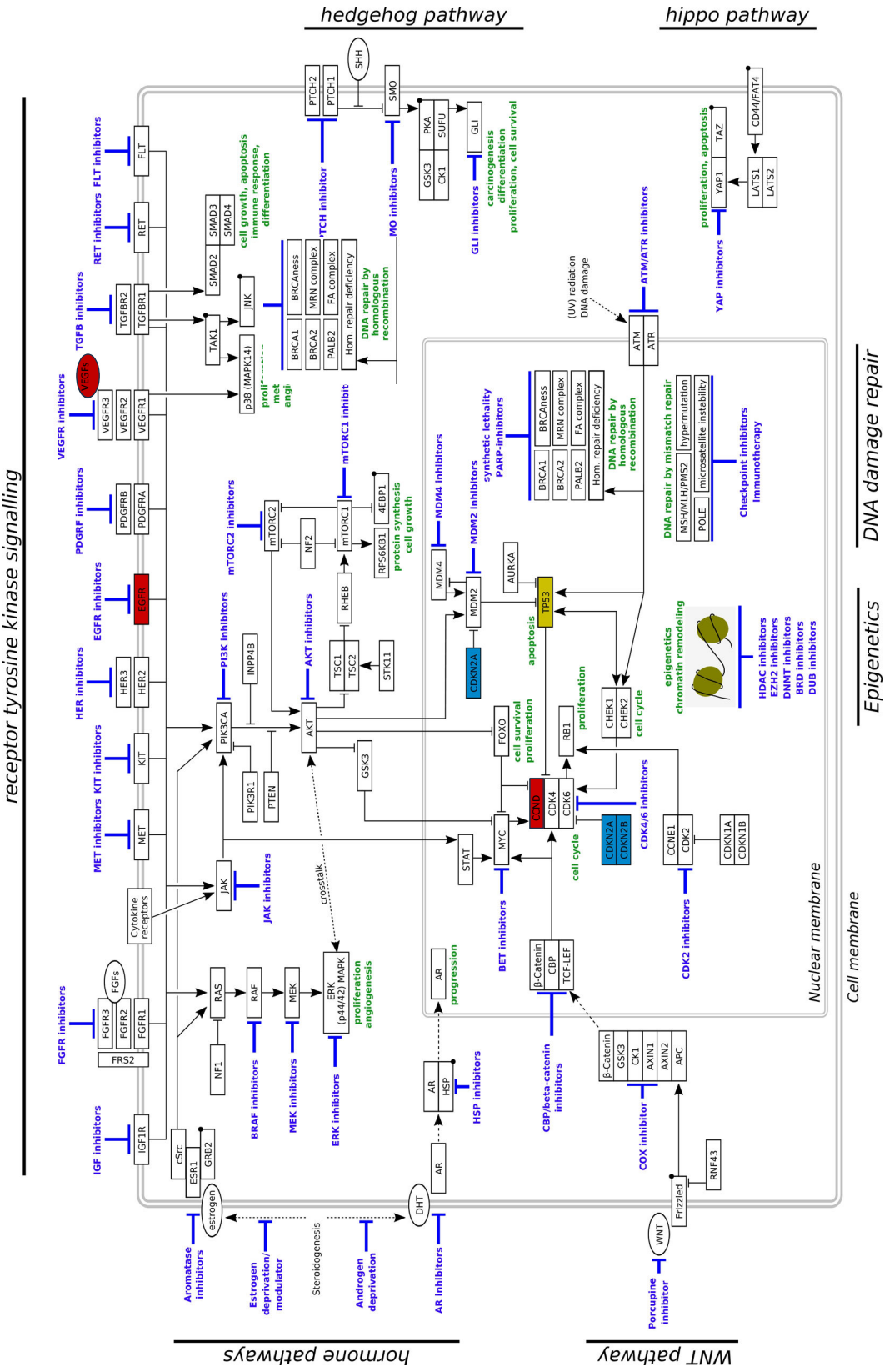
Homologous recombination deficiency (HRD) score of this sample compared to a cohort of patients with biallelic inactivation of HRD-related genes (*ATM*, *BRCA1/2*, *BRIP1*, *PALB2*, *RAD51C*), monoallelic inactivation of HRD-related genes (or second hit not found in available data), and controls with no detectable inactivation of HRD-related genes. Score is calculated as the sum of the markers described in Birkbak et al., 2012, PMID: 22576213; Abkevich et al., 2012, PMID: 23047548; Popova et al., 2012, PMID: 22933060. Higher scores mean higher likelihood of HRD.

Supplement - Copy Number Profile



The genome of a tumor often shows many large copy number variations (CNV). The figure shows each chromosome on the X-axis. The space per chromosome corresponds to its length in base pairs. The coverage profile of the sequenced tumor sample is plotted on Y-axis. Every dot contains binned coverage data of 1 Mb of DNA. Copy numbers from zero (homozygous deletion) to 4+ copies are pictured. CNVs equal to or above 4 copies are indicated by a red colour. Please note that tumor content, as well as subclonal composition of a given tumor sample, may affect copy number estimation. Thus, the plot doesn't show copy number variation of an isolated clonal cell population but provides average measures of the CNV profile of the entire sequenced sample.

