Supplementary Table 1: Principal component analysis (PCA)-derived scores of inherent resistance to single-shot radiotherapy (RTX), fractionated RTX, temozolomide (TMZ), and the combination thereof in human glioblastoma cell lines A172, LN18, LN229, T98G, U87, U138, and U251

	A172	**LN18**	**T98G**	**U138**	**U87**	**LN229**	**U251**
RRID	CVCL-0131	CVCL-0392	CVCL_0556	CVCL_0020	CVCL_0022	CVCL-0393	CVCL-0021
Single-shot RTX	0.11	-1.08	0.91	-0.98	0.29	-0.77	1.53
Fractionated RTX	0.18	0.03	0.99	-1.67	-0.38	-0.50	1.35
TMZ	-0.94	1.13	0.84	0.84	-1.03	-1.13	0.29
Single-shot RTX/TMZ	0.00	0.11	0.61	-1.34	0.02	-1.04	1.65

Supplementary Table 2: Overview of composite karyotypes in human glioblastoma cell lines A172, LN18, LN229, T98G, U87, U138, and U251

Cell line	Composite clonal karyotype	Subclones
A172	83,XXYY,der(1)t(1;14)(p13;?),der(1)t(1;18)(p22;?),+der(1)del(1)(p11)t(1;14)(q21;?),+del(1)(p22;q11),+der(2)t(2;5)(q31;?)x2,+der(3)(3;9)(q25;?),+5,+der(5)del(5)(q15)t(2;5)(?;p13)x2,+6,+7,+der(7)t(6;7)(q22;?),del(8)(q23),+del(8)(q11),+del(8)(q13),der(9)t(9;16)(p11;?)x2,+10,+11,+der(11)t(1;11)(?;p11)x2,+12,+12,+13,+der(14)t(9;14)(?;q13)x2,+15,+16,+16,+16,+17,+der(17)t(17;18)(q11;?),der(18)t(1;18)(?;q21),+der(18)t(1;18)(?;q21),+19,+19,+20,+20,add(21)(q21),+22	Yes
LN18	61,XY,+t(X;10)(q?;q11),+t(X;9)(p?;p?),+3,+t(5;15)(p13;q?),+7,+7,t(6;10)(q11;q?),+t(5;10)(q11;q?),+t(6;10)(p11;p?),+t(10)(p10),t(11;14)(q?;?),+t(11,18)(q?;q11),+t(12;16)(q?;p11),+20,+t(16;20)(p11;q?)+add(22)(q?)	Yes
LN229	86,XXX,der(X)t(x;2)(q23;?),der(X)t(X;16)(p11;?),+der(X)t(X;19)(p21;?),+1,del(1)(p10),+der(1)t(1;18)(?;q11),+2,+2,+2,+3,+3,+der(4)t(4;6)(p14;?)x2,+der(4)t(4;9)(q11;?),+5,+der(5)t(5;12)(p11;?),+der(6)t(6;16)(p13;?)x2,+der(6)t(6;7)(?;?),+7,+7,+der(7)t(5;7)(?;p11)x2,+der(8)t(6;8)(?;q22),+9,+9,+der(9)t(8;9)(?;q10),+10,+der(11)(q14),+del(12)(q13),+der(14)t(14;18)(q24;?),+16,+16,+del(17)(q12),+18,+der(19)t(X;19)(?;q12),+20,+20,+20,+21,+21,+22,+22,+der(22)t(15;22)(?;p12)x2	Yes
T98G	131,XXXYYYY,trc(7;7;7)(q?;p?;p?)x2,+t(7;8)(q?;p?)x2,dic(10;10)(q?;q?)x1,+i(15)(q10)	Yes
U87	44,X,t(1)(1:13)(p22;p?)x2,der(6)t(6;7)(p21;p?),der(6)t(6;12)(q23;?),del(7)(q10),del(10)(q21),der(12)t(6;12)(?;q22),-13,-14,der(16)t(1;16)(?;q13),del(20)(p11),+der(20)t(1;14;20)(?;?;q12),t(10;22)(?;p12)	Yes
U138	61-62,XYY,+Y,+der(1)t(1;12)(p31;?),+3,der(4)t(4;17)(q32;?),ins(4)(4;14;4)(p15;?;p13)x2,+7,+der(8)t(8;17)(p21;?),+der(11)t(11;19)(p13;?),der(12)t(1;12)(?;q14),+13,-14,+15,+18,+der(18)t(6;18)(?;q12),+del(19)(p12),+20,+20,+22,+der(22)t(5;22)(?;q11)	No
U251	66,XXY,+1,+2,+3,der(4)t(4;16;4;20)(q12;?;q?;q?),der(4)t(4;16;4;16)(q12;?;q?;?),+5,+7,+7,+iso(8)(q10),+9,+der(11)t(10;11;15)(q10;q?;q?),+der(11)t(6;10;11)(q?;q?;q?),+15,+17,+17,+del(18)(q12),+19,+20,+21	No

The second column describes the predominant clonal karyotype including all chromosomal aberrations. The third column shows whether subclones are present in the cell lines.

