

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

Liesbeth Everix, Shankari Nair, Cathryn H. S. Driver, Ingeborg Goethals, Mike M. Sathekge, Thomas Ebenhan, Charlot Vandevorode and Julie Bolcaen

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]
			[¹²³ I]	PC	PaC, NHP	[16,17]
				PC	OC, BC, PaC, SCLC, H&N, DLBCL	[18–23]
				PC	GB	[24]
				PC	GB	[25]
			[⁶⁴ Cu]	PC	Mesothelioma	[26]
				[¹¹ C]	Syn	[27]
	Rucaparib	SM	[¹⁸ F]	PC	PrC	[28]
				C	OC, PeC, PrC, PaC, BC, FTC	[4,29,30]
			[¹²⁵ I]	C	GB	[4]
				PC	BC, OC, PrC	[29,31–34]
			[¹⁴ C]	PC	PrC	[31]
				PC	OC, HCC, BC, NB	[35–38]
			[²¹¹ At]	PC	BC	[36]
				C	AST	[39]
			[¹³¹ I], [¹²⁴ I]	PC	NB	[40,41]
				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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