An SN38 dendrimer nanoparticle, DEP® irinotecan (SN38-SPL9111), demonstrates efficacy in mouse models of gastrointestinal cancer and augments anti-tumor effects of immune checkpoint blockade and PARP inhibition

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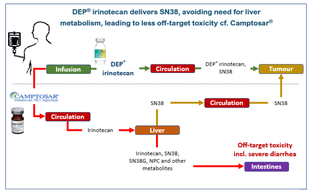
Background

Irinotecan is a topoisomerase 1 inhibitor pro-drug used to treat gastrointestinal (GI) cancers including first line treatment for both colorectal cancer (CRC) (as part of the FOLFIRI plus monoclonal antibody (mAb) regimen), and pancreatic cancer (FOLFIRINOX regimen). However, irinotecan causes severe, dose-limiting side effects, including diarrhea and neutropenia. DEP® irinotecan is a highly optimized polylysine **D**endrimer **E**nhanced **P**roduct (DEP®) nanoparticle conjugate of the irinotecan active metabolite, SN38, which avoids liver conversion of irinotecan to SN38 and achieves preferential tumor targeting. DEP® irinotecan is in phase 2 clinical investigation as monotherapy and combination therapy in patients with solid tumors (EudraCT no: 2019-001318-40). SN38 is known to enhance efficacy of immune checkpoint blockade (ICB) via effects on immune cells in the tumor microenvironment. Here, we evaluated the anti-tumor effects of DEP® irinotecan alone or in combination with either ICB (anti-programmed cell death-1 [PD-1] mAb) or poly adenosine diphosphate (ADP) ribose polymerase (PARP) inhibition (olaparib) in mouse models of GI cancer.



Materials and Methods

DEP® irinotecan (SN38-SPL9111) (Starpharma). DBL™-Irinotecan (irinotecan hydrochloride trihydrate) (Hospira). Olaparib (MedChemExpress) solubilised in DMSO and oral formulation prepared (5 mg/mL) in 10% DMSO:15% (2-Hydroxypropyl)-P-cyclodextrin in sterile water. Female mice were inoculated SC with tumor cells in 1:1 PBS:Matrigel (xenografts), or PBS alone (allografts), unless otherwise stated. Mice were randomized to treatment groups the day prior to start of therapy (d0). Drug doses expressed in mg/kg of body weight and dose corresponds to SN38 equivalents (w/w), where relevant. Mice were weighed and tumors measured twice weekly using electronic calipers, unless otherwise stated. Tumor volume (mm^3) was calculated as length (mm)/2 x width $(mm)^2$. DEP® irinotecan was delivered IV on days 1, 8, 15, unless otherwise stated. Immune checkpoint inhibitors were delivered as stated in Figure Legends. Toleration of drug was bodyweight loss ≤ 15%. Tumor volume body weights are expressed as mean ± SEM.

Results

DEP® IRINOTECAN VS IRINOTECAN

Figure 1A: DEP® irinotecan is superior to irinotecan (Camptosar®) in suppressing growth of HT29 colorectal cancer xenografts. Immunocompromised BALB/c nude mice were inoculated with HT29 cells ($5x10^6$) and therapy delivered on days 1, 8, 15, and 21 (vertical dashed lines). N=8 per group.

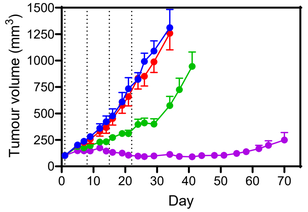


Figure 1B: DEP® irinotecan is well tolerated in HT29 tumor bearing mice. Data are presented as % body weight change from day 0.

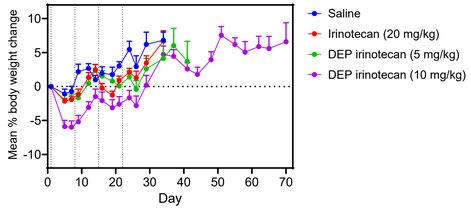


Table 1: DEP® irinotecan is superior to irinotecan (originally marketed as Camptosar®) in suppressing growth of HT29 colorectal cancer xenografts. Tumour growth inhibition (TGI) versus saline control was calculated at day 21, the last day all vehicle treated animals remained in the study. *P* values were calculated using Student's t test.

Treatment	Percent TGI (%)	*P* value (vs saline)
Irinotecan (20 mg/kg)	12	0.92
DEP® irinotecan (5 mg/kg)	67	< 0.0001
DEP® irinotecan (10 mg/kg)	100	< 0.0001

Figure 2A: DEP® irinotecan is superior to irinotecan (Camptosar®) in suppressing growth of CAPAN-1 pancreatic cancer xenografts. CAPAN-1 cells ($5x10^6$) were inoculated into immunocompromised NSG mice. N=8 per group.