Supplementary Table 3: Overview of molecular glioblastoma subtype-specific chromosomal amplifications and deletions, and subtype-specific expression of relevant driver genes

Subtype	Feature	A172	LN18	LN229	T98G	U87	U138	U251
Classical	EGFR (7p11.2) amplification	1	1	1	1	0	0	1
	CDKN2A (9p21.3) deletion	1	1	1	1	1	1	1
	NOTCH3 expression	1	0	0	0	1	0	0
	NES expression	1	0	1	0	1	0	1
	SMO expression	1	0	1	1	0	0	1
Score classical		1.0	0.4	0.8	0.6	0.6	0.2	0.8
Mesenchymal	NF1 (17q11.2) deletion	0	0	1	0	0	1	0
	CHI3L1 expression	0	0	0	0	1	0	0
	TRADD, RELB, TNFRSF1A expression	1	1	1	1	1	1	1
	CASP1 espression	0	1	0	1	1	1	1
	TLR4 expression	0	0	1	0	0	0	1
Score mesenchymal		0.2	0.4	0.6	0.4	0.6	0.6	0.6
Proneural	PDGFRA (4q12) amplification	0	0	0	0	0	0	1
	NKX2-2 expression	0	0	1	0	0	0	0
	OLIG2 expression	0	0	1	0	0	0	0
	SOX2 expression	0	0	1	0	0	0	0
	ERBB3 expression	0	0	1	0	0	0	0
Score proneural		0	0	0.8	0	0	0	0.2
Classification key feature-based		C	C/M	C/P	C	C/M	M	C

Supplementary Table 4: Genes with overlapping positive (R ≥ 0.9, red) or negative (R ≤ -0.9, blue) correlation with inherent therapy resistance in human glioblastoma cell lines as retrieved by global mRNA expression microarray analysis

Gene ID	SSIR	FIR	COMBI	TMZ	General information	Connection to glioblastoma	Inhibitors	Clinical trials
A4GALT	> 0.9	> 0.9	> 0.9	-	Lactosylceramide-4-alpha-galactosyltransferase (A4GALT) catalyzes the transfer of galactose residues onto sphingolipids thereby contributing to the generation of glycosphingolipids [1, 2].	Connections between A4GALT and glioblastoma are not reported so far. In lung cancer models, A4GALT was shown to affect tumor progression, metastasis formation, resistance to chemotherapy, and epthelial-mesenchymal transition (EMT) [3].	None	None
POLA1	> 0.9	> 0.9	> 0.9	-	DNA polymerase alpha 1 (POLA1) catalytic subunit, together with one regulatory and two primase subunits, forms the DNA polymerase alpha (POLA) complex. POLA1 is important for the initiation of DNA replication as it synthesizes RNA:DNA hybrids thereby initiating the synthesis of Okazaki fragments [4-7]. POLA1 also synthesizes cytosolic RNA:DNA hybrids thereby modulating the type I interferon immune response [8].	Connections between POLA1 and glioblastoma are not reported so far. However, MIR075, an unpublished POLA1 inhibitor, reduced the growth of glioblastomas generated by intracranial implantation of U87 cells into mice (doi.org/10.1158/1538-7445.AM2018-48489). POLA1 is of prognostic value in non-small cell lung cancer (NSCLC), and colorectal cancer [9-12].	CD437 [13] ST1926 [14, 15] MIR002 [16] GEM144 [16] (co-inhibits HDAC11) MIR020, MIR072, MIR075 (all unpublished)	None
AP2B1	> 0.9	> 0.9	> 0.9	-	AP2 complex subunit Beta 1 (AP2 B1) is one of two components that form the Assembly Protein 2 (AP2) complex which links clathrin to its receptors on vesicles. Thus, AP2B1 is important for intracellular vesicle trafficking and endocytosis [17].	Connections between AP2B1 and glioblastoma are not reported so far, but have been suggested [18]. Aberrancies in expression of AP2B1 and expression of alternative splicing forms of AP2B1 were detected in different cancer entities including lung cancer and breast cancer [19, 20].	Barbadin [21] (co-inhibits beta-Arrestin)	None
TSNAXIP1	> 0.9	-	> 0.9	-	Translin-Associated X-Interacting Protein 1 (TSNAXIP1) is a so far uncharacterized protein predicted to be involved in cell proliferation, cell differentiation, cell polarity, and spermatogenesis [22].	TSNAXIP1 was identified in a nomogram of alternative splicing forms that were of predictive value for low-grade gliomas [23].	None	None
ZZEF1	> 0.9	-	> 0.9	-	ZZ-type zinc finger and EF-hand domain-containing protein 1 (ZZEF1) specifically detects histone H3 at promoters thereby functioning co-activator of transcription [24].	ZZEF1 is deleted in a notable portion of pediatric gliomas [25]. Single-nucleotide polymorphisms (SNPs) and copy number alterations (CNAs) of ZZEF1 are associated with several types of cancer including pancreatic cancer, gastric cancer, breast cancer, and esophageal cancer [26].	None	None

