Profiling of PARP1-selective inhibitor DSB2455 in HR deficient and proficient cancer models as monotherapy and in combination

McGuinness BE#, Cowley PM, Campbell GM and Wise A

Duke Street Bio Ltd., 2 Duke St, London, UK

Abstract 346 2024

Background

First-generation non-selective PARP1/2 inhibitors have provided significant therapeutic benefit to patients whose tumours exhibit homologous repair (HR) deficiencies including BRCA mutations. However, their use has been associated with haematological toxicities that have restricted their application, particularly in combination with standard-of-care chemotherapy.

We have previously described the initial characterisation of a novel, potent and highly selective CNS-penetrant PARP1 inhibitor, DSB2455. Given that PARP2 has been shown to drive haematoxicity, this second-generation PARP1-selective approach offers a significant opportunity to enable combination approaches with chemotherapy, radiotherapy and targeted agents thus fulfilling the original mission of PARP inhibitors as chemo- and radio-sensitisers, and also expands the addressable patient population by freeing PARP1-selective inhibitor use from HR alteration dependency.

We demonstrate the potential for DSB2455 to improve treatment efficacy and support its clinical development both as monotherapy and as a chemo-sensitiser in combination with standard-of-care chemotherapy and targeted agents. The data also afford the opportunity to enable efficacy of DSB2455 in HR proficient settings, thus significantly expanding its therapeutic utility and patient reach.

In vitro Potency & ADME

		DSB2455	Olaparib	Saruparib
PARP1 Biochemical Binding (PARP2 Selectivity)	K_D (nM)	0.6 (1300-fold)	0.8 (0.6-fold)	0.7 (60-fold)
PARP1 NanoBRET (PARP2 Selectivity)		1.1 (>4,000-fold)	3.0 (0.7-fold)	1.6 (180-fold)
MDA-MB-436				
7 Day Viability (Cell Titer Glo)	IC_{50} (nM)	3	26	1
DLD1 BRCA2$^{-/-}$				
7 Day Viability (Cell Titer Glo)		7	65	2
PARP1 Chromatin Trapping		1.9	39	0.7
ADME				
Mics CLint / Heps CLint		<7.4	0.16	
Plasma Stability $T_{1/2}$ / Plasma Protein Binding		>373	88.6	
CYP Inhibition, 5 isoforms		>50		
Caco-2 A→B / Efflux Ratio		4.7	5.4	

Table 1. DSB2455 is a potent inhibitor of PARP1 in biochemical and cell-based assays with high selectivity over PARP2, with excellent *in vitro* ADME.

Liver mics, µL/min/mg; Heps, µL/min/10^6 cells; PS, plasma stability, mins; PPB, plasma protein binding, %; CYP inhibition, IC_{50}, µM; Caco-2, 10^{-6} cm/s;

In vitro Synergy Studies

Table 2. A panel of cell lines were treated with increasing concentrations of DSB2455 and the topoisomerase-I inhibitor, **SN38**, or **Camonsertib** and cell viability was assessed at 48 hr by Cell Titer Glo viability assay. Synergy between the two compounds was assessed using Synergy Finder software.[1] Calculation of the highest synergistic area (HSA) predicted synergy between DSB2455 and **SN38** or **Camonsertib** across the panel of cell lines tested.

DSB2455 + SN38

SCLC Lines	Score
DMS-79$	14.16
NCI-H1341$	14.14
NCI-H2029	10.40
NCI-H2227	9.84
NCI-H1694‡	9.7
NCI-H841	9.2
NCI-H146	7.53
NCI-H211‡	6.31
NCI-H446	5.59
NCI-H209	4.29
NCI-H1048‡	3.39