Supplement - Pathways



The figure illustrates the most important cancer biomarkers in relation to their associated cancer pathways. In addition, potential drug classes are provided. Circles: ligands; rectangular boxes: biomarkers covered in current analyses; rectangular boxes with dot: biomarkers not covered in current analyses; ⊣: repression, →: activation, ⊣: inhibiting drugs, ⇢: transport. **Biomarkers affected in your patient's tumor are highlighted.** Blue: biomarker probably inactivated; Red: biomarker probably activated; Brown: biomarker function probably changed. Please note that crosstalks, feedback regulations, interfering pathways and drug resistances are not illustrated.

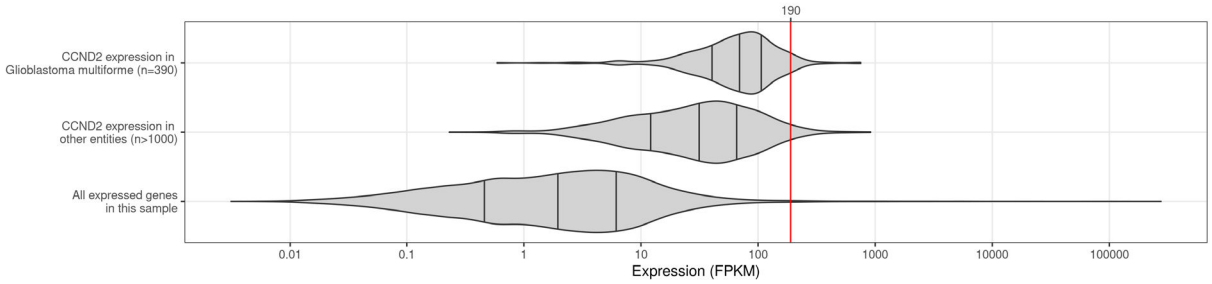
Supplement - Analysis of Tumor Gene Expression

The following table lists expression values of all therapy-relevant genes and their interpretation (if available). The distribution of the gene-specific FPKM values within all analyzed samples is depicted in the subsequent figures below.

Gene	Interpretation	FPKM	Mean	Median	Percentile
CCND2	overexpression	190	83 (51)	70 (32)	96 (97)
CDKN2A	reduced expression	0.15	6.7 (5.2)	0.70 (1.8)	9.2 (5.5)
EGFR	overexpression	546	198 (58)	41 (12)	87 (97)
TERT	overexpression	2.01	0.29 (0.1)	0.48 (0.34)	98 (98)
VEGFA	overexpression	131	90 (35)	63 (20)	80 (95)

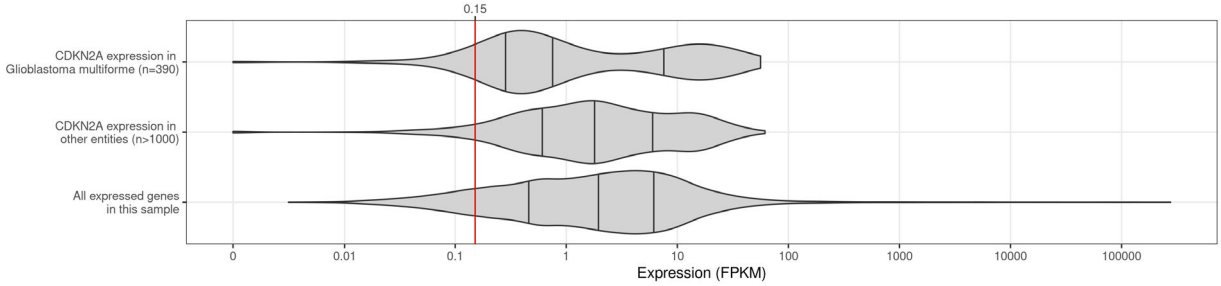
If two values are given, the first value refers to analyzed samples whose tumor entity matches the current analysis. Values in brackets refer to values from analyzed samples whose tumor entity deviates from the current analysis.
Percentile: Percentage of analyzed samples whose gene-specific FPKM value is lower than the one of the current analysis.

CCND2 Expression



The X-axis shows the gene expression in FPKM in logarithmic scale. The red bar marks the level of gene expression of the examined gene of the analyzed sample. The subdivision of the violin plots shown by longitudinal bars represents the percentiles in the respective distribution (percentiles from left to right: 0-25, 25-50, 50-75, and 75-100).
Each figure shows from top to bottom: 1) The distribution of gene expression of the indicated gene in a cohort of tumor samples matching the patient's tumor entity. 2) The distribution of gene expression of the indicated gene in a cohort of tumor samples of other tumor entities. 3) The distribution of gene expression of all expressed genes in the analyzed tumor RNA of the patient.