MAP2K4	-	> 0.9	> 0.9	-	Dual specificity Mitogen-Activated Kinase Kinase 4 (MAP2K4/MEK4/ MKK4) is a part of the MAPK (RAF-MEK-ERK) and Stress-Activated Protein (SAP) Kinase/c-Jun N-terminal Kinase (JNK) signaling pathway network [27].	MAP2K4 exhibits tumor suppressing functions by decelerating tumor progression and metastasis formation [28-33]. MAP2K4 is frequently mutated in cancer, and mutations of MAP2K4 exhibit proto-oncogenic potential [34-40]. In addition, mutations of MAP2K4 frequently conincide with resistances to MAPK-targeting therapies [41]. MAP2K4, together with ZDHHC17 and JNK/p38, contributes to progression of glioblastoma by promoting the self-renewal of glioma stem cells (GSCs) [42]. This effect can be inhibited by Genistein, an isoflavone protein tyrosine kinase (PTK) inhibitor derived from soy bean [43] which disrupts the interaction between MAP2K4 and ZDHHC17 in glioblastoma cells [42]. Genistein synergizes with radiotherapy and temozolomide (TMZ) in terms of abrogating survival of glioblastoma cells *in vitro* [44, 45]. Finally, expression of miR-744, a MAP2K4-targeting miRNA interferes with migration and invasiveness of glioblastoma cells *in vitro* [46].	MEK4 inhibitor-1 [47] MEK4 inhibitor-2 [47] 3-Arylimidazoles [48] BSJ-04-122 [49] (co-inhibits MEK7) HRX-0215 (unpublished) Genistein/NPI031L [43] (PTK inhibitor)	Genistein was tested in multiple trials on patients suffering from different diseases including different malignancies, but not in glioblastoma so far [50]. Currently, Genistein is tested in combination with systemic chemotherapy in a randomized trial on pediatric patients either suffering from lymphomas or different kinds of solid tumors including pediatric gliomas (NCT02624388).
PLAAT2/ HRASLS 2	-	> 0.9	> 0.9	-	Phospholipase A and Acyltransferase 2 (PLAAT2/HRASLS2) exhibits two enzymatic activities, a phospholipase and an acyltransferase activity. PLAAT2/HRASLS2 catalyzes the hydrolysis of dipalmitoylated phosphatidylcholine into lysophosphatidylcholin and palmitic acid as well as the acylation of phosphatidylethanolamine [51, 52].	PLAAT2/HRASLS2 is differentially expressed in the stromal cells of glioblastoma tumors [53]. PLAAT2/HRASLS2 exhibits tumor suppressive functions, most likely by attenuating the oncogenic potential of RAS GTPase [51].	LEI110 [54] (pan-HRASLS inhibitor) LEI301 [55] (pan-HRASLS inhibitor)	None
CDS1	-	> 0.9	> 0.9	-	Phosphatidate Cytidylyltransferase 1 (CDS1) catalyzes the conversion of phosphatidic acid into CDP-diacylglycerol. CDS1 is involved in syntheses of phosphatidylinositol, phosphatidylglycerol, and cardiolipin. Thus, CDS1 regulates the intracellular pool of the signal transduction-related second messenger phosphatidylinositol [56, 57].	Alterations in mRNA expression levels of CDS1 are associated with poor prognosis in glioblastoma and liver cancer [58, 59]. Functionally, CDS1 was shown to affect the lipid metabolism of glioblastoma cells upon hypoxic stress [60].	None	None
SLC25A1 1	-	> 0.9	> 0.9	-	The Solute Carrier family 25 member 11 (SLC25A11) catalyzes the electron-neutral transport of 2-oxoglutarate across mitochondrial membranes thereby allowing for the synthesis of malate and other dicarboxylic acids. SLC25A11 is involved in the generation of ATP and in maintenance of the redox equilibrium [61].	Connections between SLC25A11 and glioblastoma are not reported so far. SLC25A11 is deregulated in several types of malignancy including NSCLC, liver cancer, and melanoma [62, 63]. Germline mutations of SLC25A11 are associated with increased susceptibilty for developing paragangliomas [64].	None	None
HAP1	-	> 0.9	> 0.9	-	Huntingtin-Associated Protein 1 (HAP1) physically interacts with the huntingtin (HTT) protein. HAP1 functions in intracellular vesicle and	Expression levels of HAP1 are closely related to resistance against radiotherapy in glioblastoma and other cancer entities [67-71].	None	None