DSB2455 + Camonsertib

Cell Line	Score	Cell Line	Score	Cell Line	Score
NCI-H520⌘	16.7	OVCAR 3⌘	11.8	HS 695T*	9.4
HCC 1500*	16.4	NCI-H23	11.6	Capan-1*	9.3
NCI-H1373#	14.5	HCC 38*	11.2	IGR-OV-1*	8.7
NCI-H1838*	14.5	TOV112D	10.5	HCC 366*	8.7
MX-1	14.3	HCC 1143	10.4	LC-2/AD#	8.4
HCC 1937	13.6	EFM-192A*	10.2	HCC 78#	8.0
BT-20*	12.9	KO52†	9.8	EFO 27⌘	8.0
SK-BR-3⌘	12.7	CAOV-3	9.7	A2780 cis*	7.8
HDQ-P1	12.3	NCI-H441#	9.6	HCC 1954⌘	7.8
MCF7	12.2	SKOV-3⌘	9.6	A2780*	7.6
PC-3⌘	12.0	OVCAR 5⌘	9.5	PA-1⌘	7.4

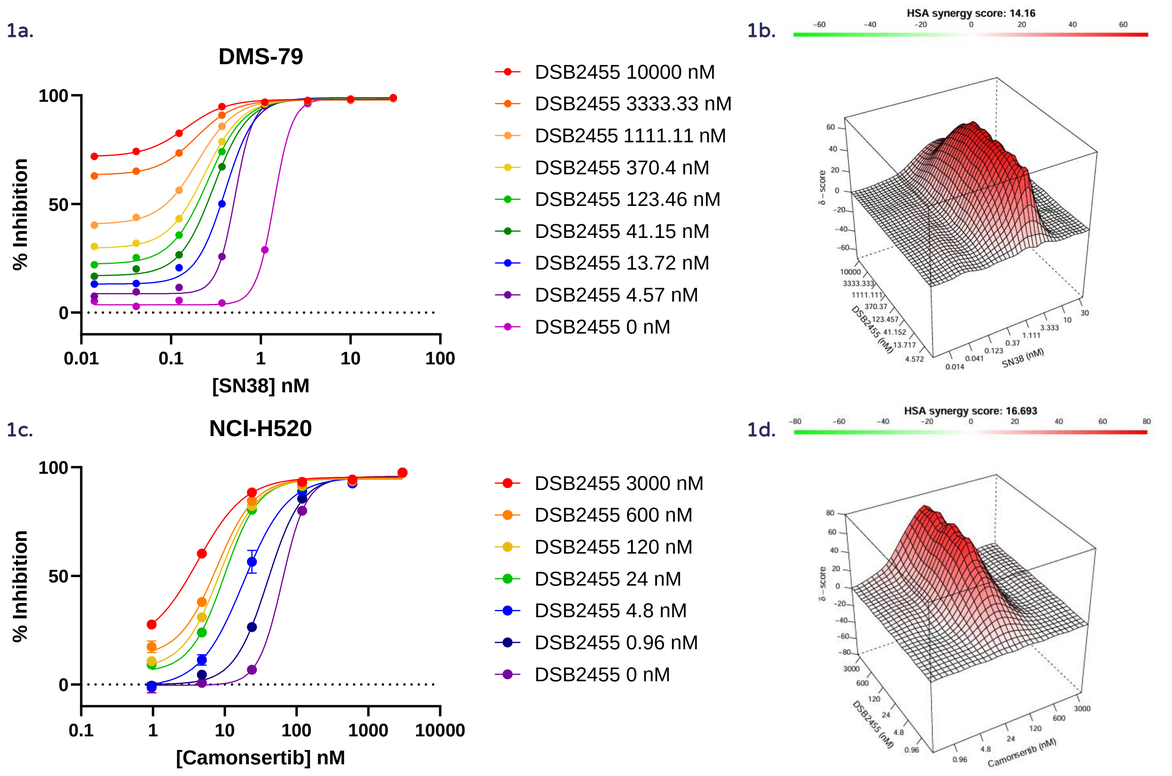
‡ BRCA1 / BRCA2 del
$ PTEN del

Interpretation of Synergy Scoring
<-10 : Antagonistic -10 – 10 : Additive >10 : Synergistic