CDKN2A Expression



The X-axis shows the gene expression in FPKM in logarithmic scale. The red bar marks the level of gene expression of the examined gene of the analyzed sample. The subdivision of the violin plots shown by longitudinal bars represents the percentiles in the respective distribution (percentiles from left to right: 0-25, 25-50, 50-75, and 75-100).
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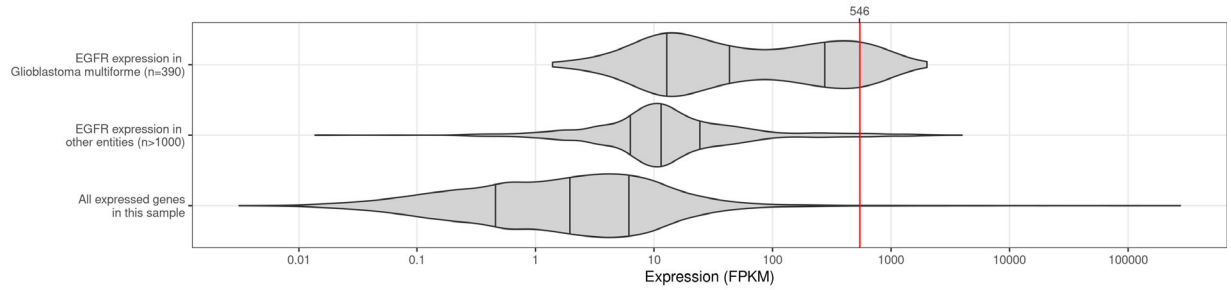
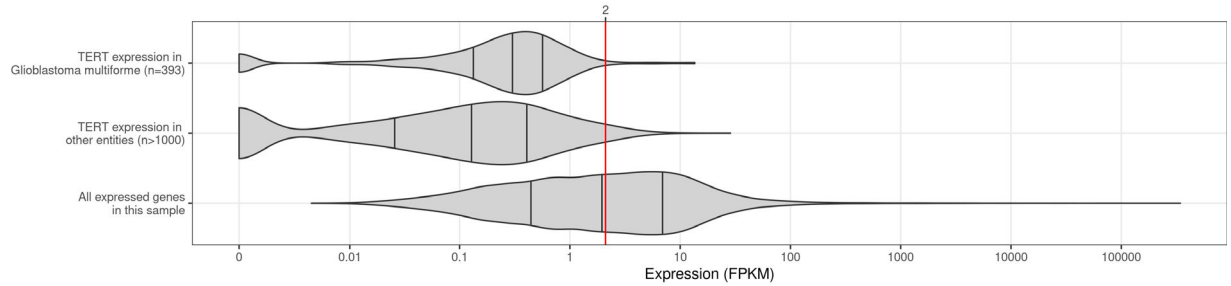
EGFR Expression



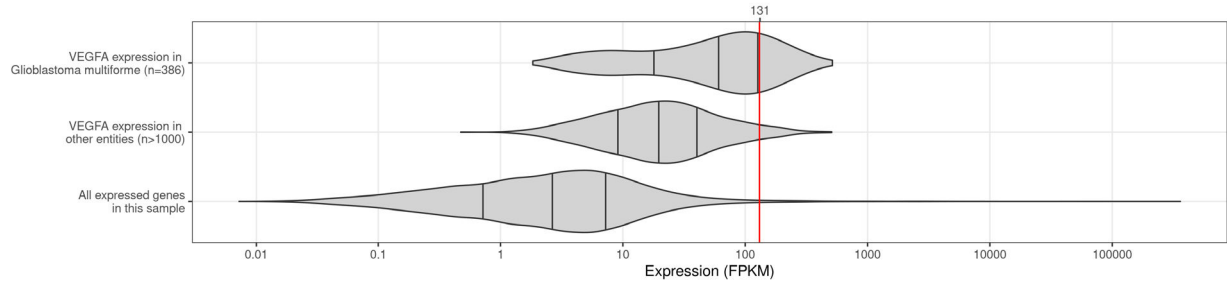
The X-axis shows the gene expression in FPKM in logarithmic scale. The red bar marks the level of gene expression of the examined gene of the analyzed sample. The subdivision of the violin plots shown by longitudinal bars represents the percentiles in the respective distribution (percentiles from left to right: 0-25, 25-50, 50-75, and 75-100).
Each figure shows from top to bottom: 1) The distribution of gene expression of the indicated gene in a cohort of tumor samples matching the patient's tumor entity. 2) The distribution of gene expression of the indicated gene in a cohort of tumor samples of other tumor entities. 3) The distribution of gene expression of all expressed genes in the analyzed tumor RNA of the patient.

TERT Expression



The X-axis shows the gene expression in FPKM in logarithmic scale. The red bar marks the level of gene expression of the examined gene of the analyzed sample. The subdivision of the violin plots shown by longitudinal bars represents the percentiles in the respective distribution (percentiles from left to right: 0-25, 25-50, 50-75, and 75-100).
Each figure shows from top to bottom: 1) The distribution of gene expression of the indicated gene in a cohort of tumor samples matching the patient's tumor entity. 2) The distribution of gene expression of the indicated gene in a cohort of tumor samples of other tumor entities. 3) The distribution of gene expression of all expressed genes in the analyzed tumor RNA of the patient.

