

DEP[®] irinotecan IO/PARP combination data presented at AACR

Melbourne, Australia; 16 October 2023: Starpharma (ASX: SPL, OTCQX: SPHRY) today provides a copy of the DEP[®] irinotecan combination data poster, showcasing the recently announced¹ data for DEP[®] irinotecan in combination with leading anticancer therapies, including immuno-oncology (IO) agents, in human colorectal cancer (CRC) models. The data show that DEP[®] irinotecan in combination with an IO agent or a PARP² inhibitor demonstrated superior anti-tumour activity and significant survival benefit when compared to these agents delivered alone in multiple CRC models.

The poster was presented over the weekend in Boston, US, at the international oncology conference, [International Conference on Molecular Targets and Cancer Therapeutics](#), co-hosted by the American Association of Cancer Research (AACR), the National Cancer Institute (NCI) and the European Organisation for Research and Treatment of Cancer (EORTC) from 11 to 15 October 2023.

This promising combination data, together with the recently released positive clinical results for DEP[®] irinotecan, provide a strong rationale for clinical evaluation of DEP[®] irinotecan with these leading classes of cancer drugs. These combinations are commercially important because they increase the potential market opportunities for DEP[®] irinotecan and illustrate valuable synergies with successful product categories.

The poster is appended.

About Starpharma

Starpharma Holdings Limited (ASX: SPL, OTCQX: SPHRY) is a world leader in dendrimer technology for medical applications. As an innovative Australian biopharmaceutical company, Starpharma is focused on developing and commercialising novel therapeutic products that address significant global healthcare needs. Starpharma boasts a strong portfolio of products, partnerships, and intellectual property.

Starpharma's innovative technology is based on proprietary polymers called dendrimers, which are precise, synthetically manufactured, nanoscale molecules. The unique properties of dendrimers – including their size, structure, high degree of branching, polyvalency, and water solubility – are advantageous in medical and pharmaceutical applications.

Starpharma uses its dendrimer technology to develop novel therapeutics and to improve the performance of existing pharmaceuticals. Starpharma's portfolio includes multiple clinical-stage oncology products, which utilise its Dendrimer Enhanced Product ("DEP[®]") drug delivery technology, and marketed products, including VIRALEZE™ and VivaGel[®] BV, which utilise SPL7013, a proprietary dendrimer with antimicrobial properties.

Starpharma's DEP[®] drug delivery platform is being used to enhance the effectiveness of existing and novel therapies and to reduce drug-related toxicities through controlled and specified drug delivery.

In addition to Starpharma's internal DEP[®] programs, Starpharma has multiple DEP[®] partnerships with international biopharmaceutical companies, including AstraZeneca (oncology), MSD (Antibody-Drug Conjugates), Chase Sun (anti-infectives), and other world-leading pharmaceutical companies. Due to the broad applicability and optionality of Starpharma's DEP[®] platform, partnered DEP[®] programs have the potential to generate significant future milestones and royalties.

Starpharma's topical antiviral nasal spray, VIRALEZE™, is now registered in more than 35 countries*, including Europe, the UK, and Asia. Starpharma's novel non-antibiotic vaginal gel, VivaGel[®] BV, for the treatment of bacterial vaginosis (BV) and prevention of recurrent BV, is registered in more than 50 countries, including in the UK, Europe, Southeast Asia, South Africa, Australia and New Zealand.

For more information about Starpharma, visit www.starpharma.com or connect with Starpharma on [LinkedIn](#).

¹ ASX Announcement dated 27 September 2023: [DEP[®] irinotecan combination data presentation](#)

² PARP: an enzyme called poly ADP ribose polymerase (PARP), which is involved in DNA repair.

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Disclosure

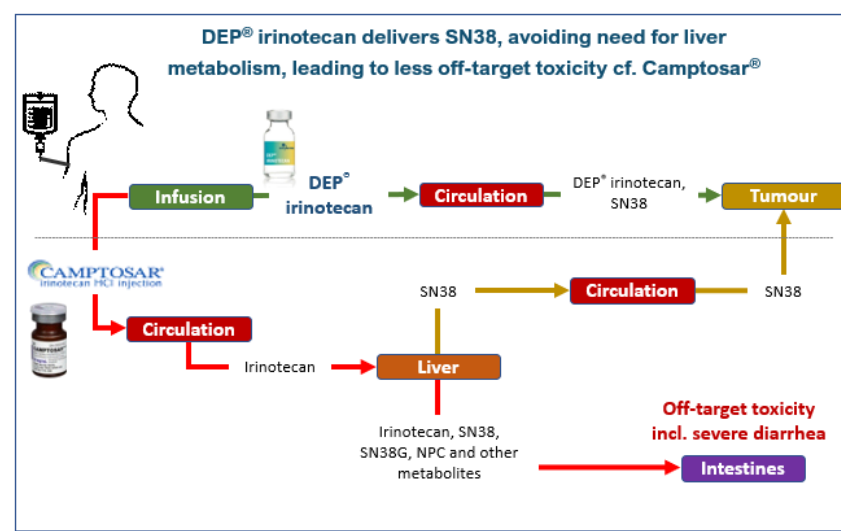
This ASX Announcement was authorised for release by the Chair, Mr Rob Thomas.

Forward-Looking Statements

This document contains certain forward-looking statements, relating to Starpharma's business, which can be identified by the use of forward-looking terminology such as "promising", "plans", "anticipated", "will", "project", "believe", "forecast", "expected", "estimated", "targeting", "aiming", "set to", "potential", "seeking to", "goal", "could provide", "intends", "is being developed", "could be", "on track", "outlook" or similar expressions, or by express or implied discussions regarding potential filings or marketing approvals, or potential future sales of product candidates. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no assurance that any existing or future regulatory filings will satisfy the FDA's and other authorities' requirements regarding any one or more product candidates nor can there be any assurance that such product candidates will be approved by any authorities for sale in any market or that they will reach any particular level of sales. In particular, management's expectations regarding the approval and commercialization of the product candidates could be affected by, among other things, unexpected trial results, including additional analysis of existing data, and new data; unexpected regulatory actions or delays, or government regulation generally; our ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing pressures; and additional factors that involve significant risks and uncertainties about our products, product candidates, financial results and business prospects. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected. Starpharma is providing this information as of the date of this document and does not assume any obligation to update any forward-looking statements contained in this document as a result of new information, future events or developments or otherwise. Clinical case studies and other clinical information given in this document are given for illustrative purposes only and are not necessarily a guide to product performance and no representation or warranty is made by any person as to the likelihood of achievement or reasonableness of future results. Nothing contained in this document nor any information made available to you is, or shall be relied upon as, a promise, representation, warranty or guarantee as to the past, present or the future performance of any Starpharma product.

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 Dendrimer Enhanced Product (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)- β -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. Tolerated of drug was bodyweight loss \leq 15%. Tumor volume body weights are expressed as mean \pm 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 (5×10^6) and therapy delivered on days 1, 8, 15, and 21 (vertical dashed lines). N=8 per group.

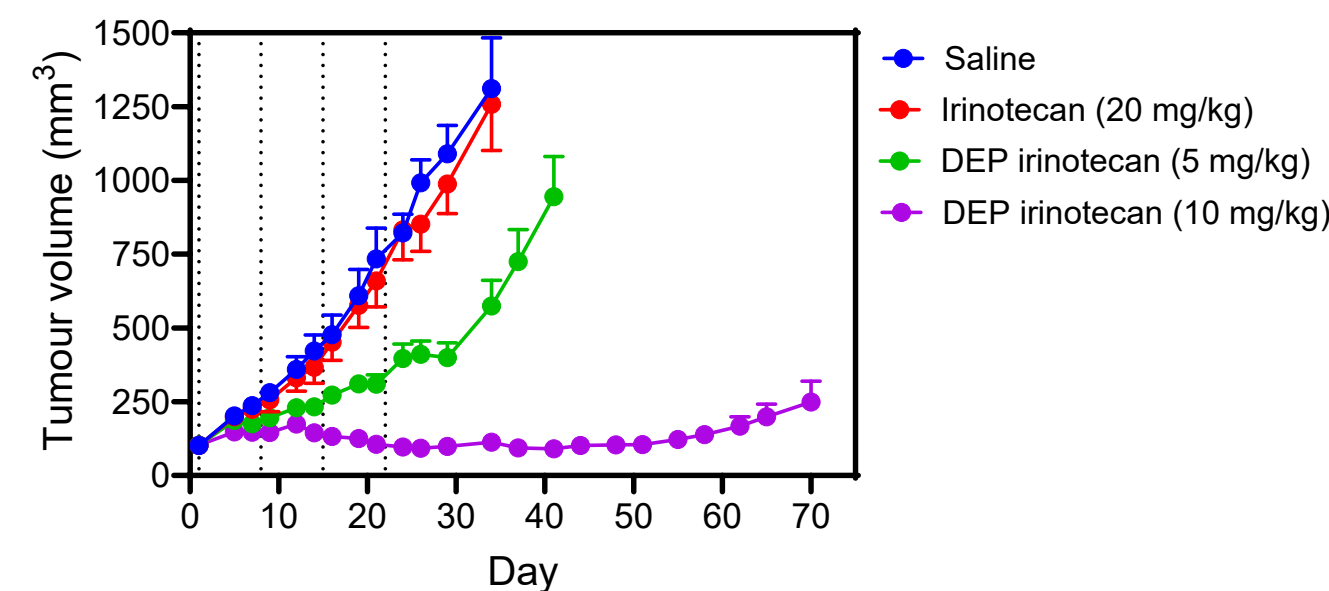


Figure 1B: DEP® irinotecan is well tolerated in HT29 tumor bearing mice. Data are presented as % body weight change from day 0.

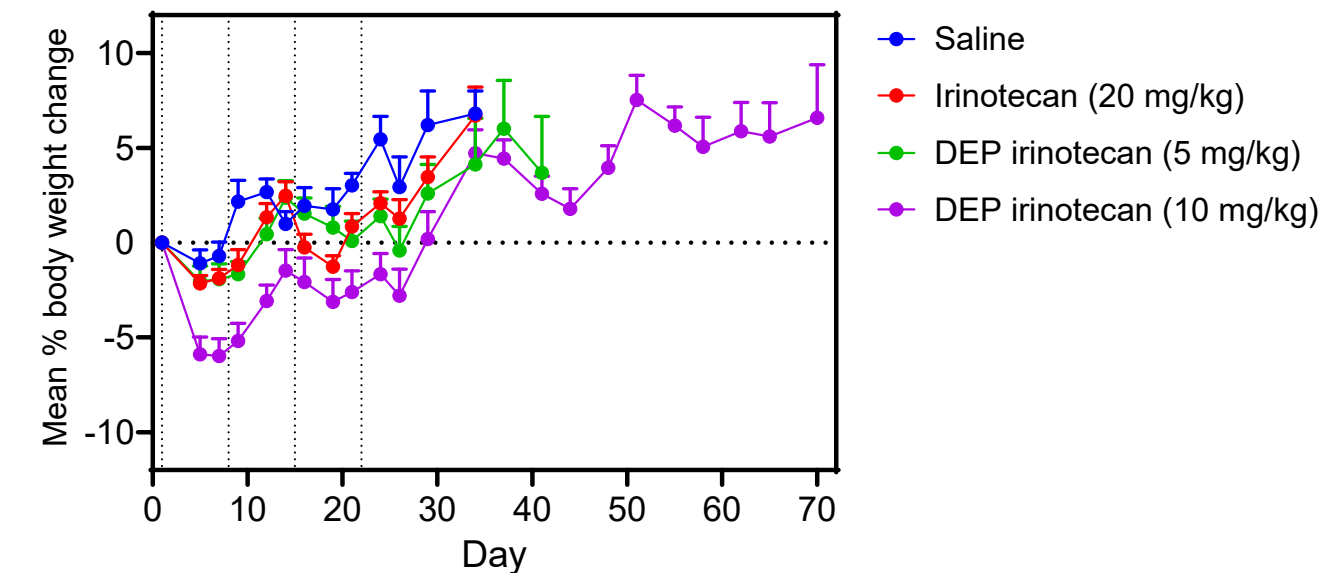


Table 1: DEP® irinotecan is superior to irinotecan (originally marketed as Camptosar®) in suppressing growth of HT29 colorectal cancer xenografts. Tumor growth inhibition (TGI) versus saline control was calculated at day 21, the last day all vehicle treated animals remained in the study. P values were 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 (5×10^6) were inoculated into immunocompromised NSG mice. N=8 per group.

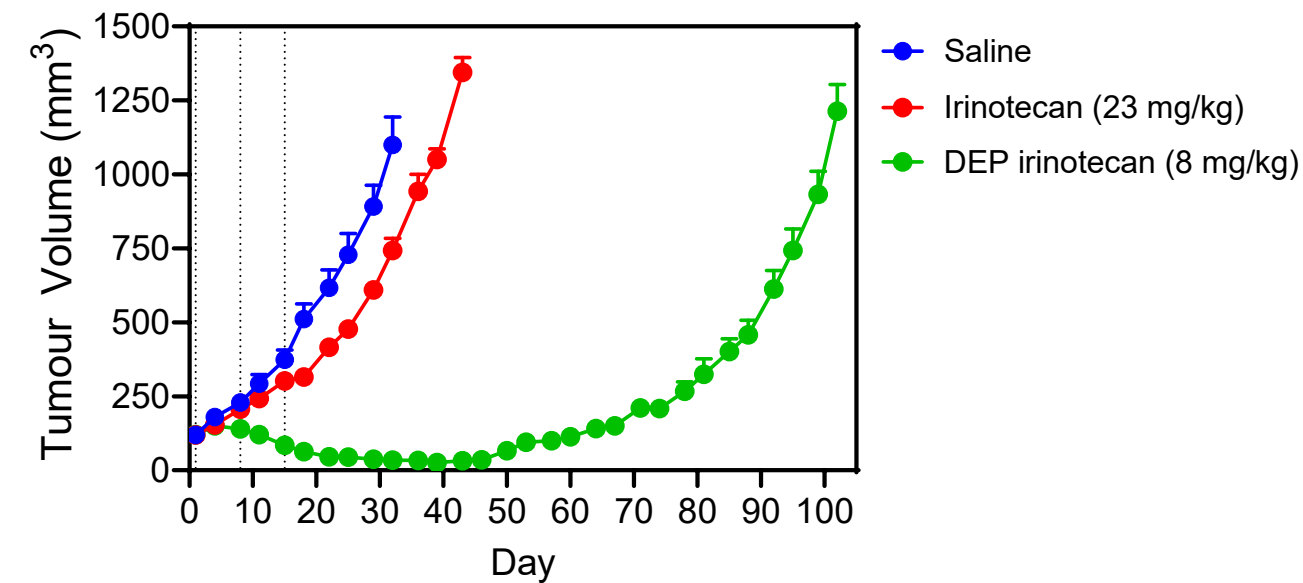


Figure 2B: DEP® irinotecan is well tolerated in CAPAN-1 tumor bearing mice. Data are presented as % body weight change from day 0.

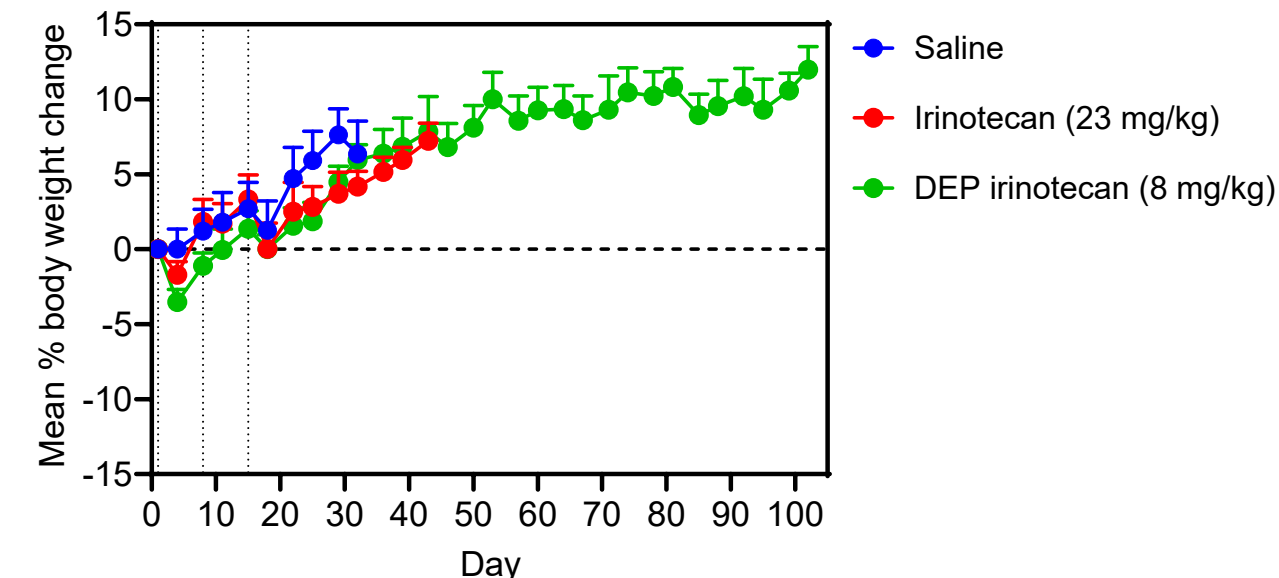


Table 2: DEP® irinotecan is superior to irinotecan (Camptosar®) in suppressing growth of CAPAN-1 pancreatic cancer xenografts. TGI versus saline control was calculated at day 32, the last day all animals remained in the study. P values were calculated using Student's t test.

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 (1×10^6). 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.

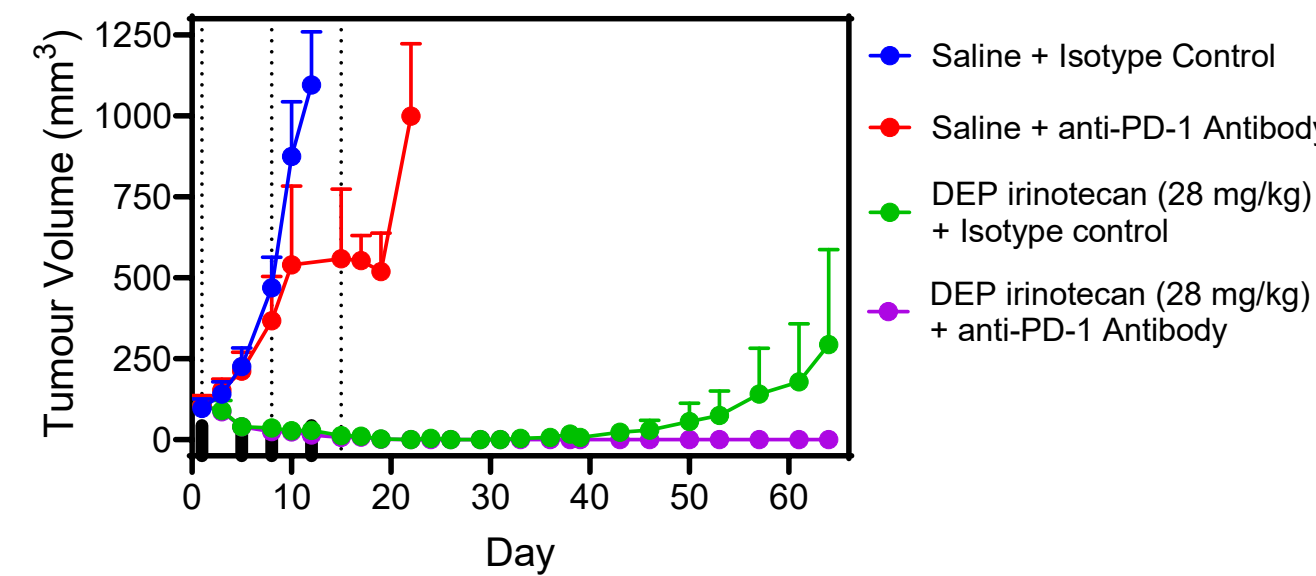


Figure 3B: Combined DEP® irinotecan and ICI is well tolerated by MC38 tumor bearing mice.

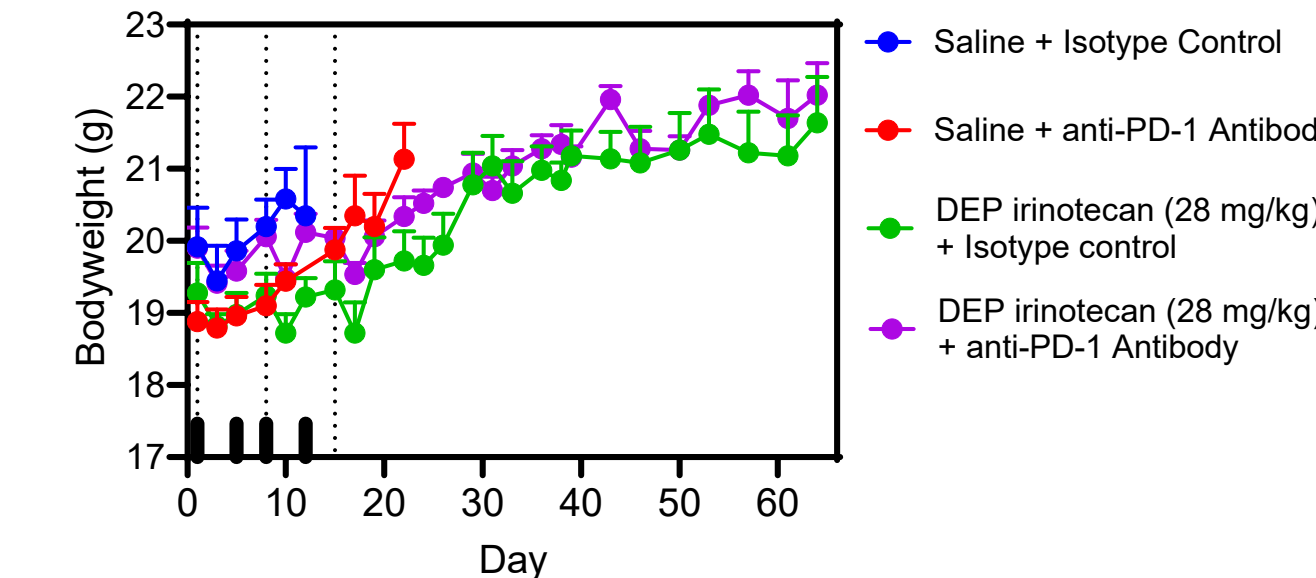


Figure 3C: Kaplan-Meier survival analysis of DEP® irinotecan plus ICI in MC38 colorectal cancer allografts. Logrank (Mantel-Cox) P < 0.0001.

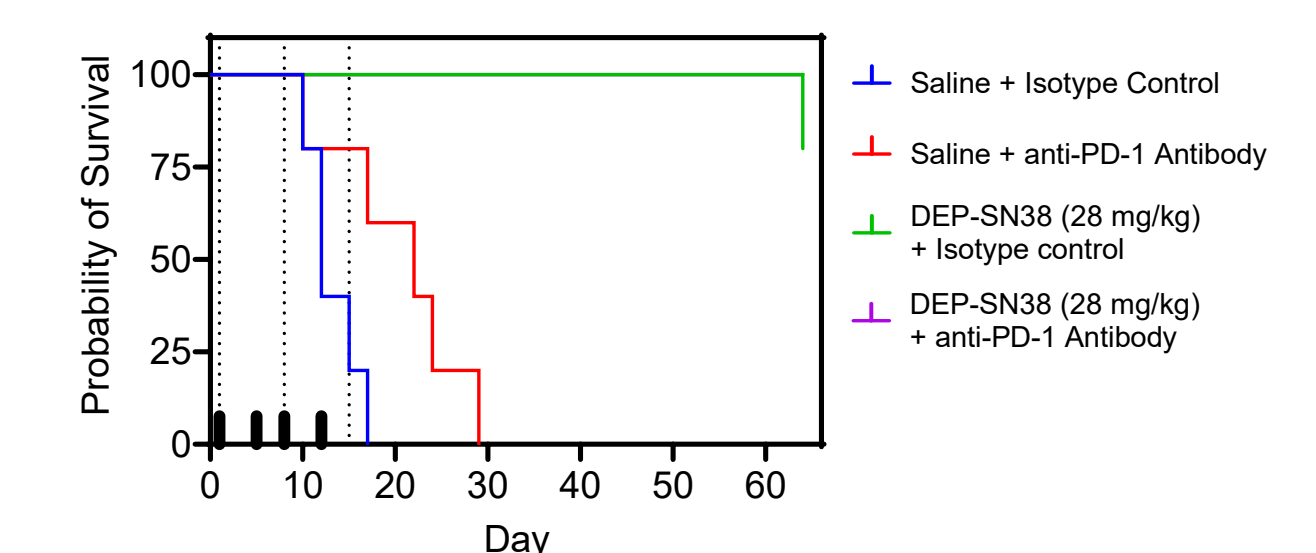


Figure 4A: DEP® irinotecan co-operates with ICI to suppress growth of ICI-resistant CT26 colorectal cancer allografts. Immunocompetent BALB/c mice were inoculated with syngeneic CT26 tumour cells (1×10^6). Anti-PD-1 mAb (rat anti-mouse PD-1, clone RMPI-14) or isotype control (rat IgG2a mAb, clone 2A3) (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.

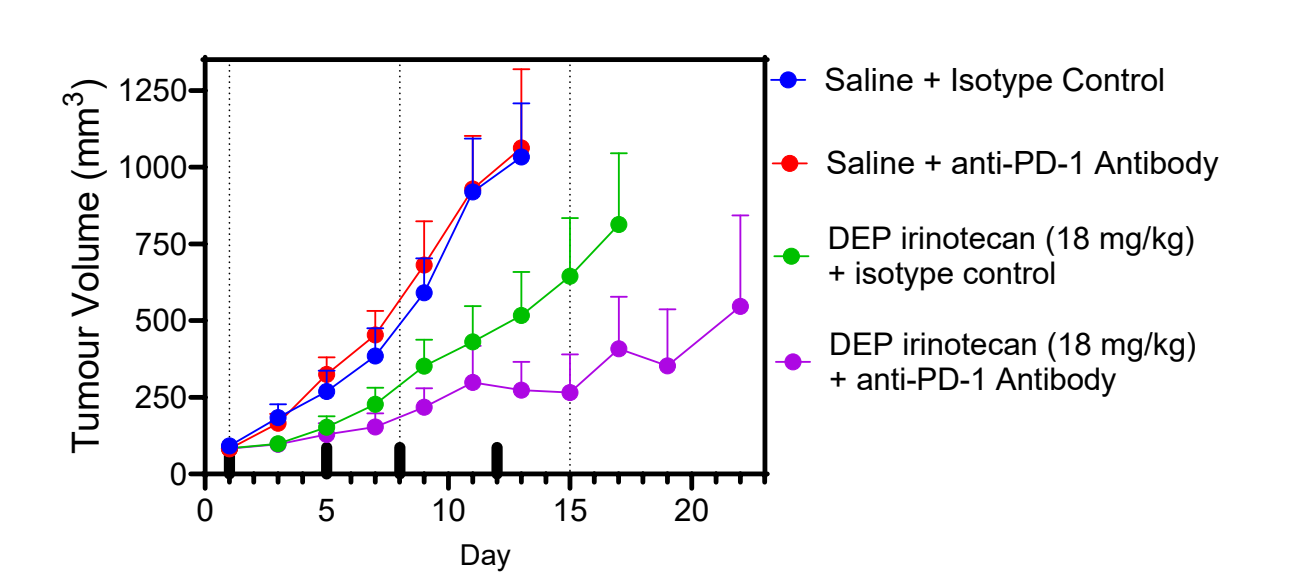


Figure 4B: Combined DEP® irinotecan and ICI is well tolerated by CT26 tumor bearing mice. Data are presented as % body weight change from day 0.

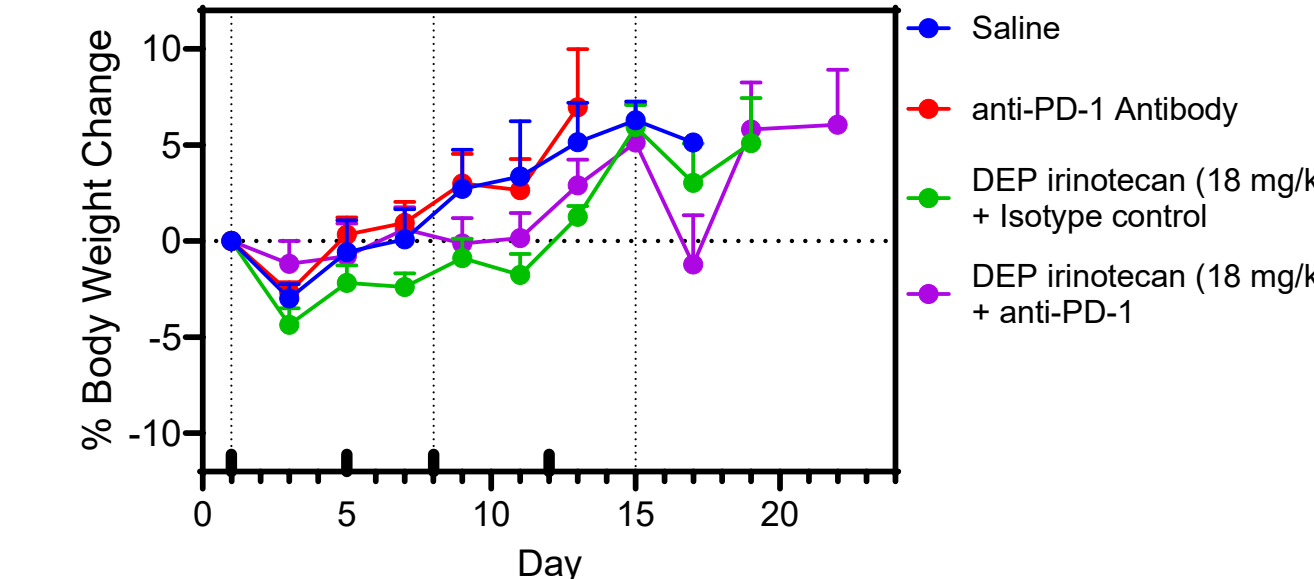


Figure 4C: Kaplan-Meier survival analysis of DEP® irinotecan plus ICI in CT26 colorectal cancer allografts. Logrank (Mantel-Cox) P < 0.0014

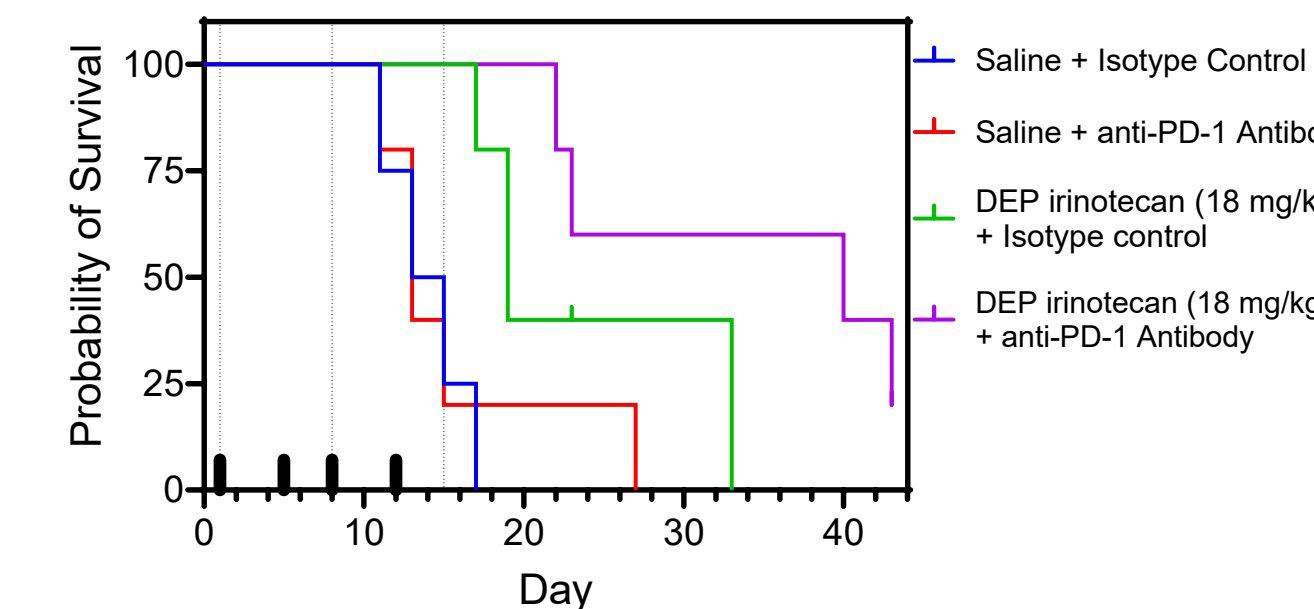


Table 3: Kaplan-Meier survival analysis of DEP® irinotecan plus ICI in CT26 colorectal cancer allografts. Two-way P values calculated using the logrank (Mantel-Cox) test.

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 (5×10^6) 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.

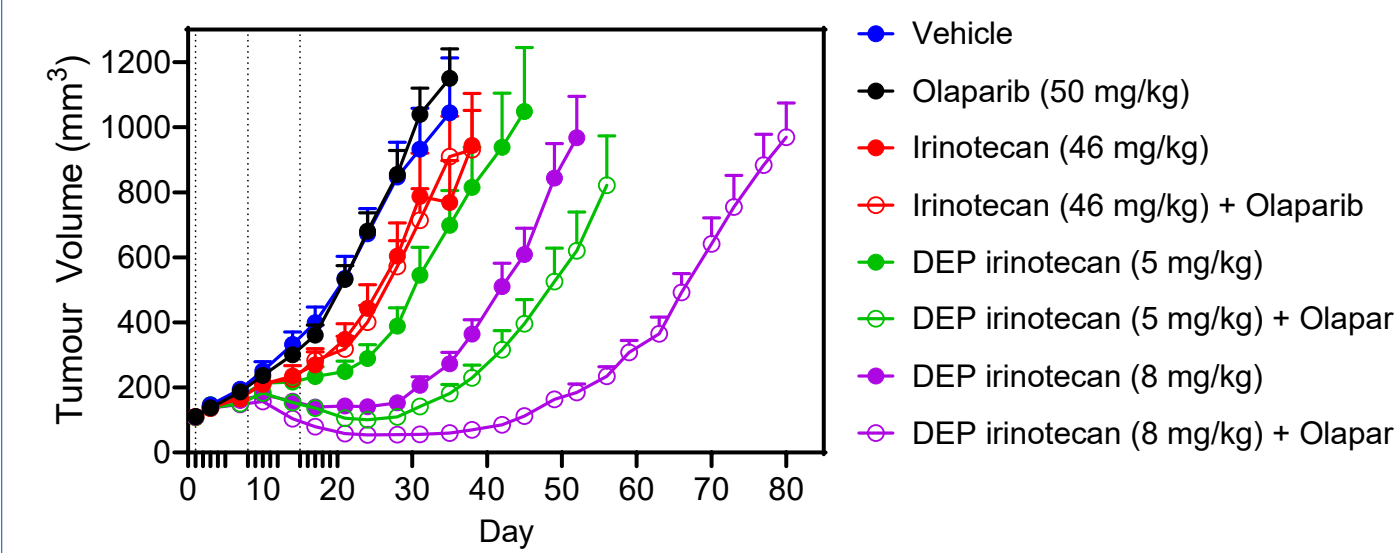


Figure 5B: Combined DEP® irinotecan and Olaparib (Lynparza®) is well tolerated by HT29 tumor bearing mice. Data are presented as % body weight change from day 0.

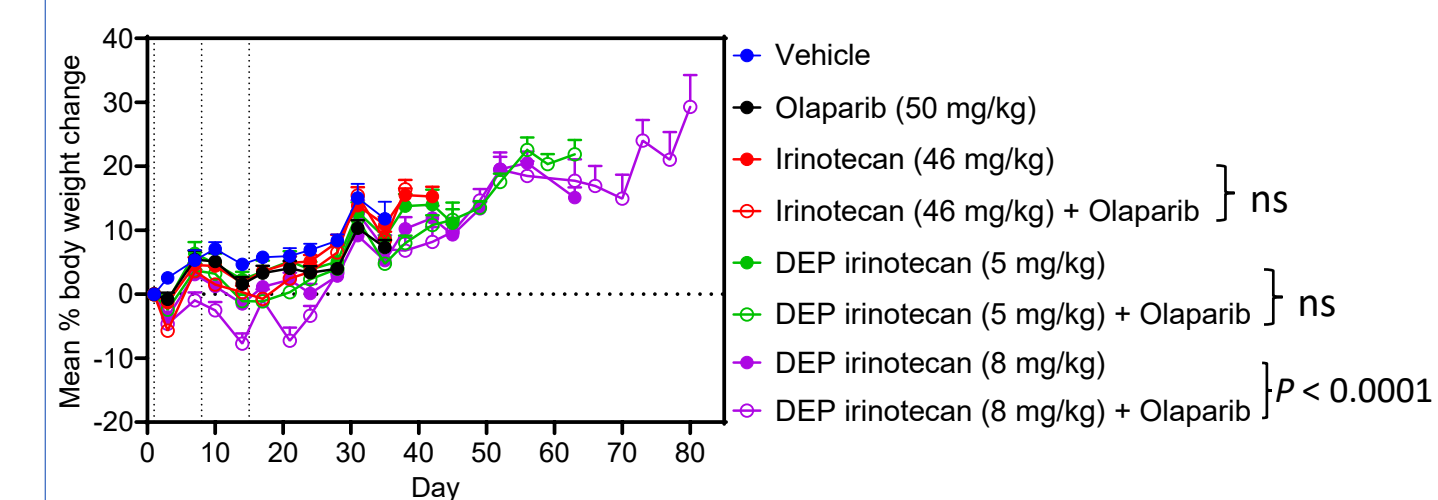


Figure 5C: Kaplan-Meier survival analysis of DEP® irinotecan plus Olaparib (Lynparza®) in HT29 colorectal cancer xenografts. Logrank (Mantel-Cox) P < 0.0001.

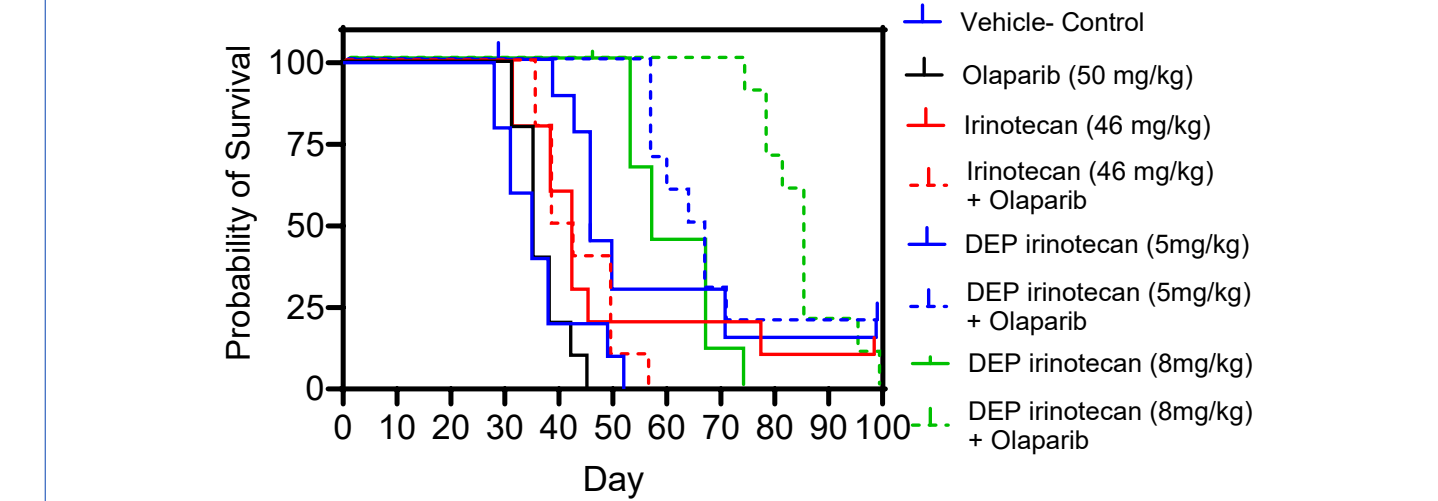


Table 4: Kaplan-Meier survival analysis of DEP® irinotecan plus Olaparib in HT29 colorectal cancer xenografts. Two-way P values were calculated using the logrank (Mantel-Cox) test.

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.