Supplemental Table 1. Association of HIF expression and patient mortality.

Cancer type	HIF-1/2α	References
Bladder	HIF-1α	1, 2
Brain	HIF-1α	3-8
	HIF-2α	9
Breast	HIF-1α	10-22
	HIF-2α	23, 24
Cervix	HIF-1α	25-29
Chondrosarcoma	HIF-2α	30
Colon	HIF-1α	31-35
Endometrial	HIF-1α	36, 37
Esophagus	HIF-1α	38-41
Gastric	HIF-1α	42-48
GIST, stomach	HIF-1α	49
Gynecological	HIF-1α	50
Head and neck-SCC	HIF-1α	51, 52
	HIF-2α	53
Hepatocellular	HIF-1α	54-58
	HIF-2α	59
Laryngeal	HIF-1α	60
Leukemia	HIF-1α	61-63
Liver	HIF-1α	64
Lung	HIF-1α	65-72
	HIF-2α	73, 74
Melanoma	HIF-2α	75
MDS	HIF-1α	76
Oral SCC	HIF-1α	77-82
Osteosarcoma	HIF-1α	83
Ovarian	HIF-1α	84-88
Pancreas	HIF-1α	89-94
	HIF-2α	93
Prostate	HIF-1α	95, 96
	HIF-2α	95
Rectal	HIF-1α	97-99
Renal	HIF-1α, HIF-2α	100
Urinary tract	HIF-1α	101

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Supplemental Table 2. Selected HIF target genes involved in metastasis.

Role in metastasis	*Type of encoded protein*	*Gene name*	*References*
Epithelial-mesenchymal transition (EMT) and tissue invasion	Transcription factor	SNAI1 (SNAIL) SNAI2 (SLUG) TWIST1, ZEB1, ZEB2 TCF3 EWS-FLI1 SMAD7 HEF1 (NEDD9)	1-2 3 4-7 6 8 9 10
	Receptor tyrosine kinase	AXL MET	11 12-14
	Transmembrane glycoprotein	CDCP1 CD44	15 16, 17
	ECM-modifying enzyme	P4HA1, P4HA2 PLOD2 ADAM12	18-20 21 22
	Scaffold protein	AKAP12	23
	Small GTPase	RAB22A	24
	G-protein coupled receptor	CXCR3, CXCR4 CXCR6, CXCR7 CCR1, CCR5, CCR7	25, 26 27, 28 25, 29, 30
	Chemokine/ cytokine	CSF1, CXCL16 HMGB1, CXCL8 (IL8)	25 31 32
Intravasation/circulation/ extravasation/metastasis	Histone modifier	JMJD2B, JMJD2C	33, 34
	Membrane protein	PLAUR (uPAR) ITGA5 AEG1 (MTDH) C1QBP ANGTPL4, L1CAM CD47 CD73 CAV1	35, 36 37 38 39 40 41-43 41, 44 45
	ECM modifier	MMP1, MMP2	36, 46, 47
	Metabolic enzyme	CKB GLS1	48 49
	Receptor / Signaling	RHOA, ROCK1 TRKB (NTRK2) PTGS2 (COX2)	50 51, 52 53, 54
	Growth factor	PDGFB PGF, VEGFA	55 25, 56
Pre-metastatic niche formation	ECM-modifying enzyme	LOX LOXL2, LOXL4	57-59 58, 59
	S100 protein	S100A8, S100A9	60, 61
Cancer stem cell specification and maintenance	Transporter	ABCB1 (MDR1) ABCG2 (BCRP) SLC7A11	62 63 64
	Enzyme	ALKBH5 DUSP9 GSTO1 PHGDH SIAH1 TERT GCLM	65, 66 67 68 69 70 71 72

	Membrane receptor	CD47 A2BR CALR	73 74 75
	S100 protein	S100A10	76
	Interleukin	IL6, IL8	32, 62
	Transcription factor	HES1, HEY1 REST SNAI1 WWTR1 ZNF217	77 78 1-2 70 66, 79
	Epigenetic modifier	KDM4C (JMJD2C) KDM6B (JMJD3) TET1, TET3	34 80 81, 82

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Supplemental Table 3. HIF target genes encoding mediators of immune evasion.