VEGFA Expression



The X-axis shows the gene expression in FPKM in logarithmic scale. The red bar marks the level of gene expression of the examined gene of the analyzed sample. The subdivision of the violin plots shown by longitudinal bars represents the percentiles in the respective distribution (percentiles from left to right: 0-25, 25-50, 50-75, and 75-100).
Each figure shows from top to bottom: 1) The distribution of gene expression of the indicated gene in a cohort of tumor samples matching the patient's tumor entity. 2) The distribution of gene expression of the indicated gene in a cohort of tumor samples of other tumor entities. 3) The distribution of gene expression of all expressed genes in the analyzed tumor RNA of the patient.

The genes shown represent a manual selection. Please note that the tumor content of the sample has a significant influence on the measured gene expression. In particular, a loss of expression (heterozygous, homozygous) in combination with a low tumor content may not be reliably detected. An altered gene expression does not necessarily lead to a (therapeutically) relevant, altered protein biosynthesis. We recommend using an independent method such as direct staining of the target structure at the protein level to support therapeutic decisions based on gene expression data. The RNA sequencing method used cannot detect post-translational protein modifications.

Supplement - Possible Therapeutic Strategies

Please note that the provided information on potential drugs is only a specific selection and makes no claim of completeness. Furthermore, the listing is limited to targeted therapies and does not include common chemotherapies.

Approvals affecting your patient's tumor entity are highlighted in blue.

VEGFA, overexpression, complete gene:

Relevant therapeutics for gene *VEGFA*

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
Cabozantinib (Cabometyx) VEGFR inhibitor AXL inhibitor MET inhibitor RET inhibitor	Hepatocellular carcinoma	EMA	adults, previously treated with sorafenib	
		FDA	previously treated with sorafenib	
	Renal cell carcinoma	EMA	advanced cancer, adults, first-line in patients with intermediate or poor risk or following VEGF-targeted therapy	
		EMA	first-line treatment, advanced renal cell carcinoma, adult patients	Nivolumab
		FDA	advanced disease	
		FDA	first-line treatment, advanced renal cell carcinoma	Nivolumab
	Thyroid carcinoma	EMA	adults, locally advanced or metastatic differentiated thyroid carcinoma refractory or not eligible to radioactive iodine (RAI), progression during or after prior systemic therapy	
		FDA	age ≥12 years, locally advanced or metastatic differentiated thyroid cancer, progressed following prior VEGFR-targeted therapy, radioactive iodine-refractory or ineligible	
Cabozantinib (Cometriq) VEGFR inhibitor AXL inhibitor MET inhibitor RET inhibitor	Thyroid carcinoma	EMA	adult patients, progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma	
		FDA	progressive, metastatic medullary thyroid cancer	
Ponatinib VEGFR inhibitor BCR-ABL inhibitor FGFR inhibitor KIT inhibitor PDGFR inhibitor SRC inhibitor	Chronic myelogenous leukemia (CML)	EMA	**(ABL T315I)** - chronic phase, accelerated phase, or blast phase CML, resistant to dasatinib or nilotinib - who are intoloerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate - or who have the T315I mutation	
		FDA	**(ABL T315I)** adult patients, - chronic-phase CML, resistant or intolerant to at least two prior kinase inhibitors - accelerated phase or blast phase CML if no other kinase inhibitors are indicated - or T315I-positive CML (in all CML phases)	
	Ph-positive acute lymphoblastic leukemia (Ph+ ALL)	EMA	**(ABL T315I)** - resistant to dasatinib - intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate - or who have the T315I mutation	
		FDA	**(ABL T315I)** adult patients if no other kinase inhibitor is indicated or *ABL* T315I-positive	
		FDA	newly diagnosed	Vincristin, Methotrexat, Dexamethasone, Cytarabine, Prednisone
Vandetanib EGFR inhibitor VEGFR inhibitor	Thyroid carcinoma	EMA	adults and adolescents 12 years and older - advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate) – advanced RET-mutant medullary thyroid cancer (MTC)	

