Table S1. UM-targeted therapies against *GNAQ* and *GNA11* in preclinical studies and their outcomes.

Drug	Target Mechanisms	UM Sample Types	Validation Methods	Anti-tumor Actions	References
AEB071 (Sotrastaurin)	PKC	UM cell lines (C918, Mel202, Mel270, Mel285, Mel290, MUM-2C, OCM-1, OCM-3, OMM-GN11, OMM1.3, UPMD1, and 92.1) and UM PDXs	AA, ATM, PA, PCR, and WB	Promotes apoptosis, and G1 cell cycle arrest Inhibits tumor growth, and NF-κB activity	(Chen et al., 2014; Wu, Li, et al., 2012)
AEB071 (Sotrastaurin) + BYL719 (Alpelisib)	PKC + PI3Kα	UM cell lines (C918, Mel202, Mel270, Mel290, OMM1, OMM1.3, and 92.1) and UM PDXs	AA, ATM, VA, and WB	Synergistic effect between Sotrastaurin + Alpelisib relative to monotherapies (Increase apoptosis, and inhibit and tumor growth)	(Musi et al., 2014)
AEB071 (Sotrastaurin) + CGM097	PKC + MDM2	UM cell lines (Mel202, Mel285, Mel290, MM28, MM33, MM66, MP38, MP41, MP42, MP65, OMM1, OMM2.5, and 92.1) and UM PDXs	AA, ATM, PA, and WB	Additive effect between Sotrastaurin + CGM097 relative to monotherapies (Increase apoptosis, inhibit proliferation, and tumor growth)	(Carita et al., 2016)
AEB071 (Sotrastaurin) + RAD001 (Everolimus)	PKC + mTOR			Synergistic effect between Sotrastaurin + Everolimus relative to monotherapies (Increase apoptosis, inhibit proliferation, and tumor growth)	

AEB071 (Sotrastaurin) + MEK162 (Binimetinib)	PKC + MEK	UM cell lines (C918, Mel202, Mel270, Mel285, Mel290, MM28, MM33, MM66, MP38, MP41, MP42, MP65, MUM-2C, OMM-GN11, OMM1, OMM1.3, OMM2.5, UPMD1, and 92.1) and UM PDXs	AA, ATM, PA, and WB	Strong synergy between Sotrastaurin + Binimetinib compared to monotherapies. (Promote apoptosis, inhibit proliferation, and tumor growth)	(Carita et al., 2016; Chen et al., 2014)
AEB071 (Sotrastaurin) + PD-0325901 (Mirdametinib)		UM cell lines (C918, Mel202, Mel270, Mel285, Mel290, MUM-2C, OMM-GN11, OMM1.3, UPMD1, and 92.1) and UM PDXs		Strong synergy between Sotrastaurin + Mirdametinib compared to monotherapies. (Promote apoptosis, and inhibit proliferation)	(Chen et al., 2014)

AHT956	PKC	UM cell lines (C918, Mel202, Mel270, Mel285, Mel290, MUM-2C, OMM-GN11, OMM1.3, UPMD1, and 92.1)	PA, and WB	Promotes G1 cell cycle arrest	(Chen et al., 2014)
AZD6244 (Selumetinib)	MEK1/2	UM cell lines (C918, M619, Mel202, Mel270, Mel285, Mel290, MUM-2B, MUM-2C, OCM-1, OCM-1A, OCM-3, OMM1.3, and 92.1) and metastatic UM patient tumor tissues	MA, PA, PCR, and WB	Promotes G1 cell cycle arrest Inhibits migration, and proliferation	(Ambrosini et al., 2012; Wu, Zhu, et al., 2012)
AZD6244 (Selumetinib) + AZD8055	MEK1/2 + mTOR	UM cell lines (C918, Mel270, Mel290, OCM-1A, OCM-3, and 92.1) and UM PDXs	AA, ATM, BA, IHC, VA, and WB	Synergistic effect between Selumetinib + AZD8055 relative to monotherapies (Inhibit cell viability) Apoptosis and tumor regression was preferentially induced in *BRAF* mutant UM cell lines and xenografts models	(Ho et al., 2012)
AZD6244 (Selumetinib) + Dacarbazine	MEK1/2 + Alkylating agent			Non-significant synergy between Selumetinib + Dacarbazine	