					organelle transport by linking HTT to motor proteins such as dynactin. In addition, HAP1 is important for autophagosomal degradation of proteins [65, 66].	HAP1 is also supposed to have functions in the pathogenicity of pancreatic cancer and breast cancer [66].		
TXNDC17	-	> 0.9	> 0.9	-	Thioredoxin Domain Containing protein 17 (TXNDC17) catalyzes the reduction of disulfides. TXNDC17 exhibits a peroxidase activity which is involved in the elimination of hydrogen peroxide from cells. TXNDC17 is also involved in Nuclear Factor κB (NF-κB) and Tumor Necrosis Factor alpha (TNFA) signaling [72].	Connections between TXNDC17 and glioblastoma or other cancer entities are not reported so far. However, inhibition of protein disulfide isomerases in general is supposed to represent a promising approach for treatment of glioblastoma and other cancer entities [73].	None	None
NPEPPS	-	> 0.9	> 0.9	-	Puromycin-Sensitive Aminopeptidase M1 (NPEPPS) is a zinc metallopeptidase which hydrolyzes amino acids from the N-termini of substrate proteins such as enkephalins and Superoxide Dismutase 1 (SOD1) [74-76].	NPEPPS affects the migratory and the differentation behaviour of glioblastoma cells *in vitro* [77].	Puromycin (pan-inhibitor of M1 aminopeptidases)	None
KLHL11	-	> 0.9	> 0.9	-	Kelch-like famiy member protein 11 (KLHL11) is part of the cullin-RING-based BCR (BTB-CUL3-RBX1) ubiquitin ligase complex which ubiquitinates the NF-2-Related Factor 2 (NRF2), a core component of the oxidative stress response, upon oxidative stress [78, 79].	Connections between KLHL11 and glioblastoma or other cancer entities are not reported so far. However, inhibition of NRF2/KEAP1 signaling per se represents a promising approach for cancer treatment [80-83].	No specific inhibitor of KLHL11 available so far. Modulators (both, activators and inhibitors) of the NRF2/KEAP1 signaling hub are readily available and also trial-tested [84-86], e.g. Resveratrol [87] Curcumin [88] Brusatol [89] Oltipraz [90] Omaveloxolone [91, 92] ML385 [93] ML334 [94]	None Modulators of the NRF2/KEAP1 signaling hub are currently trial tested in patients with different malignancies [84-86], but so far not in glioblastoma patients.
PSMB3	-	> 0.9	> 0.9	-	The Proteasomal Subunit beta 3 (PSMB3) is a non-catalytic subunit of the 20S core proteasome. Thus, PSMB3 has a crucial function in the protein homeostasis of cells [95].	Connections between PSMB3 and glioblastoma or other cancer entities are not reported so far. However, the proteasome as a target for cancer therapy is of great importance [96].	No specific inhibitor of PSMB3 available so far. Inhibitors of the 20S/26S core/holo-proteasome are readily available and also trial-tested [96, 97], e.g.	None Inhibitors of the 20S/26S core/holo-proteasome are currently trial tested in patients with different malignancies [96, 97], but so far not in glioblastoma patients.

							Bortezomib [98, 99] Carfilzomib [100] Celastrol [101, 102] Delanzomib [103] Ixazomib [104] MG-132 [105]	Bortezomib is an FDA-approved drug for the treatment of multiple myeloma and of mantle cell lymphoma [106].
TGFBR2	< - 0.9	-	< - 0.9	-	Transforming Growth Factor (TGF) beta Receptor-2 (TGFBR2) is a subunit of the serine/threonine kinase associated receptor which, together with TGFBR1/ALK5, forms the TGF beta receptor (TGFBR) [107].	Expression of TGFBR2 correlates with expression levels of platelet derived growth factor receptor (PDFGR), a signature marker of the proneural molecular glioblastoma subtype, in glioblastoma cells [108]. In addition, TGFBR2 modulates TGF beta and Smad2/3-dependent signaling in glioblastoma cells [109].	No specific inhibitor of TGFBR2 available so far. Inhibitors of TGFBR1 are readily available and also trial-tested [110], e.g. Galunisertib [111] Vactosertib [112, 113] LY364947 [114] LSKL [115]	None Inhibitors of TGFBR1 are currently trial tested in patients with different malignancies including glioblastoma [110]. Galunisertib/LY2157299 was tested in combination with radiotherapy and TMZ in a phase 1B/2A trial on patients suffering from glioblastoma, but failed to improve clinical outcome (NCT01220271) [116].
MYNN	-	< - 0.9	< - 0.9	-	Myoneurin (MYNN) is a member of the protein family called BTB/POZ and zinc finger domain-containing proteins. This protein family is involved in the regulation of gene expression [117].	Connections between MYNN and glioblastoma or other cancer entities are not reported so far.	None	None
SYT14	-	< - 0.9	< - 0.9	-	Synaptotagmin-14 (SYT14) is a calcium-independent member of the synaptotagmin protein family which exhibits functions in synaptic transmission and exocytosis [118].	Connections between SYT14 and glioblastoma or other cancer entities are not reported so far.	CN110420328A (unpublished)	None
MED15	-	< - 0.9	< - 0.9	-	Mediator complex subunit 15 (MED15) is a central component of the mediator complex (MC) which acts as a co-activator in RNA polymerase II-dependent transcription [119].	Connections between MED15 and glioblastoma are not reported so far. Alterations in expression of MED15 were detected in testis cancer, prostate cancer, and bladder cancer [120-123].	None	None
SYPL2	-	< - 0.9	< - 0.9	-	Synaptophysin-like 2 (SYPL2) mediates the communication between membranes of the T-tubular and the junctional sarcoplasmic reticulum (SR). As such, SYPL2 is involved in calcium homeostasis of the skeletal muscular system [124].	Connections between SYPL2 and glioblastoma or other cancer entities are not reported so far. However, expression levels of Synaptophysin-like 1 (SYPL1) clearly correlate with clinical outcomes in cancer patients, e.g. in patients suffering from papillary thyroid cancer, and liver cancer [125, 126].	None	None
C1GALT1	-	< - 0.9	< - 0.9	-	Core 1 Glycoprotein-N-Acetyl-galactosamine-3-beta-Galactosyl-Transferase 1 (C1GALT1) catalyzes O-linked glycosylation of	Connections between C1GALT1 and glioblastoma are not reported so far.	None	None