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
RET inhibitor		FDA	symptomatic or progressive medullary thyroid cancer, unresectable (non-operable) locally advanced or metastatic disease OR indolent, asymptomatic or slowly progressing disease only after careful consideration of the treatment related risks	
Lenvatinib VEGFR inhibitor FGFR inhibitor KIT inhibitor PDGFR inhibitor RET inhibitor	Endometrial carcinoma	EMA	adult, advanced or recurrent, previous platinum-based treatment, surgery or radiation impossible	Pembrolizumab
		FDA	**not MSI-high or dMMR** advanced endometrial carcinoma, disease progression following prior systemic therapy but curative surgery or radiation ineligible.	Pembrolizumab
	Hepatocellular carcinoma	EMA	adult patients, no prior systemic therapy, advanced or unresectable hepatocellular carcinoma (HCC)	
		FDA	unresectable hepatocellular carcinoma	
	Renal cell carcinoma	EMA	adults, advanced renal cell carcinoma, first line treatment	Pembrolizumab
		EMA	adults, advanced renal cell carcinoma, following one prior vascular endothelial growth factor (VEGF)-targeted therapy	Everolimus
		FDA	advanced renal cell carcinoma, previously treated with an anti-angiogenic therapy	Everolimus
	Thyroid carcinoma	EMA	adult, differentiated (papillary/follicular/Hürthle cell), progressive or locally advanced or metastatic and refractory to radioactive iodine	
		FDA	locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer	
Pazopanib VEGFR inhibitor FGFR inhibitor KIT inhibitor PDGFR inhibitor	Renal cell carcinoma	EMA	adults, advanced renal cell carcinoma, no previous treatment or in patients who have already been treated with cytokines	
		FDA	adults, advanced renal cell carcinoma	
	Soft tissue sarcoma	EMA	adults, previously treated with chemotherapy for metastatic disease or who have progressed within 12months after (neo) adjuvant therapy	
		FDA	adults, advanced disease, prior chemotherapy	
Nintedanib VEGFR inhibitor FGFR inhibitor PDGFR inhibitor	Non-small cell lung carcinoma	EMA	adults, locally advanced, metastatic or locally recurrent, NSCLC of adenocarcinoma tumor histology, previous chemotherapy	Docetaxel
Sunitinib VEGFR inhibitor FLT3 inhibitor KIT inhibitor PDGFR inhibitor	Gastrointestinal stroma tumor	EMA	adults, unresectable and/or metastatic disease, after failure of imatinib treatment due to resistance or intolerance	
		FDA	adults, after progression on or intolerance to imatinib mesylate	
	Pancreatic neuroendocrine tumor	EMA	adults, unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression	
		FDA	progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in adult patients with unresectable locally advanced or metastatic disease.	
	Renal cell carcinoma	EMA	adults, advanced/metastatic	
		FDA	adults, advanced RCC or adjuvant treatment of adult patients at high risk of relapse following nephrectomy	
Sorafenib VEGFR inhibitor FLT3 inhibitor KIT inhibitor pan-RAF(dimer) inhibitor PDGFR inhibitor	Hepatocellular carcinoma	EMA		
		FDA	unresectable hepatocellular carcinoma (HCC)	
	Renal cell carcinoma	EMA	advanced disease, failed prior interferon-alpha or interleukin-2 based therapy or considered unsuitable for such therapy	
		FDA	locally advanced / metastatic Renal Cell (clear cell) Carcinoma (RCC), failure or intolerance to prior systemic therapy	
	Thyroid carcinoma	EMA	progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	
		FDA	locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC), refractory to radioactive iodine	
Regorafenib VEGFR inhibitor KIT inhibitor	Colon cancer	EMA	adult patients, metastatic disease, previously treated with, or are not considered candidates for, available therapies	
		FDA	metastatic disease, previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy; if KRAS wild type, an anti-EGFR therapy	

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
pan-RAF(dimer) inhibitor PDGFR inhibitor RET inhibitor	Gastrointestinal stroma tumor	EMA	adult patients, unresectable or metastatic GIST, progressed on/ intolerant to prior treatment with imatinib and sunitinib	
		FDA	adult patients, unresectable or metastatic GIST, progressed on/intolerant to prior treatment with imatinib and sunitinib	
	Hepatocellular carcinoma	EMA	adult patients, previously treated with sorafenib	
		FDA	adult patients, previously treated with sorafenib	
	Neoplasm of the rectum	EMA	adult patients, metastatic disease, previously treated with, or are not considered candidates for, available therapies	
		FDA	metastatic disease, previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an antiVEGF therapy, and, if RAS wild-type, an anti-EGFR therapy	
Axitinib VEGFR inhibitor PDGFR inhibitor	Renal cell carcinoma	EMA	adult, advanced renal cell carcinoma, failure of prior treatment with sunitinib or a cytokine	
		FDA	advanced renal cell carcinoma after failure of one prior systemic therapy	
		FDA	first-line treatment of patients with advanced renal cell carcinoma	Avelumab
		FDA	first-line treatment of patients with advanced renal cell carcinoma	Pembrolizumab
Bevacizumab VEGF inhibitor	Breast cancer	EMA	first-line treatment, adult, metastatic, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate exclusion: received taxane and anthracyclinecontaining regimens in the adjuvant setting within the last 12 months	Capecitabine
		EMA	first-line treatment, adult, metastatic	Paclitaxel
	Cervix cancer	EMA	adult, cannot receive platinum therapy with persistent, recurrent, or metastatic carcinoma	Paclitaxel, Topotecan
		EMA	adult, cannot receive platinum therapy, with persistent, recurrent, or metastatic carcinoma	Paclitaxel, Cisplatin
	Colon cancer	EMA	adult, metastatic	5-FU based chemotherapy
	Fallopian tube carcinoma	EMA	adult, first recurrence of platinum-sensitive cancer, no prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	Paclitaxel, Carboplatin, Gemcitabin
		EMA	adult, platinum-resistant recurrent cancer, no more than two prior chemotherapy regimens and no prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	Paclitaxel, Topotecan, Doxorubicin
		EMA	front-line treatment of adult patients with advanced cancer	Paclitaxel, Carboplatin
	Glioblastoma multiforme	FDA	adults, recurrent	
	Neoplasm of the rectum	EMA	adult, metastatic	5-FU based chemotherapy
	Non-small cell lung carcinoma	EMA	first-line, adults, unresectable advanced, metastatic or recurrent, not predominantly squamous cell histology	Carboplatin, Cisplatin
		EMA	**EGFR activating mutation** first-line treatment, adults, unresectable advanced, metastatic or recurrent non-squamous	Erlotinib
	Ovarian cancer	EMA	adult, first recurrence of platinum-sensitive epithelial ovarian cancer, no prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	Paclitaxel, Carboplatin, Gemcitabin
		EMA	adult, platinum-resistant recurrent epithelial ovarian cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	Paclitaxel, Topotecan, Doxorubicin
		EMA	front-line treatment, adult, advanced epithelial ovarian cancer	Paclitaxel, Carboplatin
	Primary peritoneal carcinoma	EMA	adult, first recurrence of platinum-sensitive primary peritoneal cancer, no prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	Paclitaxel, Carboplatin, Gemcitabin
		EMA	adult, platinum-resistant recurrent primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	Paclitaxel, Topotecan, Doxorubicin
		EMA	front-line treatment, adult, advanced primary peritoneal cancer	Paclitaxel, Carboplatin

