

Supplementary Material: Perspective on the Use of DNA Repair Inhibitors as a Tool for Imaging and Radionuclide Therapy of Glioblastoma

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Table S1. Overview of cancer clinical trials of ATMi and ATRi.

Target	Drug	Combined Therapy*	Clinical Phase	Condition/Disease	Biomarker Selection/Evaluation	Trial Number (Status) Reference
ATM	AZD1390	RT	I	GB, Brain neoplasms, malignant LMD	/	NCT03423628 (r)
ATM	AZD0156	Olaparib/Irinotecan/ Fluorouracil/Leucovorin	I	AST (including glioma)	/	NCT02588105 (anr)
ATM	KU-60019	CK2 (CX4945)	NA	Kidney C	/	NCT03571438 (r)
ATM	M3541	RT	I	ST	/	NCT03225105 (c)
ATR	VX-970 (VE-822, M6620, berzosertib, Merck®)	/	II	AST	ATRX, ATM, HRR, BRCA, MYC, FBXW7, or cyclin E changes; γH2AX, phospho-CHK1	NCT03718091 (anr)
		Carboplatin/Gemcitabine	II	OC, PFTC	/	NCT02595892 (anr)
		Topotecan	II	SCLC and SCC	/	NCT03896503 (s)
		Cisplatin/ Gemcitabine	II	mUC	p53/p21/ERCC2 mut	NCT02567409 (anr)
		Irinotecan	II	GEJC	TP53 mut, DDR mut	NCT03641313 (s)
		Carboplatin/ Docetaxel	II	mCRPC	DNA damage assay, HRR mut	NCT03517969 (anr)
		Carboplatin/Gemcitabine/ Pembrolizumab	I/II	NSCLC	ATM mut	NCT04216316 (r)
		Topotecan	I/II	SCC	/	NCT02487095 (anr)
		Avelumab	I/II	mST/uST	DDR mut	NCT04266912 (r)
		Veliparib/cisplatin	I	AST	γH2AX/RAD51/NBS1/pKAP-1 (DNA damage and apoptosis)	NCT02723864 (c)
		Whole brain RT	I	BM-NSCLC/SCLC/ NET	ATR/CHK1/RAD51	NCT02589522 (anr)
		RT	I	HER2 Negative BC	DNA damage assay, HRR mut	NCT04052555 (r)
		Carboplatin/Gemcitabine	I	OC, PFTC	ATR	NCT02627443 (anr)
		Cisplatin/RT	I	HNSCC	DNA damage	NCT02567422 (anr)
		Irinotecan	I	mST/uST	DDR mut	NCT02595931 (r)
ATR	AZD6738 (ceralasertib, Astra-Zeneca®)	Cisplatin/Carboplatin/ Etoposide/ Durvalumab	II	Advanced SCLC	/	NCT04699838 (r)
		Durvalumab/Olaparib	II	Biliary Tract C	/	NCT04298021 (r)
		Cediranib/ Olaparib	II	BC	HER2, BRCA	NCT04090567 (r)

		Olaparib/AZD1775/ AZD5363	II	AST	IDH1-2/ATM/CHK2/ APOBEC /MRE11/PTEN/PIK3CA/AKT/ ARID1A/TP53/KRAS	NCT02576444 (anr)
		Durvalumab	II	Biliary Tract C	/	NCT04298008 (r)
		Durvalumab	II	mST	/	NCT03780608 (anr)
		Durvalumab	II	NSCLC	/	NCT03334617 (r)
		Durvalumab	II	Advanced NSCLC	Included (ns)	NCT03833440 (r)
		Durvalumab	II	NSCLC	Included (ns)	NCT02664935 (anr)
		Olaparib	II	Relapsed SCLC	/	NCT03428607(c)
		Olaparib	II	Recurrent OC	BRCA/other HRD mut	NCT03462342 (r)
		Olaparib	II	Gynaecological C	ARID1A loss	NCT04065269 (r)
		Olaparib	II	ST	IDH1/IDH2 mut	NCT03878095 (r)
		Olaparib	II	mCRPC	BRCA, ATM	NCT03787680 (anr)
		Olaparib	II	Advanced SCLC	/	NCT02937818 (anr)
		Olaparib	II	Osteosarcoma	/	NCT04417062 (r)
		Olaparib	II	Advanced BC	ctDNA screening	NCT03182634 (r)
		Olaparib	II	mTNBC	BRCA1-2/HRR mut	NCT03330847 (anr)
		Olaparib	II	Selected ST	BAF250a/ARID1A/ATM	NCT03682289 (r)
		/	II	TNBC	Gene signature	NCT03740893 (r)
		/	II	AST	ATM mut	NCT04564027 (r)
		Paclitaxel	I (+)	Refractory C	/	[1]
		Carboplatin	I (+)	AST	/	[2]
		Olaparib	I	HNSCC	25-gene signature	NCT03022409 (c)
		Gemcitabine	I	AST	/	NCT03669601 (r)
		RT	I	ST	DDR mut	NCT02223923 (unknown)
		DS-8201a	I	AST	HER2/TP53/ATM/RAS	NCT04704661 (r)
		Acalabrutinib	I	CLL	/	NCT03328273 (anr)
ATR	VX-803 (M4344, Merck®)	Carboplatin	I	AST	ARID1A/ATRX/DAXX/ ATM mut	NCT02278250 (c)
		Niraparib	I	PARP-resistant recurrent OC	/	NCT04149145 (anr)
		Pembrolizumab/RT	I	Recurrent HNSCC	/	NCT04576091 (r)
		Pembrolizumab	I	AST	/	NCT04095273 (r)
		/	I	AST and Lymphomas	/	NCT03188965 (r)
ATR	BAY1895344 (elimusertib, Bayer®)	Niraparib	I	AST and OC	/	NCT04267939 (r)
		Fluorouracil/Irinotecan/ Leuco- vorin	I	Stomach and Intestines C	/	NCT04535401 (r)
		Cisplatin/Gemcitabine	I	AST – UC	/	NCT04491942 (s)
		Gemcitabine	I	Pancreatic C, OC, AST	/	NCT04616534 (s)
		Irinotecan/Topotecan	I	NSCLC, PD-NEC, PDA	/	NCT04514497 (r)
ATR	M1774	Niraparib	I	mST or locally AST/uST	ARID1A/ATRX/DAXX/ATM mut	NCT04170153 (r)
ATR	RP-3500	Talazoparib/Gemcitabine	I/II	AST	ATRI sensitizing mut, DNA damage	NCT04497116 (r)