					mucin-like proteins [127]. C1GALT1 has documented functions in angiogenesis, platelet production, and kidney development [128].	Yet, alterations in gene expression of C1GALT1 are associated with poor prognosis in head and neck cancer and gastric cancer [129, 130].		
POLR1F/ TWISTNB	-	< - 0.9	< - 0.9	-	RNA Polymerase 1 subunit F (POLR1F/TWISTNB) is part of the RNA polymerase 1 (POL1) complex which synthesizes ribosomal RNAs (rRNAs). POLR1F/TWISTNB regulates the 5'-3' RNA polymerase activity of the POL1 complex [131, 132].	Connections between POLR1F/TWISTNB and glioblastoma are not reported so far. POLR1F/TWISTNB is overexpressed in lung cancer and testis cancer [133].	No specific inhibitor of POLR1F/TWISTNB available so far. Inhibitors of POL1 transcription in general are readily available [134], e.g. BMH-21 [135] CX-3543 [136] CX-5461 [137]	None
CFH	-	< - 0.9	< - 0.9	-	Complement Factor H (CFH) belongs to the Regulator of Complement Activation (RCA) cluster of genes [138]. The CFH glycoprotein is secreted into the blood where it regulates the activity of the complement system and thus, immune responses [139].	Overexpression of CFH in glioblastoma cells as the result of overexpression of non-metabolic indoleamine 2,3-dioxygenase 1 (IDO1) suppresses anti-tumor immune responses thereby impairing survival in syngeneic mouse models of glioblastoma [140]. Furthermore, CFH promotes the progression of glioblastoma cells by affecting AKT1 and miR-149 [141]. Finally, CFH expression is accelerated in ovarian cancer and lung cancer [142, 143].	None	None

Supplementary Table 5: CGC genes with overlapping positive (R ≥ 0.7) correlation with inherent therapy resistance in human glioblastoma cells, for which drugs are readily available

Name	SSIR	FIR	COMBI	TMZ	General Information	Connection to Glioblastoma	Inhibitors	Clinical Trials
AR	≥ 0.7	≥ 0.7	≥ 0.7	-	Androgen Receptor (AR) is a nuclear receptor activated by androgenic hormones like testosterone and dihydrotestosterone. AR acts as an activator of transcription regulating the expression of androgen-responsive genes like KLK2 and KLK3 [144]. As such, AR exhibits functions in the development and the maintenance of the reproductive system as well as in the cardiovascular, the musculoskeletal, and the haematopoietic system [145, 146].	Overexpression of AR has been associated with reduced survival in glioblastoma patients [147-152]. Activation of AR signaling in glioblastoma cells accelerates their proliferation, clonogenic ability, migratory behaviour, invasiveness, and therapy resistance (both to radiotherapy and TMZ) [151-158], and these effects can be reversed by AR-targeting approaches [152, 156-158].	AR inhibitors are readily available and also trial-tested [146, 159-161], e.g. Apalutamide/ARN-509 [162] Bicalutamide/ICI-176334 [163, 164] Darolutamide/OMD-201 [165] Enzalutamide/MVD3100 [166] Flutamide/SCH-13521 [167] Nilutamide/RU23908 [168, 169] Cyproterone acetate [170] ALZ003 [152]	AR inhibitors are currently trial-tested in patients with different malignancies focussing on prostate cancer [146, 159-161]. No trials in glioblastoma patients so far. Several AR inhibitors such as Apalutamide and Darolutamide are FDA-approved for treatment of prostate cancer [171].
STAT5b	≥ 0.7	≥ 0.7	≥ 0.7	-	Signal Transducer and Activator of Transcription 5b (STAT5b) induces the transcription of target genes such as FOXP3 and IL2RA [172] upon its activation by the Janus Kinase (JAK) in response to extracellular signals (e.g. IL2, IL4, CSF1) [173].	STAT5b has been associated with poor prognosis in glioblastoma patients [174]. Pro-malignant signaling mediated by the Epidermal Growth Factor Receptor variant III (EGFR vIII)/STAT5 axis was shown to contribute significantly to survival and migration of glioblastoma cells [175, 176], and inhibition of STAT5 suppressed the proliferation, invasion, and stemness of glioblastoma cells *in vitro* and *in vivo* [177, 178].	No specific inhibitor of STAT5b available so far. However, pan-STAT5 inhibitors are readily available and also trial-tested [179], e.g. STAT5-IN-1 [180] (pan-STAT5 inhibitor) IQDMA [181] (pan-STAT5 inhibitor) Pimozide [182] (pan-STAT5 inhibitor) AC-4-130 [183] (pan-STAT5 inhibitor) IST5-002 [184] (pan-STAT5 inhibitor) BD750 [185] (pan-STAT5 inhibitor, co-inhibits JAK3)	Pan-STAT5 inhibitors are currently trial tested in patients with different malignancies focussing on the haematopoetic system [179]. No trials in glioblastoma patients so far.