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
	Renal cell carcinoma	EMA	first line treatment, adult, advanced and/or metastatic	Interferon-alfa
Ziv-aflibercept VEGF inhibitor	Colon cancer	EMA	adults, metastatic, resistant to or has progressed after a treatment with oxaliplatin	FOLFIRI
		FDA	adults, metastatic disease, resistant to or has progressed following an oxaliplatin-containing regimen	FOLFIRI
Fruquintinib VEGFR inhibitor	Colon cancer	EMA	adult patients, metastatic disease, previously treated with standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, progressed on / intolerant to treatment with either trifluridine-tipiracil or regorafenib	
		FDA	adults, metastatic CRC, previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF and if RAS-wildtype an anti-EGFR therapy	
	Neoplasm of the rectum	EMA	adult patients, metastatic disease, previously treated with standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, progressed on / intolerant to treatment with either trifluridine-tipiracil or regorafenib	
		FDA	adults, metastatic CRC, previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF and if RAS-wildtype an anti-EGFR therapy	
Ramucirumab VEGFR inhibitor	Colon cancer	EMA	adult, metastatic CRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine	Irinotecan, Fluorouracil (5-FU), Leucovorin
		FDA	metastatic with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine	Irinotecan, Fluorouracil (5-FU), Leucovorin
	Hepatocellular carcinoma	EMA	adults, advanced or unresectable, serum alpha fetoprotein of ≥ 400 ng/ml, previously treated with sorafenib	
		FDA	alpha-fetoprotein of ≥400 ng/mL, post sorafenib treatment	
	Non-small cell lung carcinoma	EMA	adults, locally advanced or metastatic, with disease progression after platinum-based chemotherapy	Docetaxel
		EMA	**EGFR activating mutation** adults, first-line, metastatic	Erlotinib
		FDA	metastatic disease, disease progression on or after platinum-based chemotherapy, patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Ramucirumab	Docetaxel
		FDA	**EGFR Ex19del, EGFR Ex21 (L858R) mutations** first-line treatment, metastatic	Erlotinib
	Stomach cancer	EMA	adults, advanced gastric cancer or gastro-oesophageal junction adenocarcinoma, disease progression after prior platinum and fluoropyrimidine chemotherapy	Paclitaxel
		EMA	adults, advanced gastric cancer or gastro-oesophageal junction adenocarcinoma, disease progression after prior platinum or fluoropyrimidine chemotherapy, if treatment in combination with paclitaxel is not appropriate	
		FDA	advanced or metastatic gastric cancer or gastroesophageal junction (GEJ) adenocarcinomawith disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy	
		FDA	advanced or metastatic with progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy	Paclitaxel
Tivozanib VEGFR inhibitor	Renal cell carcinoma	EMA	adults, first-line, with advanced cancer and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC	
		FDA	adults, relapsed or refractory advanced, who have received two or more prior systemic therapies	

***EGFR*, deletion, exons 2-7 (EGFRvIII), focal, NM_005228.5:**
***EGFR*, amplification, complete gene, non focal (10 copies), NM_005228.5:**
***EGFR*, overexpression, complete gene:**

Relevant therapeutics for gene *EGFR*

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
Lazertinib EGFR inhibitor 3rd generation EGFR TKI	Non-small cell lung carcinoma	FDA	**EGFR exon 19 deletion or exon 21 L858R** adults, locally advanced or metastatic, 1st-line	Amivantamab
Mobocertinib EGFR inhibitor 3rd generation EGFR TKI	Non-small cell lung carcinoma	FDA	**EGFR exon 20 insertion mutation** adult, locally advanced or metastatic, disease progression on or after platinum-based chemotherapy	
Osimertinib EGFR inhibitor 3rd generation EGFR TKI	Non-small cell lung carcinoma	EMA	- for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. - for the first-line treatment of adult patients NSCLC with activating EGFR mutations. - for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.	
		EMA	**EGFR exon 19 deletions or L858R** first line, locally advanced or metastatic	Carboplatin, Cisplatin, Pemetrexed
		FDA	- adjuvant therapy after tumor resection, adult patients, non small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations - adults, locally advanced, unresectable (stage III) NSCLC whose disease has not progressed during or following concurrent or sequential platinum-based chemoradiation therapy and whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations - first-line treatment, adult patients, metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. - adult patients, metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.	
		FDA	**EGFR exon 19 deletions or p.L858R** first line, adult patients, locally advanced or metastatic	Carboplatin, Cisplatin, Pemetrexed
Cetuximab EGFR inhibitor	Colon cancer	EMA	**EGFR expression, RAS wildtype** metastatic, - in combination with irinotecan-based chemotherapy, - in first-line in combination with FOLFOX - as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.	Irinotecan, 5-FU based chemotherapy
		FDA	**EGFR expression, KRAS wildtype** metastatic - in combination with FOLFIRI for first-line treatment, - in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy - as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.	Irinotecan, 5-FU based chemotherapy
	Neoplasm of head and neck	EMA	- in combination with radiation therapy for locally advanced disease; - in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.	Carboplatin, Cisplatin, Oxaliplatin