Gene	Protein	Mechanism of immune evasion	A/S/M*	References
BIRC2	BIRC2	Blocks NK and T cell recruitment	S	1, 2
CA9	CA9	Creates immunosuppressive acidic TME#	S/M	3-5
CCL20	CCL20	Mediates Treg recruitment		6, 7
CCL26	CCL26	Mediates recruitment of MDSCs and TAMs		8
CCL28	CCL28	Mediates Treg recruitment	A	9
CD47	CD47	Blocks phagocytosis of cancer cells	S	10-12
CD70	CD70	Induces T cell apoptosis	S	13-15
CD274	PDL1	Induces T cell exhaustion		11, 16, 17
CXCL1	CXCL1	Mediates recruitment of TAMs	A	18-20
CXCL5	CXCL5	Recruits immunosuppressive TANs^		21
CXCL12	SDF1	Recruits TAMs and MDSCs	A	22, 23
GAL3ST1	GCST	Increases platelet binding to cancer cells		24
NT5E	CD73	Generates immunosuppressive adenosine	A/S/M	11, 25-29
ENTPD1	CD39	Generates substrate for CD73	A	11, 29, 30
ENTPD2	CD39L1	Generates immunosuppressive AMP	M	29, 31
HAVCR2	TIM3	Induces T cell exhaustion		32-34
HLA-G	HLA-G	Inhibits NK and T cells		35, 36
IL10	IL10	Maintains Tregs; induces TAM polarization Inhibits dendritic cells	A	37-41
IL23	IL23	Stimulates Treg proliferation Increases IL10 and TGFb expression	M	42
LDHA	LDHA	Inhibits NK and T cell activity	M	43-45
MIR-25/93	mIR-25/93	Inhibits cGAS+ expression		46
NAMPT	NAMPT	Induces PDL1 expression	M	47, 48
NANOG	NANOG	Increases TGF-β** expression	S	49, 50
PDK1	PDK1	Inhibits pyruvate oxidation	M	51, 52
PGF	PGF	Promotes polarization of TAMs Inhibits DC maturation	A	53
SLC2A1	GLUT1	Mediates glucose uptake	M	54, 55
SLC6A8	SLC6A8	Induces macrophage polarization	M	56, 57
SLC16A3	*MCT4*	Pumps lactate out of cancer cells	M	58
STC1	STC1	Inhibits phagocytosis and T cell activation	S	59, 60
VEGFA	VEGF-A	Recruits TAMs; inhibits DC maturation	A	61-64
VSIR	VISTA	Promotes MDSC activity		65
VTCN1	B7-H4	Inhibits T cell proliferation Inhibits T cell cytokine production		66, 67

*A, angiogenesis; S, cancer stem cell specification; M, metabolism
#TME, tumor microenvironment
^TANs, tumor-associated neutrophils
+cGAS, cyclic guanosine monophosphate synthase
** TGF-β, transforming growth factor β

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Supplemental Table 4. Clinical trials of belzutifan registered at ClinicalTrials.gov.

NCT Identifier	Tumor type(s)[&]	Ph[#]	n[^]	Drugs[*]
02974738	Advanced solid tumors			Belzutifan
03401788	VHL-associated RCC	2	50	Belzutifan
03634540	ccRCC	2	118	Belzutifan + Cabozantinib
04195750	Advanced RCC	3	736	Belzutifan vs Everolimus
04489771	Advanced RCC	2	150	Belzutifan
04736706	Advanced ccRCC	3	1431	Belz + Pemb + Lenv vs Pemb + Lenv
04846920	Advanced ccRCC	1	52	Belzutifan
04924075	Pheochromocytoma Paraganglioma Pancreatic neuroendocrine	1	140	Belzutifan
04976634	Solid tumors	2	400	Belz + Pemb + Lenv
05030506	Advanced RCC	1	45	Belz + Pemb + Lenv
05239728	ccRCC s/p nephrectomy	3	1600	Belz + Pemb vs Pemb

[&]RCC, renal cell carcinoma; ccRCC, clear cell RCC
[#]Ph, phase 1, 2, or 3 trial
[^]n, number of subjects
[*]drug abbreviations: belzutifan (Belz), cabozantinib (Cabo), lenvatinib (Lenv), and pembrolizumab (Pemb)