MAP2K4	≥ 0.7	≥ 0.7	≥ 0.7	-	Dual specificity Mitogen-Activated Kinase Kinase 4 (MAP2K4/MEK4/ MKK4) is a part of the MAPK (RAF-MEK-ERK) and Stress-Activated Protein (SAP) Kinase/c-Jun N-terminal Kinase (JNK) signaling pathway network [27].	MAP2K4 exhibits tumor suppressing functions by decelerating tumor progression and metastasis formation [28-33]. MAP2K4 is frequently mutated in cancer, and mutations of MAP2K4 exhibit proto-oncogenic potentials [34-40]. Mutations of MAP2K4 often conincide with resistances to MAPK-targeting therapies [41]. MAP2K4 contributes to glioblastoma progression by promoting the self-renewal of GSCs [42]. This effect can be reverted by Genistein [42]. Genistein synergizes with radiotherapy and TMZ *in vitro* [44, 45]. Expression of miR-744, a MAP2K4-targeting miRNA, interferes with migration and invasiveness of glioblastoma cells *in vitro* [46].	MEK4 inhibitor-1 [47] MEK4 inhibitor-2 [47] 3-Arylimidazoles [48] BSJ-04-122 [49] (co-inhibits MEK7) HRX-0215 (unpublished) Genistein/NPI031L [43] (protein tyrosine kinase (PTK) inhibitor)	Genistein was tested in multiple clinical trials in patients with different diseases including different malignancies, but not in glioblastoma patients so far [50]. Currently, Genistein is tested in combination with systemic chemotherapy in a randomized trial on pediatric patients either suffering from lymphomas or from solid tumors including pediatric gliomas (NCT02624388).

Supplementary Table 6: Intersect leading edge genes for which drugs are readily available

Leading edge genes at the SSIR and FIR intersection of the reactive oxygen species (ROS) pathway gene set for which inhibitors are readily available				
Name	**General Information**	**Connections to Glioblastoma**	**Inhibitors**	**Clinical Trials**
G6PD	Glucose-6-phosphate-1-dehydrogenase (G6PD) is an enzyme of the pentose phosphate pathway [186] whose main function is the production of NADPH, a key electron donor in defense against oxidizing agents, and reductive biosynthetic reactions [60, 187, 188].	G6PD is essential for protection from oxidative stress in GSCs [189]. Overexpression of G6PD correlates with reduced survival, and poor prognosis in glioblastoma patients, and with increased proliferation and therapy resistance in glioblastoma cell lines [190-192].	6-Aminonicotinamide [193] RRx-001 [194-196] (epigenetically active [197]) Polydatin [198] G6PDi-1 [199] Wedelolactone [200]	RRx-001 is currently tested in a phase I trial in combination with fractionated radiotherapy (30x 2 Gy) and TMZ in patients suffering from primary glioblastoma or anaplastic glioma (NCT02871843). .
GCLC	Glutamate-Cysteine Ligase catalytic subunit (GCLC) catalyzes the ligation of L-cysteine with L-glutamate, a rate-limiting step in the synthesis of gluthathione (GSH) [201, 202]. Thus, GCLC is essential for protection from oxidative stress and for intracellular redox homeostasis [202].	Expression of GCLC in glioblastoma cells is regulated by CD147 [203, 204], and isocitrate dehydrogenase 1 (IDH1) [205, 206].	L-Buthionine-Sulfoximine (L-BSO) [207] 2-Deoxy-d-ribose [208] $NaAsO_2$ [209]	L-BSO was tested in a phase I trial on pediatric neuroblastoma patients (NCT00005835) [210, 211]. No trial data for glioblastoma so far.
TXNRD1	Thioredoxin Reductase 1 (TXNRD1) is a selenocysteine-containing flavoenzyme of the pyridine nucleotide-disulfide oxidoreductase family. TXNRD1 is an integral component of the thioredoxin reductive system (TRX) which eliminates reactive oxygen species (ROS) thereby ensuring redox homoeostasis in cells [212, 213].	Deregulations in expression of thioredoxin reductases (TXNRs) including TXNRD1 are associated with malignancy, progression, and angiogenesis in glioblastoma [214-217]. Interference with TXNRD1/TXN function sensitizes glioblastoma cells to chemotherapy and to radiotherapy [218-222].	Auranofin [223-226] (pan-TXNR inhibitor) Curcumin [227] Diffractaic acid [228] Ethaselene [229] Laromustine [230] (pan-TXNR inhibitor) Myricetin [231] Piperlongumine [232] Santamarine [233] TRi-1/HUN20688 [234] TrxR1-5 [218] TrxR1-6 [218] IP-Se-06 [235]	Ethaselene is tested in a phase Ic trial (NCT02166242) in non-small cell lung cancer patients. No trial data on glioblastoma so far.
TXN	Thioredoxin (TXN) acts as a homodimer and is active in S-nitrosylation of cysteines, an integral step in response to intracellular nitric oxides [212, 213].	Deregulation of TXN expression is reported for many cancers including glioblastoma [215, 236, 237]. Interference with TXN function sensitizes glioblastoma cells to radiotherapy [238].	Arsenic trioxide [239] Diallyl trisulfite [238] Pleurotin [240] PX-12/DB05448 [240] Diallyl trisulfite [238]	PX-12 was tested in several trials on different malignancies [241-243], but not on glioblastoma so far.
NDUFB4	NADH:Ubiquinone oxidoreductase subunit B4 (NDUFB4) is a non-catalytic subunit of the NADH:Ubiquinone oxidoreductase enzyme complex (complex I) of the mitochondrial electron transport chain [244].	NDUFB4, alongside with other genes of the ATP generating system, is upregulated in different glioblastoma subtypes [245]. Deregulations of NDUFB4 are a hallmark of many treatment-resistant cancers [246-248].	No specific inhibitor of NDUFB4 available so far. Inhibitors of the oxidative phosphorylation (OXPHOS)-related respiratory chain complex I are readily available and also trial-tested, e.g. Metformin [249-252] Intervenolin [253, 254] Gboxin [255] Olaparib [256] EVT-701 [257]	OXPHOS inhibitors, e.g. ME-143, ME-344, IACS-010759, and BAY-87-2243 are trial tested in different types of malignancy [258, 260, 265], but so far not in glioblastoma.

			ME-143 [258, 259] ME-344 [259, 260] IACS-010759 [261] BAY-87-2243 [262, 263] Multiple natural products, e.g. rotenoids and piericidins, as well as synthetic compounds, e.g. insecticides [264].	
STK25	Serine/Threonine kinase 25 (STK25) is a member of the germinal centre kinase III (GCK III) subfamily belonging to the sterile 20 kinase superfamily. STK25 is involved in serine/threonine liver kinase B1 (LKB1) signaling, regulating neuronal polarization and morphology of the Golgi apparatus. STK25 is translocated from the Golgi apparatus to nuclei in response to anoxia, and also plays a role in the regulation of cell death [266, 267].	Connections between STK25 and glioblastoma are not reported so far. STK25 exhibits tumor-suppressive functions as it directly activates the tumor-suppressing Hippo signaling pathway [268]. STK25 also inhibits glycolysis [269]. However, tumor-promoting functions of STK25 are reported as well, particularly in liver cancer [270, 271].	None	None
GSR	Gluthione Disulfide Reductase (GSR) is a homodimeric flavoprotein and member of the class-I pyridine nucleotide-disulfide oxidoreductase family. GSR is a core enzyme of the antioxidant defense, as it reduces oxidized glutathione disulfide (GSSG) to its sulfhydryl form GSH [201, 202].	GSR mediates drug resistance in glioblastoma cells via its function to regulate redox homeostasis [272]. GSR is deregulated in several cancer entities including lung cancer and liver cancer [273-275].	GSH [276] 2-AAPA [277] LCS3 [278] (co-inhibits TXNRD1)	None
ABCC1	ATP Binding Cassette subfamily C member 1 (ABCC1) is a member of the superfamily of ATP-Binding Cassette (ABC) transporters. ABCC1 is involved in drug resistance, functioning as a multispecific organic anion transporter with a substrate range encompassing oxidized GSH, cysteinyl leukotrienes, activated aflatoxins, glucuronides, and sulfate conjugates of steroid hormones [279, 280].	ABCC1 alongside with other ABC transporters is overexpressed in many cancer entities including glioblastoma [281, 282]. ABCC1 contributes to therapy resistance by eliminating therapeutic agents from cancer cells. In glioblastoma, several miRNAs that target ABCC1 have been identified, and their expression levels determine the degree of therapy resistance in these tumors [283-287].	MK-571 [288] Reversan [289] Thienopyrimidines [290]	None
Leading edge genes at the SSIR and TMZ intersection of the mammalian target of rapamycin complex 1 (mTORC1) pathway gene set for which inhibitors are readily available				
Name	**General Information**	**Connections to Glioblastoma**	**Inhibitors**	**Clinical Trials**
PSMG1	Proteasome assembly chaperone 1 (PSMG1) dimerizes with PSMG2 to form a chaperone complex with molecular adaptor activity that is crucial for the assembly of the 20S core proteasome [291].	PSMG1 as well as other proteasomal components are frequently deregulated in cancers [292-295], including glioblastoma [296].	No specific inhibitor of PSMG1 available so far. Inhibitors of the 20S/26S core/holo-proteasome are readily available and trial-tested [96, 97], e.g. Bortezomib [98, 99] Carfilzomib [100] Celastrol [101, 102] Delanzomib [103] Ixazomib [104] MG-132 [105]	None Inhibitors of the 20S/26S core/holo-proteasome are currently trial tested on different malignancies [96, 97], but not on glioblastoma. Bortezomib/Velcade is an FDA-approved drug for the treatment of multiple myeloma and mantle cell lymphoma [106].