* ATM mut
⌘ ATM amp
U2AF1 mut
† SRSF2 mut

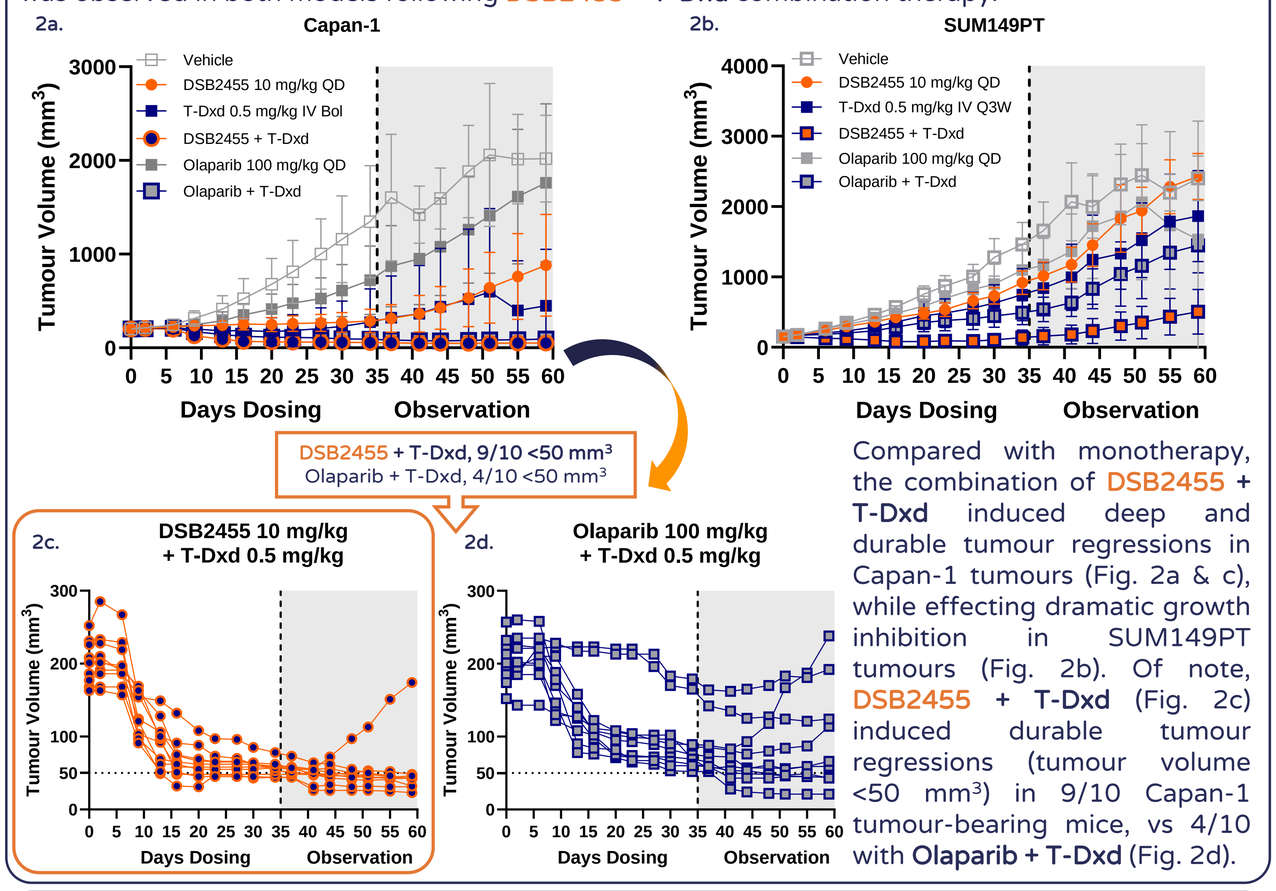
1. Ianevski et al (2022) Nucleic Acids Research. doi: 10.1093/nar/gkac382

Figure 1. Serial dilutions of DSB2455 + **SN38** (a & b) or DSB2455 + **Camonsertib** (c & d) were applied to cells in a chequerboard design for 48hrs. Cell viability was then determined by Cell Titer Glo. Increasing concentrations of DSB2455 enhanced cytotoxicity of the combination compounds in both SCLC cell line DMS-79 (a) & NSCLC cell line NCI-H520 (c), while demonstrating excellent synergy scores in Synergy Finder (b & d).