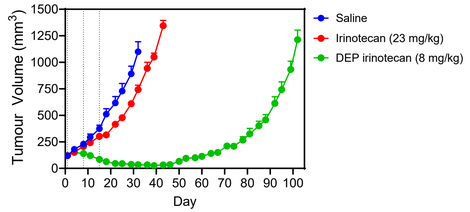


Figure 2B: DEP® irinotecan is well tolerated in CAPAN-1 tumor bearing mice. Data are presented as % body weight change from day 0.

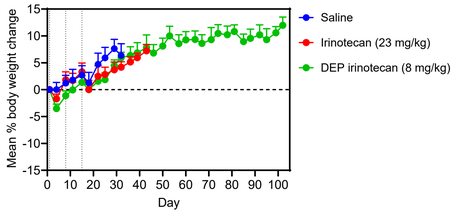


Table 2: DEP® irinotecan is superior to irinotecan (Camptosar®) in suppressing growth of CAPAN-1 pancreatic cancer xenografts. TGI versus saline control was calculated at day 32, the last day all animals remained in the study. *P* values were calculated using Student's t test.

Treatment	Percent TGI (%)	*P* value (vs saline)
Irinotecan (23 mg/kg)	36	0.0026
DEP irinotecan (8 mg/kg)	109	< 0.0001

DEP® IRINOTECAN + IMMUNE CHECKPOINT INHIBITION

Figure 3A: DEP® irinotecan co-operates with immune checkpoint inhibition (ICI) to suppress growth of MC38 colorectal cancer allografts. Immunocompetent C57BL/6 mice were inoculated with syngeneic MC38 tumour cells ($1x10^6$). Anti-PD-1 mAb (rat anti-mouse PD-1, clone RMPI-14) or isotype control (rat IgG2a mAb, clone 2A3) (Bio X Cell) delivered IP on days 1, 5, 8, and 12 (200 mg/dose, black ticks) in PBS. N=5 per group.

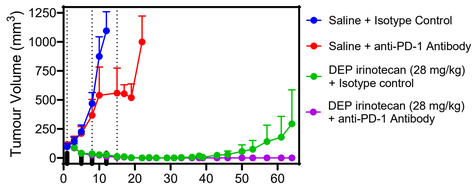


Figure 3B: Combined DEP® irinotecan and ICI is well tolerated by MC38 tumor bearing mice.

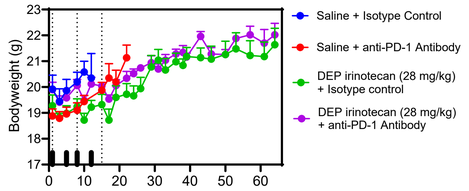


Figure 3C: Kaplan-Meier survival analysis of DEP® irinotecan plus ICI in MC38 colorectal cancer allografts. Logrank (Mantel-Cox) $P < 0.0001$.

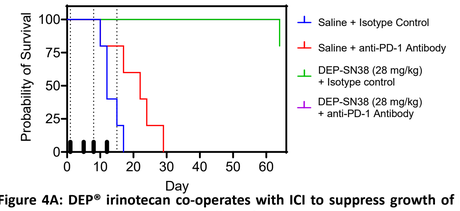


Figure 4A: DEP® irinotecan co-operates with ICI to suppress growth of ICI-resistant CT26 colorectal cancer allografts. Immunocompetent BALB/c mice were inoculated with syngeneic CT26 tumour cells ($1x10^6$). Anti-PD-1 mAb (rat anti-mouse PD-1, clone RMPI-14) or isotype control (rat IgG2a mAb, clone 2A3) (Bio X Cell), delivered IP on day 1 (200 mg/dose), and then on days 5, 8, and 12 (100 mg/dose, black ticks) in PBS. N=5 per group.

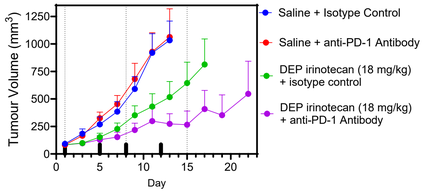


Figure 4B: Combined DEP® irinotecan and ICI is well tolerated by CT26 tumor bearing mice. Data are presented as % body weight change from day 0.

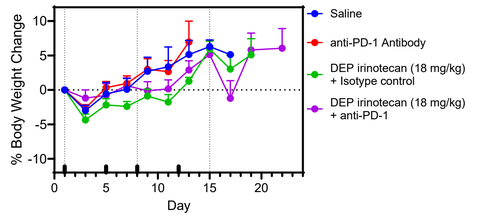


Figure 4C: Kaplan-Meier survival analysis of DEP® irinotecan plus ICI in CT26 colorectal cancer allografts. Logrank (Mantel-Cox) $P < 0.0014$

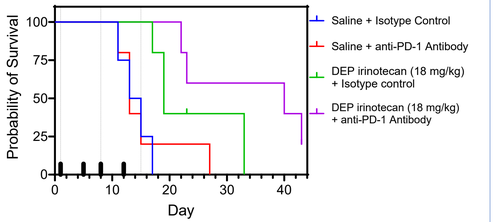


Table 3: Kaplan-Meier survival analysis of DEP® irinotecan plus ICI in CT26 colorectal cancer allografts. Two-way *P* values calculated using the logrank (Mantel-Cox) test.

Treatment	Median Survival (days)	*P* value (vs saline)
Saline	14	na
anti-PD-1	13	ns
DEP® irinotecan (18 mg/kg) + isotype control	19	0.0072
DEP® irinotecan (18 mg/kg) + anti-PD-1	40	0.0027
DEP® irinotecan (18 mg/kg) + isotype control v DEP® irinotecan (18 mg/kg) + anti-PD-1	NA	0.1259

DEP® IRINOTECAN + PARP INHIBITION

Figure 5A: DEP® irinotecan co-operates with the PARP inhibitor, Olaparib (Lynparza®), to suppress growth of HT29 colorectal cancer xenografts. Immunocompromised BALB/c nude mice were inoculated with HT29 cells ($5x10^6$) and DEP® irinotecan therapy delivered on days 1, 8, and 15 (vertical dashed lines). Olaparib was delivered orally for 3 weeks on a 5 days on/2 days off cycle as indicated by ticks. N=10 per group.

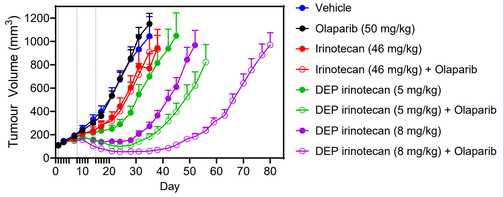


Figure 5B: Combined DEP® irinotecan and Olaparib (Lynparza®) is well tolerated by HT29 tumor bearing mice. Data are presented as % body weight change from day 0.

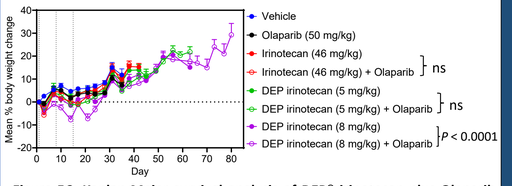


Figure 5C: Kaplan-Meier survival analysis of DEP® irinotecan plus Olaparib (Lynparza®) in HT29 colorectal cancer xenografts. Logrank (Mantel-Cox) $P < 0.0001$.

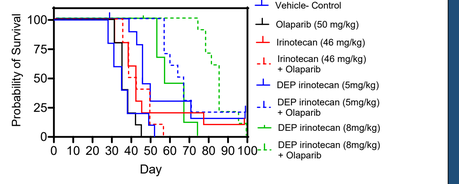


Table 4: Kaplan-Meier survival analysis of DEP® irinotecan plus Olaparib in HT29 colorectal cancer xenografts. Two-way *P* values were calculated using the logrank (Mantel-Cox) test.

Treatment	Median survival (days)	*P* value (vs saline)
Vehicle	35.0	na
Olaparib (50 mg/kg)	35.0	na
Irinotecan (46 mg/kg)	42.0	ns
Irinotecan (46 mg/kg) + Olaparib	40.0	ns
DEP® irinotecan (5mg/kg)	45.0	0.0130
DEP® irinotecan (5 mg/kg) + Olaparib	64.5	< 0.0001
DEP® irinotecan (10 mg/kg)	56.0	< 0.0001
DEP® irinotecan (10 mg/kg) + Olaparib	84.0	< 0.0001

Conclusions

- DEP® irinotecan was well tolerated and demonstrated enhanced anti-tumor efficacy vs. irinotecan (Camptosar®) in GI cancer xenografts.
- DEP® irinotecan in combination with ICI enhanced anti-tumor effects vs. ICI (anti-PD1) alone in both MC38 and CT26 allograft models of CRC.
- DEP® irinotecan in combination with PARP inhibitor, Olaparib (Lynparza®), enhanced anti-tumor effects vs. either agent alone in HT29 CRC xenografts.
- In a phase 1/2 clinical trial (see poster B039), DEP® irinotecan monotherapy has achieved durable efficacy responses for up to 72 weeks in colorectal cancer (CRC) patients, with a disease control rate of 48%, in heavily pre-treated patients that have progressed after treatment with standard irinotecan. There have been no immune-mediated adverse events.
- Up to 85-95% of CRC patients do not respond to ICB because their cancer is microsatellite stable (MSS). All CRC patients who responded to DEP® irinotecan in the clinical study were MSS.
- The data showing DEP® irinotecan enhances anti-tumor responses of ICI and PARP inhibition in models of CRC, together with promising clinical efficacy and safety of DEP® irinotecan in CRC and ovarian cancer, provide a strong rationale for clinical evaluation of DEP® irinotecan in combination with these important classes of therapy.

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