AZD6244 (Selumetinib) + Docetaxel	MEK1/2 + Taxane	UM cell lines (MM28, MM66, MP38, MP41, MP46, and MP65) and UM PDXs	ATM, PD, PK, VA, and WB	Slight increase in ORR for Selumetinib + Docetaxel relative to monotherapies	(Decaudin et al., 2018)
AZD6244 (Selumetinib) + AZ6197	MEK1/2 + ERK			Significant increase in ORR for both Selumetinib + AZ6197 and Selumetinib + AZD2014 relative to monotherapies	
AZD6244 (Selumetinib) + AZD2014 (Vistusertib)	MEK1/2 + mTORC1/2				
AZD6244 (Selumetinib) + Enzastaurin	MEK1/2 + PKC	UM cell lines (C918, M619, Mel202, Mel285, MUM-2B, MUM-2C, OCM-1, OCM-1A, OCM-3, OMM1.3, and 92.1)	AA, PA, and WB	Increase in antiproliferative effects for Selumetinib + Enzastaurin relative to monotherapies	(Wu, Zhu, et al., 2012)
AZD6244 (Selumetinib) + GDC0941	MEK1/2 + PI3K	UM cell lines (Mel202, Mel285, Mel290, MM28, MM66, MP38, MP41, MP46, MP65, OMM1, OMM2.5, and 92.1)	AA, PA, and WB	Synergistic effect between Selumetinib + GDC0941 relative to monotherapies No induction of apoptosis	(Amirouchene-Angelozzi et al., 2016)

AZD6244 (Selumetinib) + MK2206	MEK1/2 + AKT	UM cell lines (C918, Mel202, Mel270, Mel290, OCM-1A, OMM1.3, and 92.1) and UM PDXs	AA, ATM, VA, and WB	Synergistic effect between Selumetinib + MK2206 relative to monotherapies (Promote autophagy, and inhibit tumor growth *in vivo*)	(Ambrosini et al., 2013)
Crizotinib	c-MET	UM cell lines (C918, Mel285, Mel290, OMM1, OMM1.3, and 92.1) and UM PDXs	ATM, IHC, LUCA, MA, PA, and WB	Inhibits migration, and proliferation Non-significant tumor growth inhibition in UM xenografts Prevents macrometastasis of UM cells from developing *in vivo*	(Surriga et al., 2013)
Enzastaurin	PKC	UM cell lines (C918, M619, Mel202, Mel285, MUM-2B, MUM-2C, OCM-1, OCM-1A, OCM-3, OMM1.3, and 92.1)	AA, PA, and WB	Promotes apoptosis, and G1 cell cycle arrest Inhibits proliferation	(Wu, Zhu, et al., 2012)
Enzastaurin + U0126	PKC + MEK1/2	UM cell lines (C918, M619, Mel202, Mel285, MUM-2B, MUM-2C, OCM-1, OCM-1A, OCM-3, OMM1.3, and 92.1)	AA, PA, and WB	Increase in antiproliferative effects for Enzastaurin + U0126 relative to monotherapies	(Wu, Zhu, et al., 2012)

FR900359	GDI ERK1/2	UM cell lines (HCmel12, Mel202, OCM-1A, OCM-3, OMM1.3, UM002B, and 92.1)	AA, BA, IF, LUCA, MA, PA, PCR, and WB	Promotes apoptosis, G1 cell cycle arrest, and melanocytic re-differentiation Inhibits colony formation, migration, and proliferation	(Lapadula et al., 2019; Onken et al., 2018; Schrage et al., 2015)
GSK1120212 (Trametinib)	MEK1/2	UM cell lines (Mel202, MM28, MM66, MP38, MP41, MP46, OMM1.3, OMM1.5, UPMD1, and 92.1) and UM PDXs	AA, ATM, IHC, LUCA, PA, PCR, and WB	Reduced sensitivity of UM cell lines compared to CM cell lines Promotes apoptosis Induces tumor stasis	(Ma et al., 2021; Paradis et al., 2021)
GSK1120212 (Trametinib) + GSK2126458	MEK1/2 + PI3K	UM cell lines (Mel202, Mel270, Mel285, Mel290, OMM1, UPMD1, UPMD2, and 92.1)	AA, PA, and WB	Greater effect between Trametinib + GSK2126458 relative to monotherapies (Promotes apoptosis, and cell cycle arrest)	(Khalili et al., 2012)
GSK1120212 (Trametinib) + LSX196 (IDE196 = Darovasertib)	MEK1/2 + PKC	UM cell lines (Mel202, MM66, MP41, MP46, OMM1.3, UPMD1, and 92.1)	AA, LUCA, PA, PCR, and WB	Strong synergy between Trametinib + LSX196	(Ma et al., 2021)
GSK1120212 (Trametinib) +				Limited synergy between Trametinib + VS-4718 Vs	