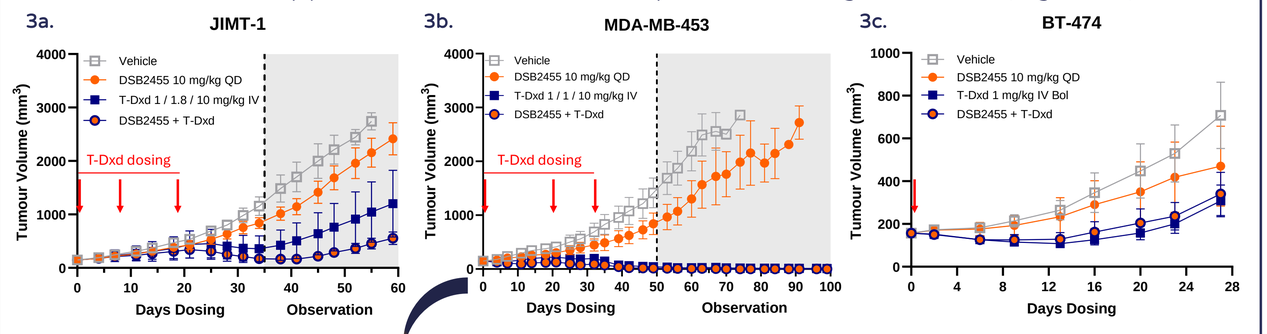
In vivo Combination Studies

Figure 2. Once daily oral administration of DSB2455 was given in combination with iv ADC, **Trastuzumab deruxtecan (T-Dxd)**, to BALB/c mice bearing (a) Capan-1 or (b) SUM149PT xenografts. Treatments were initiated when tumours reached 200 mm^3 or 150 mm^3, respectively. 35 days' dosing was followed by 25 days' treatment-free observation. Durable tumour suppression was observed in both models following DSB2455 + **T-Dxd** combination therapy.



Compared with monotherapy, the combination of DSB2455 + **T-Dxd** induced deep and durable tumour regressions in Capan-1 tumours (Fig. 2a & c), while effecting dramatic growth inhibition in SUM149PT tumours (Fig. 2b). Of note, DSB2455 + **T-Dxd** (Fig. 2c) induced durable tumour regressions (tumour volume <50 mm^3) in 9/10 Capan-1 tumour-bearing mice, vs 4/10 with **Olaparib + T-Dxd** (Fig. 2d).

Figure 3. HR-proficient xenografts of breast cancer lines (a) JIMT-1, (b) MDA-MB-453 & (c) BT-474, were established in the right flanks of NOD-SCID, NCG and NOD-SCID mice, respectively. Treatments were initiated when tumours reached 150 mm^3. Anti-tumour efficacy of DSB2455 + **T-Dxd** combination therapy was observed in 2 of 3 HR proficient xenograft models (Fig. 3a–c).



Most notably, DSB2455 + **T-Dxd** combination treatment led to complete regression in 100% of MDA-MB-453 tumour-bearing mice (Fig. 3d). This was maintained following cessation of treatment, while only 38% of **T-Dxd** monotherapy-treated mice achieved complete remission (Fig. 3e).