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
Erlotinib EGFR inhibitor	Neoplasm of the pancreas	FDA	- Locally advanced squamous cell cancer of the head and neck in combination with radiation therapy. - recurrent and/or metastatic squamous cell cancer of the head and neck in combination with platinum-based chemotherapy followed by cetuximab as maintenance therapy - single-agent, recurrent or metastatic squamous cell cancer of the head and neck, prior platinum-based therapy has failed	Carboplatin, Cisplatin, Oxaliplatin, Fluorouracil (5-FU)
		EMA	metastatic disease	Gemcitabin
	Non-small cell lung carcinoma	FDA	first line treatment; locally advanced, unresectable or metastatic	Gemcitabin
		EMA	**EGFR mutation** - first-line treatment of patients with locally advanced or metastatic cancer - switch maintenance treatment in patients with locally advanced or metastatic cancer with stable disease after first-line chemotherapy. - treatment of patients with locally advanced or metastatic cancer after failure of at least one prior chemotherapy regimen. - tumors without EGFR activating mutations, indicated when other treatment options are not considered suitable.	
Gefitinib EGFR inhibitor	Non-small cell lung carcinoma	FDA	**EGFR exon 19 deletion or L858R** locally advanced or metastatic NSCLC, treatment after progression following at least one prior chemotherapy regimen	
		EMA	**EGFR activating mutation** adult patients, locally advanced or metastatic NSCLC	
		FDA	**EGFR exon 19 deletion or L858R** first-line treatment, metastatic	
Necitumumab EGFR inhibitor	Non-small cell lung carcinoma	FDA	metastatic squamous non-small cell lung cancer	Cisplatin, Gemcitabin
Panitumumab EGFR inhibitor	Colon cancer	EMA	**RAS wildtype** adult patients, metastatic disease - in first-line in combination with FOLFOX or FOLFIRI - in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).	FOLFOX, FOLFIRI
		EMA	**RAS wildtype** adult patients, metastatic disease, monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens	
		FDA	**RAS wildtype** first-line therapy	FOLFOX
		FDA	**RAS wildtype** metastatic, following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy	
Lapatinib EGFR inhibitor HER2 inhibitor	Breast cancer	EMA	**HER2 overexpression** adult patients, HR-negative metastatic disease, progressed on prior trastuzumab therapy(ies)	Trastuzumab
		EMA	**HER2 overexpression** adult patients, advanced or metastatic, progression under prior treatment which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting	Capecitabine
		EMA	**HER2 positive** postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy	Exemestane, Letrozole, Anastrozole
		FDA	**HER2 overexpression** advanced or metastatic disease, following prior therapy including an anthracycline, a taxane, and trastuzumab; disease progression on trastuzumab	Capecitabine
		FDA	**HER2 overexpression** metastatic disease, postmenopausal women, hormonal therapy indicated	Letrozole
Neratinib EGFR inhibitor HER2 inhibitor	Breast cancer	EMA	**HER2 positive, HR positive** adjuvant treatment, adult patients with early breast cancer, following treatment with trastuzumab	
		FDA	**HER2 positive** adult patients, extended adjuvant treatment, early stage, to follow adjuvant trastuzumab-based therapy	