VS-4718 (PND-1186)	MEK1/2 + FAK	UM cell lines (Mel202, MM28, MM66, MP38, MP41, MP46, OMM1.3, OMM1.5, UPMD1, and 92.1) and UM PDXs	AA, ATM, IHC, LUCA, PA, PCR, and WB	Synergistic effect between Trametinib + VS-4718 (Increase apoptosis, inhibit proliferation including cancer initiating cells, and induce tumor regression and cytotoxic effect in UM xenografts and liver metastasis models)	(Ma et al., 2021; Paradis et al., 2021)
GSK1120212 (Trametinib) + RAD001 (Everolimus)	MEK1/2 + mTOR	UM cell lines (Mel202, MM28, MM33, MM66, MP38, MP41, MP46, MP65, OMM1, OMM2.5, and 92.1)	AA, PA, PCR, and WB	Moderate synergy between Trametinib + Everolimus No induction of apoptosis (except in 92.1 cell line)	(Amirouchene-Angelozzi et al., 2014)
NAV-2729	ARF6	UM cell lines (Mel202, and 92.1), UM PDXs, and UM patient tumor tissues	ATM, IA, IF, LUCA, NEA, PA, PCR, and WB	Inhibits colony formation, proliferation, and tumor growth	(Yoo et al., 2016)
PF562771	FAK	UM cell lines (Mel270, and OMM1.3)	IF, LUCA, PCR, VA, and WB	Inhibits cell viability	(Feng et al., 2019)

RAD001 (Everolimus)	mTOR	UM cell lines (Mel202, MM28, MM33, MM66, MP38, MP41, MP46, MP65, OMM1, OMM2.5, and 92.1), UM PDXs, and UM patient tumor tissues	AA, ATM, PA, PCR, and WB	Inhibits proliferation, and tumor growth	(Amirouchene-Angelozzi et al., 2014)
RAD001 (Everolimus) + GDC0941	mTOR + PI3K	UM cell lines (Mel202, Mel285, Mel290, MM28, MM66, MP38, MP41, MP46, MP65, OMM1, OMM2.5, and 92.1) and UM PDXs	AA, ATM, PA, and WB	Synergistic effect between Everolimus + GDC0941 relative to monotherapies (Increase apoptosis, and enhance anti-tumor activity *in vivo*)	(Amirouchene-Angelozzi et al., 2016)
VS-4718 (PND-1186)	FAK	UM cell lines (Mel202, Mel270, MM28, MP38, MP41, MP46, OMM1.3, OMM1.5, and 92.1) and UM PDXs	AA, ATM, IF, IHC, LUCA, PA, PCR, and WB	Promotes apoptosis Inhibits colony formation, and proliferation Reduces tumor size	(Feng et al., 2019; Paradis et al., 2021)

VS-4718 (PND-1186) + LSX196 (IDE196 = Darovasertib)	FAK + PKC	UM cell lines (Mel202, MM66, MP41, MP46, OMM1.3, UPMD1, and 92.1)	AA, LUCA, PA, PCR, and WB	Limited synergy between VS-4718 + LSX196	(Ma et al., 2021)
VS-4718 (PND-1186) + VS-6766	FAK + RAF/MEK	UM cell lines (MM28, MP38, MP41, MP46, OMM1.3, OMM1.5, and 92.1)	PA, LUCA, and WB	Synergistic antiproliferative effect for VS-4718 + VS-6766	(Paradis et al., 2021)
VS-6063 (Defactinib) + VS-6766	FAK + RAF/MEK	UM cell lines (MM28, MP38, MP41, MP46, OMM1.3, OMM1.5, and 92.1)	PA, LUCA, and WB	Synergistic antiproliferative effect for VS-6063 + VS-6766	(Paradis et al., 2021)
YM-254890	GDI	UM cell lines (Mel202, MM66, MP41, MP46, OMM1.3, UPMD1, and 92.1)	AA, LUCA, PA, PCR, and WB	Promotes apoptosis Inhibits colony formation, and proliferation	(Ma et al., 2021)

Abbreviations: AA: apoptosis assay; ATM: animal tumor model; BA: binding assay; CM: cutaneous melanoma; GDI: guanine nucleotide dissociation inhibitor; IF: immunofluorescence; IHC: immunohistochemistry; LUCA: luciferase assay; MA: migration assay; NEA: nucleotide exchange assay; NF-κB: nuclear factor of kappa B; ORR: overall response rate; PA: proliferation assay; PCR: polymerase chain reaction; PD: pharmacodynamic assay; PDX: patient derived xenograft; PK: pharmacokinetic assay; VA: viability assay; WB: western blotting.

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