PSMA4	Proteasome 20S subunit alpha 4 (PSMA4) constitutes a core subunit of the 20S core proteasome, thus playing an important role in protein homeostasis [297].	Connections between PSMA4 and glioblastoma are not reported so far. However, polymorphisms of PSMA4 have been associated with increased susceptibility to lung cancer [298].	No specific inhibitor of PSMG1 available so far. Inhibitors of the 20S/26S core/holo-proteasome are readily available and trial-tested [96, 97], e.g. Bortezomib [98, 99] Carfilzomib [100] Celastrol [101, 102] Delanzomib [103] Ixazomib [104] MG-132 [105]	None Inhibitors of the 20S/26S core/holo-proteasome are currently trial tested on different malignancies [96, 97], but not on glioblastoma. Bortezomib/Velcade is an FDA-approved drug for the treatment of multiple myeloma and mantle cell lymphoma [106].
HPRT1	Hypoxanthine phosphoribosyltransferase 1 (HPRT1) is an enzyme that catalyzes the conversions of hypoxanthine to inosine monophosphate and of guanine to guanosine monophosphate. Thus, HPRT1 plays a crucial role in purine salvage pathway-dependent synthesis of purine nucleotides [299, 300].	Connections between HPRT1 and glioblastoma are not reported so far. HPRT1 is upregulated in various cancer entities, resulting in worsened prognoses and increased levels of therapy resistance [300-303].	None	None
RRM2	Ribonucleotide Reductase regulatory subunit M2 (RRM2) is one of two subunits that form ribonucleotide reductase. RRM2 catalyzes the conversion of ribonucleotides into desoxyribonucleotides [304].	RRM2 is overexpressed in glioblastoma [305], and its overexpression correlates with reduced patient survival and increased resistance to therapy [305-308]. Similar data are reported for other cancer entities [309-315]	Hydroxyurea COH29 [316] Osalmid [317] Pectolinarigenin [307] 4-Hydroxysalicylanilide [318] (for review see [312])	4-Hydroxysalicylanilide was tested in a phase I trial on patients with multiple myeloma (NCT03670173) [318]. No trial data on glioblastoma so far.
SLC7A11	Solute Carrier family 7 member 11 (SLC7A11) is part of a heteromeric anionic amino acid transporter with specificity for cysteine and glutamate. In this system called Xc(-), the anionic form of cysteine is imported into cells in exchange for glutamate [319-321].	SLC7A11 is frequently overexpressed in glioblastoma [322], and its overexpression correlates with reduced survival and poor prognosis [308, 322]. Mechanistically, overexpression of SLC7A11 increases the stem cell-like properties of glioblastoma cells [323]. Similar findings were published for other cancer entities [319, 324].	No specific inhibitor of SLC7A11 available so far. Inhibitors of the Xc(-) system are readily available [96, 97], e.g. Erastin [325] Sulfasalazine [326] Imidazole ketone erastin [327] HG106 [328]	None
SLC1A5/ASCT2	Solute Carrier family 1 member 5 (SLC1A5/ASCT2) is a sodium-dependent neutral amino acid transporter with high specifity for glutamine. As such, SLC1A5 plays an important role in the redox homeostasis in cells [329].	SLC1A5/ASCT2 contributes to tumorigenesis and tumor progression in several cancer entities including head-and-neck cancer, stomach cancer and liver cancer [330-335]. Variants of SLC1A5 were shown to reprogram cancer cells thereby facilitating therapy resistances [336]. SLC1A5/ASCT2 is also overexpressed in astrocytomas and glioblastomas [337, 338].	L-γ-Glutamyl-p-nitroanilide (GPNA) [339] V9302 [340] Sulfonamide/sulfonic acid ester scaffolds [341] Lc-proline biphenyl esters [342]	None

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