Applications in glioblastoma are highlighted in bold. * AZD1775 (WEE1i), AZD5363 (AKTi), Carboplatin/Cisplatin/Docetaxel/Etoposide/Fluorouracil/Gemcitabine/Irinotecan/Paclitaxel (chemotherapy), Leucovorin (folate analog), CX4945 (CK2 inhibitor), DS-8201a/Topotecan (topoisomerase I inhibitor), Cediranib (VEGFRi), Durvalumab/Pembrolizumab/Avelumab

(anti-PD-L1), Olaparib/Talazoparib/Niraparib/Veliparib (PARPi), Acalabrutinib (Bruton's TKI). Abbreviations: anr (active non recruiting), AST (advanced solid tumors), BC (breast cancer), BM (brain metastases), C (cancer), c (completed), CLL (chronic lymphocytic leukemia), CRPC (castration-resistant prostate cancer), DDR (DNA damage repair), GB (glioblastoma), GEJC (gastric or gastroesophageal junction cancer), HNSCC (head and neck squamous cell carcinoma), HRR (homologous recombination repair), LMD (malignant leptomenin-geal disease), m (metastatic), mut (mutant/mutated/mutations), NA (not applicable), NET (neuroendocrine tumors), ns (not specified), NSCLC (non-small cell lung cancer), OC (ovarian cancer), PDA (pancreatic adenocarcinoma), PD-NEC (poorly differentiated neuroendocrine carcinoma), PFTC (peritoneal, or fallopian tube cancer), r (recruiting), RT (radiotherapy), s (suspended), SCC (small cell cancer), SCLC (small cell lung cancer), ST (solid tumours), TNBC (triple-negative breast cancer), u (unresectable), UC (urothelial cancer), * “BRCAness” signature.

Table S2. Cancer radiopharmaceuticals targeting DDR kinases.

Target	Drug	Type	Label	Stage	Study Population/Cancer Type	Reference
ATM	AZD1390	SM	[¹¹ C]	C	Healthy subjects	[3,4]
	AZD1390 and AZD0156	SM	[¹¹ C]	PC	NHP	[5]
ATR	VE-821	SM	[¹⁸ F]	PC	GB	[6]
CHK1/2	Prexasertib (LY2606368)	SM	[¹⁴ C]	C	AST	[7]
	LY2603618 (rabusertib)	SM	[¹⁴ C]	C	AST	[8]
CHK1	GDC-0425	SM	[¹⁴ C]	PC	Healthy rats	[9]
PARP	Olaparib	SM	[¹⁸ F]	C	Non-specified brain tumour type	[4]
				C	Non-specified brain tumour type, GB	[10]
				PC	GB	[11–14]
				C	H&N	[4,15]
				PC	PaC, NHP	[16,17]
				PC	OC, BC, PaC, SCLC, H&N, DLBCL	[18–23]
			[¹²³ I]	PC	GB	[24]
			[¹³¹ I]	PC	GB	[25]
			[⁶⁴ Cu]	PC	Mesothelioma	[26]
			[¹¹ C]	Syn	/	[27]
	Rucaparib	SM	[¹⁸ F]	Talazoparib	PrC	[28]
				C	OC, PeC, PrC, PaC, BC, FTC	[4,29,30]
				C	GB	[4]
				PC	BC, OC, PrC	[29,31–34]
				PC	PrC	[31]
			[¹²⁵ I]	PC	OC, HCC, BC, NB	[35–38]
			[¹²⁵ I]	PC	BC	[36]
			[¹⁴ C]	C	AST	[39]
			[²¹¹ At]	PC	NB	[40,41]
	Pamiparib	SM	[¹⁴ C]	C	Advanced cancer	[42]
	MAPi*	SM	[¹²³ I]	PC	GB	[43]
	I2-PARPi	SM	[¹³¹ I], [¹²⁴ I]	PC	GB	[44]

	Pirenzepine and metabolite LS 75	SM	[¹⁸ F]	PC	Syn	[45]
DNA-PK	Samotolisib derivative (LY3023414)	SM	[¹⁴ C]	C	Healthy subjects	[4]
	chromen-4 derivatives	SM	[¹¹ C]	Syn	/	[46]

Therapeutic radionuclides are highlighted in italics. Applications in glioblastoma are highlighted in bold. *Meitner-Auger PARP1 inhibitor. Abbreviations: AST (advanced solid tumours), BC (breast cancer), C (clinical study), DLBCL (diffuse large B-cell lymphoma), FTC (fallopian tube cancer), GB (glioblastoma), H&N (head and neck cancer), HCC (hepatocellular carcinoma), NB (neuroblastoma), NHP (non-human primates), OC (ovarian cancer), PaC (pancreas cancer), PC (preclinical study), PeC (peritoneal cancer), PrC (prostate cancer), SCLC (small cell lung cancer), Syn (only synthesized).

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