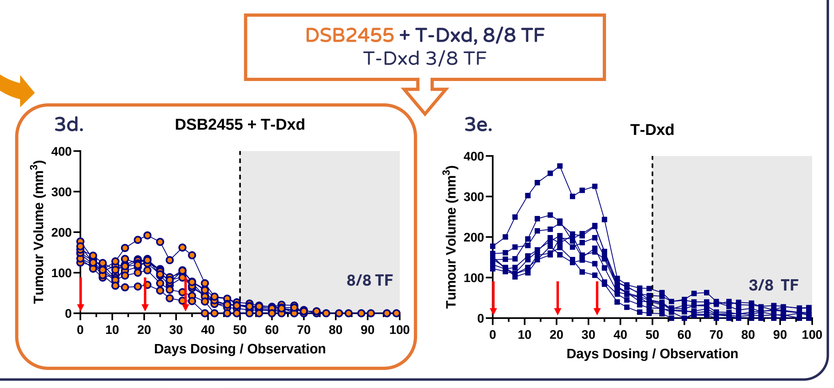


Figure 4. DSB2455 treatment in combination with ATR inhibitor **Camonsertib** was also investigated in the SUM149PT xenograft model. Once daily dosing of DSB2455 + intermittent **Camonsertib** (3 on/4 off) induced dramatic tumour regression that was maintained for 25 days following cessation of treatment.

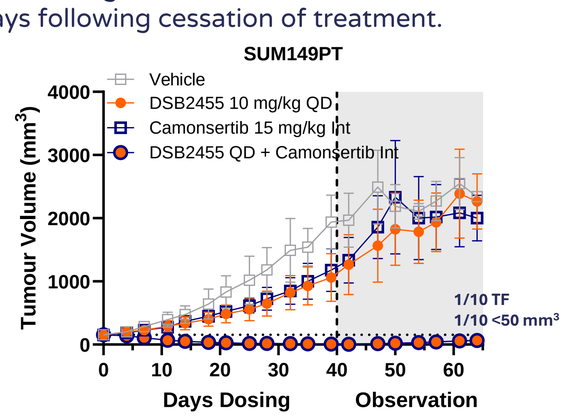
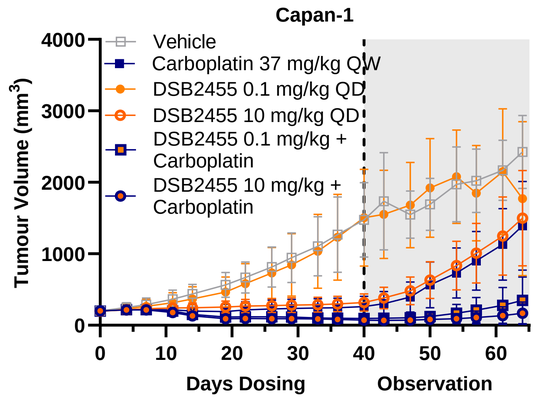


Figure 5. DSB2455 at doses as low as 0.1 mg/kg enhanced the efficacy of **Carboplatin** treatment, leading to prolonged tumour suppression after cessation of treatment versus **Carboplatin** monotherapy. DSB2455 monotherapy at 10 mg/kg was equally efficacious with **Carboplatin**.



Conclusions

- The highly selective nature of the next generation PARP1 inhibitor DSB2455 provides the opportunity to combine PARP1 inhibition with radiotherapy, standard-of-care chemotherapy and targeted agents, where first generation approaches were limited by PARP2 inhibition-mediated toxicities.
- In addition to its efficacy as monotherapy, DSB2455 can be successfully combined with **T-Dxd**, **Camonsertib** and **Carboplatin** to improve treatment outcomes.
- DSB2455 + **T-Dxd** combination therapy demonstrated efficacy in 2 of 3 HR proficient models, thus expanding the utility of this class of compounds and increasing treatment options for a wider population of patients.
- These data support the clinical development of PARP1-selective inhibitor DSB2455 as both monotherapy and as a chemo-sensitizer, where it may enhance the therapeutic effect of currently approved treatments.

Acknowledgements

Biochemical, biophysical and nanoBRET assays were carried out by Proteros Biostructures GmbH; *in vitro* biology, ADME and PK studies were conducted by BioDuro-Sundia; chromatin trapping was performed by Sai Life Sciences; SN38 synergy studies and *in vivo* studies were performed by Pharmaron; Camonsertib synergy studies were performed by Crown Biosciences.

#Corresponding Author
Barry McGuinness, PhD.
COO, Duke Street Bio Ltd.
bmcguinness@dukesb.com;
www.dukesb.com