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
Afatinib EGFR inhibitor HER2 inhibitor HER4 inhibitor	Non-small cell lung carcinoma	FDA	**HER2 positive** adult, advanced or metastatic disease, two or more prior anti-HER2 based regimens in the metastatic setting	Capecitabine
		EMA	**EGFR activating mutation** -adult, EGFR TKI-naïve, locally advanced or metastatic NSCLC	
		FDA	metastatic squamous NSCLC, progressed after treatment with platinum-based chemotherapy	
		FDA	**non-resistant EGFR** metastatic, first line treatment	
Dacomitinib EGFR inhibitor HER2 inhibitor HER4 inhibitor	Non-small cell lung carcinoma	EMA	**EGFR activating mutation** first-line, adult patients, locally advanced or metastatic NSCLC	
		FDA	**EGFR exon 19 deletion or L858R** metastatic NSCLC	
Amivantamab EGFR inhibitor MET inhibitor	Non-small cell lung carcinoma	EMA	**EGFR Exon 20 insertion mutation** adult, advanced or metastatic, after failure of platinum-based chemotherapy	
		EMA	**EGFR Exon 20 insertion** adults, advanced disease, first-line	Carboplatin, Pemetrexed
		EMA	**EGFR exon 19 deletions or exon 21 L858R substitution mutation** adults, advanced NSCLC after failure of prior therapy including an EGFR tyrosine kinase inhibitor	Carboplatin, Pemetrexed
		FDA	**EGFR Exon 20 insertion mutation** adult, locally advanced or metastatic, progress after platinum-based chemotherapy	
		FDA	**EGFR Exon 20 insertion mutation** adults, locally advanced or metastatic, 1st line	Carboplatin, Pemetrexed
		FDA	**EGFR exon 19 deletions or exon 21 L858R substitution mutation** 1st-line, locally advanced or metastatic NSCLC	Lazertinib
		FDA	**EGFR exon 19 deletions or exon 21 L858R substitution mutation** adults, locally advanced or metastatic disease after progression on or after treatment with an EGFR tyrosine kinase inhibitor	Carboplatin, Pemetrexed
Vandetanib EGFR inhibitor VEGFR inhibitor RET inhibitor	Thyroid carcinoma	EMA	adults and adolescents 12 years and older - advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate) – advanced RET-mutant medullary thyroid cancer (MTC)	
		FDA	symptomatic or progressive medullary thyroid cancer, unresectable (non-operable) locally advanced or metastatic disease OR indolent, asymptomatic or slowly progressing disease only after careful consideration of the treatment related risks	

CDKN2A, homozygous deletion, complete gene, focal, NM_000077.5:
CDKN2A, reduced expression, complete gene:
CCND2, overexpression, complete gene:

Relevant therapeutics for genes *CDKN2A* and *CCND2*

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
Abemaciclib CDK4/6 inhibitor	Breast cancer	EMA	**HR positive, HER2 negative** adult patients, adjuvant treatment, node-positive early breast cancer at high risk of recurrence	Tamoxifen, Fulvestrant, Toremifene
		EMA	**HR positive, HER2 negative** advanced or metastatic; in pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist	Exemestane, Letrozole, Anastrozole
		EMA	**HR positive, HER2 negative** advanced or metastatic; in pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist	Fulvestrant
		FDA	**HR positive, HER2 negative** adult patients, adjuvant treatment, node-positive early breast cancer at high risk of recurrence	Tamoxifen, Exemestane, Letrozole, Anastrozole
		FDA	**HR positive, HER2 negative** adult patients, advanced or metastatic, progression following endocrine therapy and prior chemotherapy in the metastatic setting	

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
		FDA	**HR positive, HER2 negative** adult patients, advanced or metastatic, progression following endocrine therapy	Fulvestrant
		FDA	**HR positive, HER2 negative** adult patients, advanced or metastatic	Exemestane, Letrozole, Anastrozole
Palbociclib CDK4/6 inhibitor	Breast cancer	EMA	**HR positive, HER2 negative** locally advanced or metastatic breast cancer, prior endocrine therapy, should be combined with a luteinizing hormone releasing hormone (LHRH) agonist in pre- or perimenopausal women	Fulvestrant
		EMA	**HR positive, HER2 negative** locally advanced or metastatic, should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist in pre-menopausal women	Exemestane, Letrozole, Anastrozole
		FDA	**HR positive, HER2 negative** adult patients, advanced or metastatic breast cancer, disease progression following endocrine therapy	Fulvestrant
		FDA	**HR positive, HER2 negative** adult patients, advanced or metastatic breast cancer	Exemestane, Letrozole, Anastrozole
Ribociclib CDK4/6 inhibitor	Breast cancer	EMA	**HR positive, HER2 negative** locally advanced or metastatic cancer, as initial endocrine-based therapy; pre- or perimenopausal women: endocrine therapy should be combined with a LHRH agonist	Exemestane, Letrozole, Anastrozole
		EMA	**HR positive, HER2 negative** locally advanced or metastatic cancer, as initial endocrine-based therapy; pre- or perimenopausal women: endocrine therapy should be combined with a LHRH agonist	Fulvestrant
		EMA	**HR positive, HER2 negative** locally advanced or metastatic cancer, received prior endocrine therapy	
		FDA	**HR positive, HER2 negative** - adult patients, advanced or metastatic breast cancer with an aromatase inhibitor as the first endocrine-based therapy - adjuvant stage II and III early breast cancer at high risk of recurrence	Exemestane, Letrozole, Anastrozole
		FDA	**HR positive, HER2 negative** adult patients, advanced or metastatic breast cancer, following disease progression on endocrine therapy in postmenopausal women or in men	Fulvestrant

TERT, c.-146C>T (C250T), NM_198253.3:
TERT, overexpression, complete gene:

Relevant therapeutics for gene *TERT*

Drug name	Tumor entity	Approval	Approval limited to biomarkers/others	Approval in combination with other drugs
Eribulin TERT-targeting inhibitor Microtubuli inhibitor	Breast cancer	EMA	adult, locally advanced or metastatic, progress after at least one chemotherapeutic regimen for advanced disease, prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.	
		FDA	metastatic, at least two prior chemotherapy regimens (including an anthracycline and a taxane)	
	Liposarcoma	EMA	adult, unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease	
		FDA	unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen	