AACR Poster # 1716 Anticancer activity of the taxane nanoparticles, DEP docetaxel and DEP cabazitaxel

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INTRODUCTION

Docetaxel (Taxotere®) and cabazitaxel (Jevtana®) are mitotic inhibitors that function as effective cytotoxic agents and are widely used in many chemotherapy regimens. However, treatment with taxanes is limited by serious adverse toxicities, notably bone marrow toxicity (neutropenia, leukopenia and anemia) and hepatotoxicity. Taxanes are poorly water soluble and must be formulated with surfactants such as polysorbate, which can cause systemic adverse events (*e.g.* anaphylaxis and fluid retention) requiring pre-dosing with corticosteroids. These combined drug and excipient toxicities limit their clinical use and make them ideal candidates for improvement using dendrimer technology.

Starpharma's novel dendrimer nanoparticle DEP platform has broad applicability in drug delivery through improved drug solubility, efficacy and pharmacokinetics, reductions in certain toxicities (*e.g.* bone marrow toxicity) and generation of new intellectual property. The DEP platform has shown reproducible benefits across a wide range of drug classes including small molecules, peptides and proteins. Currently there are four DEP candidates in the clinic; DEP docetaxel (DEP DTX), DEP cabazitaxel (DEP CTX), and DEP irinotecan. The fourth DEP candidate, AZD0466, is a promising Bcl-2/Bcl-xL inhibitor, partnered with AstraZeneca, and is in Phase 1 clinical trials in the US (See AACR Poster # P-56, P-1718 & Abs 3066).

Starpharma's DEP DTX and DEP CTX are both PEGylated G5 polylysine dendrimers with the drug conjugated to the surface via a hydrolytically labile linker. Both products have demonstrated superior efficacy and survival compared to the standard drug formulations in a range of xenograft cancer models in immunocompromised mice.

METHODS AND RESULTS

Mouse xenograft studies were carried as following:

Balb/c nude mice were inoculated subcutaneously with MDA-MB-231 (breast) cancer cell line (Exp 1 and 2, 10 mice/group).
SCID mice were inoculated subcutaneously with DU145 (prostate) cancer cell line (Exp 3, 10 mice/group).
NOD-scid interleukin-2 receptor gamma chain null were inoculated subcutaneously with CAPAN-1 (colon) cancer cell line (Exp 4, 9 mice/group).

In each experiment mice were dosed with saline as control and;

- Exp 1 – DEP DTX (28 mg/kg) and docetaxel (15 mg/kg) by IV injection on days 1, 8 and 15 at 0.1 ml/10g body weight (all drug groups were dosed at the pre-determined maximum tolerated dose for each therapy).
- Exp 2 – DEP CTX (10 mg/kg), and cabazitaxel (9 mg/kg) by IV injection on days 1, 8 and 15 at 0.1 ml/10g body weight (all drug groups were dosed at the pre-determined maximum tolerated dose for each therapy).
- Exp 3 – DEP CTX (10 mg/kg), and cabazitaxel (11 mg/kg) by IV injection on days 1, 8 and 15 at 0.1 ml/10g body weight (all drug groups were dosed at the pre-determined maximum tolerated dose for each therapy).
- Exp 4 – Abraxane (40 mg/kg), gemcitabine (80 mg/kg), DEP DTX (20 mg/kg), DEP DTX (20 mg/kg) + gemcitabine (80 mg/kg), DEP CTX (7.5 mg/kg) and DEP CTX (7.5 mg/kg) + gemcitabine (80 mg/kg). Abraxane, DEP DTX and DEP CTX were given *via* IV injection and gemcitabine by IP injection on days 1, 8 and 15 at 0.1 ml/10g body weight.

Throughout experiments all dosing groups were generally well tolerated with mean weight loss not exceeding 10% and tumour size not exceeding the ethical end point of 1200 mm^3. Both criteria were determined as ethical endpoints for all animals.
Tumour growth data (mean ± standard error of the mean (SEM)) were analysed in GraphPad Prism. Statistics were carried out using two-way ANOVA followed by Dunnett's post-hoc test. Kaplan-Meier survival curves were analysed using the Log-rank (Mantel-Cox) test. For Exp 4 – two-way ANOVA with repeated measures followed by i) Dunnett's multiple comparison test to compare monotherapies to vehicle control and ii) Tukey's multiple comparisons test for comparisons between treatment groups.

(Note: If error bars do not display on the graphs, they are not visible because they are shorter than the height of the symbol).

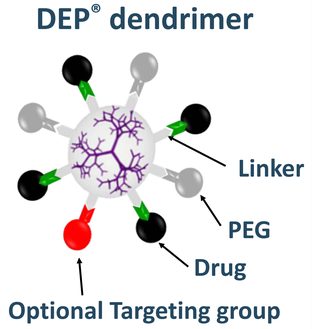
DENDRIMER CONJUGATES AS THERAPEUTICS

Improved efficacy:

DEP improves anti-cancer efficacy through better drug targeting & improved pharmacokinetics.

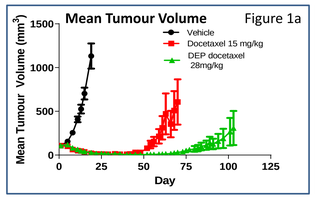
Benefits in combination:

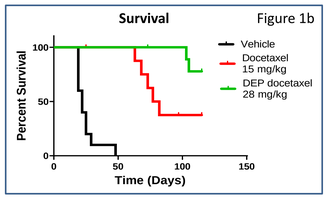
DEP drugs are ideal candidates for combination therapy including with immuno-oncology (IO) agents and other chemo. DEP® drugs show synergistic benefits over the original versions and given they have been shown to reduce bone marrow toxicity and do not require pre-treatment with cortisone, they are particularly well suited to combine with IO.



Reduced side-effects:

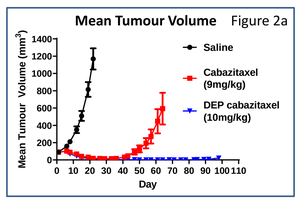
DEP reduces important side effects such as bone marrow toxicity / low white blood cells (neutropenia) and alopecia (hair loss). DEP® removes the need for toxic detergents in current formulations, which are highly soluble in aqueous formulations.

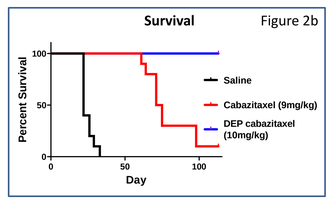




DEP DTX MONOTHERAPY (EXPERIMENT 1)

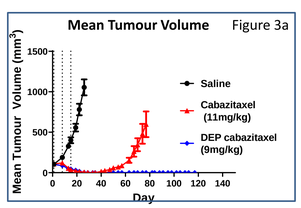
Complete tumour regression was observed in both the DEP DTX (until day 75) and docetaxel (until day 45) treated animals bearing the breast cancer tumour cell line, MDA-MB-231 (Figure 1a). The tumour inhibition and survival effects of DEP DTX were significantly improved compared with the docetaxel treated group (Figures 1a and 1b; P< 0.007 and 0.007 respectively).

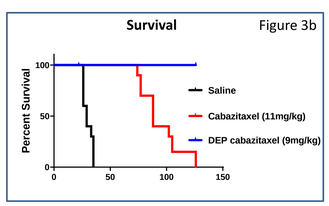




DEP CTX MONOTHERAPY (EXPERIMENT 2)

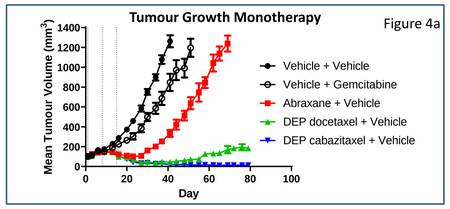
Complete tumour regression was observed in both the DEP CTX and cabazitaxel treated animals bearing the breast cancer tumour cell line, MDA-MB-231 (Figures 2a and 2b). Tumour regrowth in the cabazitaxel group was evident by day 43 with 9 of 10 tumours reaching an ethical tumour volume endpoint by day 98. DEP CTX treatment significantly prolonged mouse survival beyond that of cabazitaxel (P <0.001).

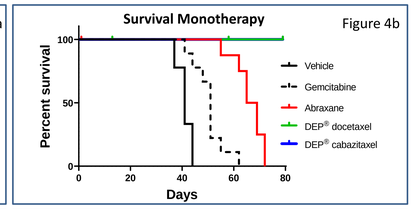


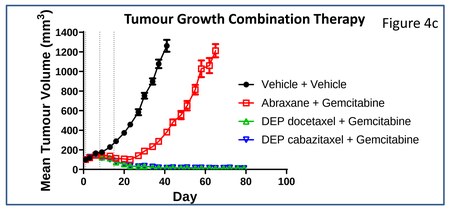


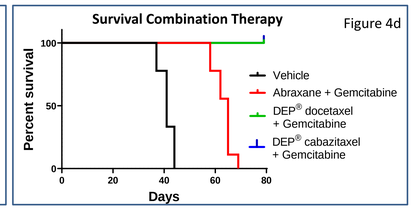
DEP CTX MONOTHERAPY (EXPERIMENT 3)

Complete tumour regression and 100% survival with no tumour regrowth out to day 126, was observed in DEP CTX treated animals bearing the prostate cancer tumour cell line, DU145 (Figures 3a and 3b). The tumour inhibition and survival effects of DEP CTX were markedly improved compared with the cabazitaxel treated group where tumour regrowth was evident in all animals by day 60. The differences were highly statistically significant (P<0.0001).







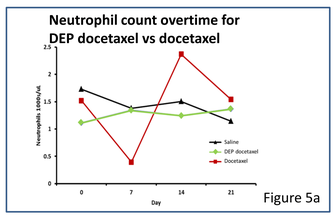


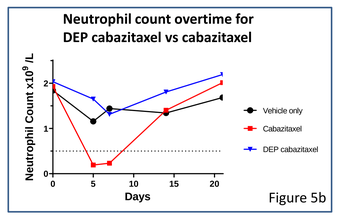
DEP CTX MONOTHERAPY (EXPERIMENT 4)

Results from a human pancreatic cancer model (CAPAN-1) (Figures 4a – 4d) showed;
Abraxane administered alone and in combination with gemcitabine inhibited tumour growth to a similar extent (Percent tumour growth inhibition on Day 37 = 85% and 81 %, respectively).
DEP CTX and DEP DTX treatment inhibited tumour growth more effectively than Abraxane (P= 0.004, Abraxane vs DEP DTX; P <0.0001, Abraxane vs DEP CTX).
DEP CTX given alone and in combination with gemcitabine induced complete regression of CAPAN-1 tumours for the duration of the study.
DEP DTX given alone and in combination with gemcitabine resulted in complete tumour regression to day 58, after which slow tumour regrowth occurred in the DEP DTX cohort, but not the gemcitabine combination cohort, treated mice (P<0.0001, t-test, Day 107 tumour volume).

DEP TOXICITY ASSESSMENT;

The relative toxicities of the DEP DTX formulation and docetaxel were compared in a study where equivalent doses (based on docetaxel; 9mg/kg) were administered to male and female rats by intravenous injection on Day 0. Blood samples were taken at day 0 prior to dosing, then at days 7, 14 and 21. The level of neutrophils, expressed as the mean absolute count across all animals in the dose group (n=6 per group) at each time point, are shown in Figures 5a and 5b. Of particular significance was the absence of neutropenia for the DEP taxane candidates.





CONCLUSION AND CLINICAL PROGRESS

In summary, both DEP taxanes are well tolerated and show significantly better efficacy, survival benefits and lower toxicity compared to current standard of care therapies Taxotere® and Jevtana®. Both DEP taxanes work well in combination with other agents, which further improves their anticancer effectiveness.

Both DEP taxanes are water-soluble and do not require surfactants such as polysorbate 80 for dissolution which negates the need for pretreatment with corticosteroids in the clinical setting. Of particular significance is the lack of neutropenia in preclinical studies, the major dose-limiting toxicity of current taxane therapies. This lack of bone marrow toxicities may allow for more effective combination treatments when used with other anticancer agents, including immunotherapies.

In clinical studies both candidates have experienced significantly fewer side effects such as nausea and bone marrow toxicity (neutropenia, anaemia, thrombocytopenia) than are typically seen with conventional taxanes, and no anaphylaxis has been observed.

DEP CTX and DEP DTX are two of four clinical stage products from Starpharma's DEP platform. Both compounds are currently under investigation in Phase 2 clinical trials against a broad range of tumour types at a number of leading UK cancer hospitals including; Guy's and St Thomas', University College London Hospital, Imperial College London, Velindre Cancer Centre, The Christie, The Beatson, The Leeds Teaching Hospital and The Newcastle upon Tyne.