

Efficacy and safety of dendrimer-enhanced cabazitaxel (DEP CTX) in patients with advanced solid cancers; a Phase 1/2 trial

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Dendrimer nanoparticle delivery of cabazitaxel (DEP CTX)

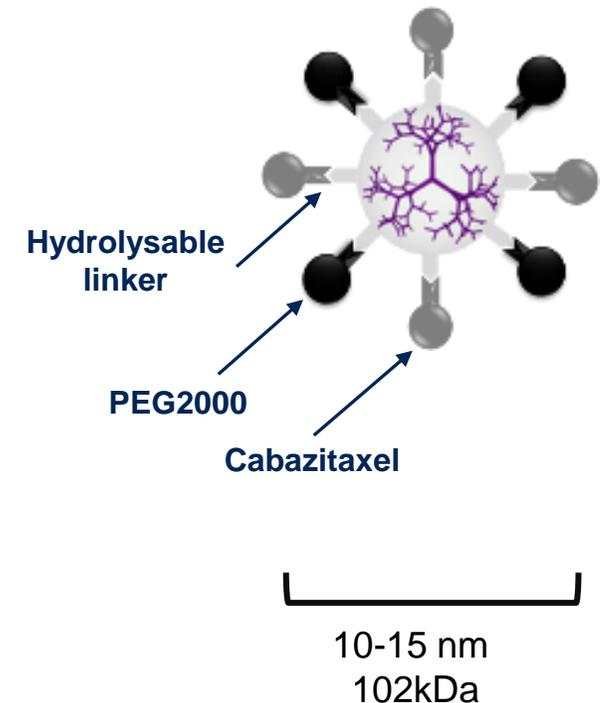
- 3D lysine polymer provides a scaffold for targeting payloads including cytotoxics to tumor microenvironment
- Cabazitaxel is a taxane approved for treatment of prostate cancer
- We conducted a Phase 1/2 trial of DEP CTX in advanced solid tumors
- Safety compares favourably with standard cabazitaxel
- Efficacy in patients with tumors including prostate, ovary and upper GI

Dendrimer platform¹

DEP CTX designed to improve safety and efficacy of cytotoxic payload

- Branched poly-lysine polymer
- Scalable, precise manufacturing in concentric layers
 - 5 generations, 64 attachment points per dendrimer
- Covalent linkage (1:1) to:
 - **cabazitaxel** (CTX) - linker renders payload inert until released
 - **PEG** - solubility without polysorbate; molecular weight/PK
- Hydrolysis of linker in tumor interstitium releases free drug

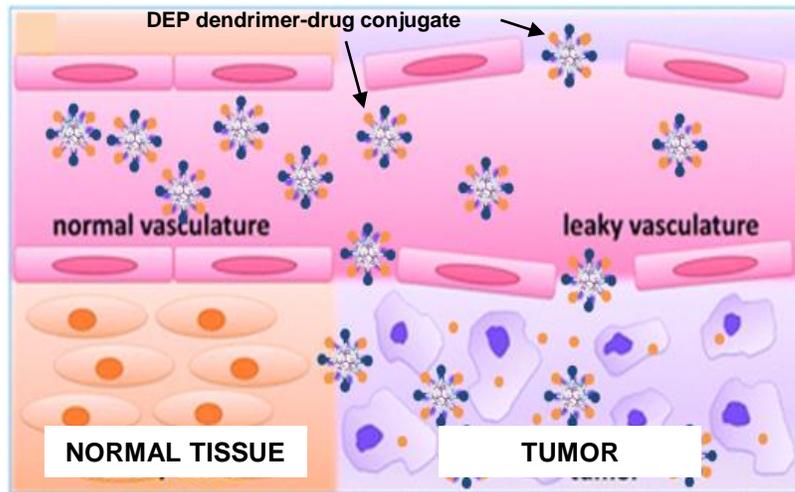
DEP dendrimer (1:1 ratio CTX:PEG)



1. Kaminskas et al, Nanomedicine 2011, 6(6):1063-1084

Preclinical selective delivery and anti-tumor activity

Size-dependent tumor accumulation^{1,2}



- DEP CTX preferentially escapes from permeable tumor vasculature
- Prolonged retention in tumor interstitium

Tumor accumulation PET-CT image

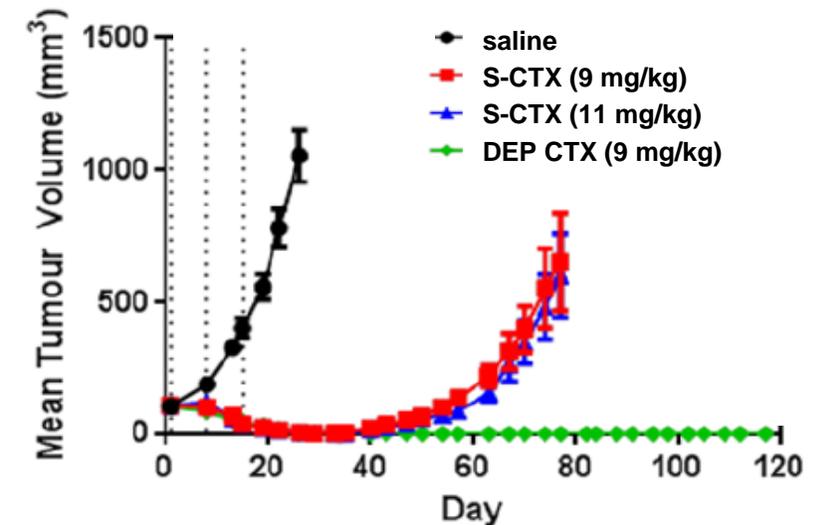


⁸⁹Zr-labelled DEP CTX

DU145 (human prostate cancer) xenograft

48 hours post IV injection

DEP CTX enhanced efficacy: xenograft model

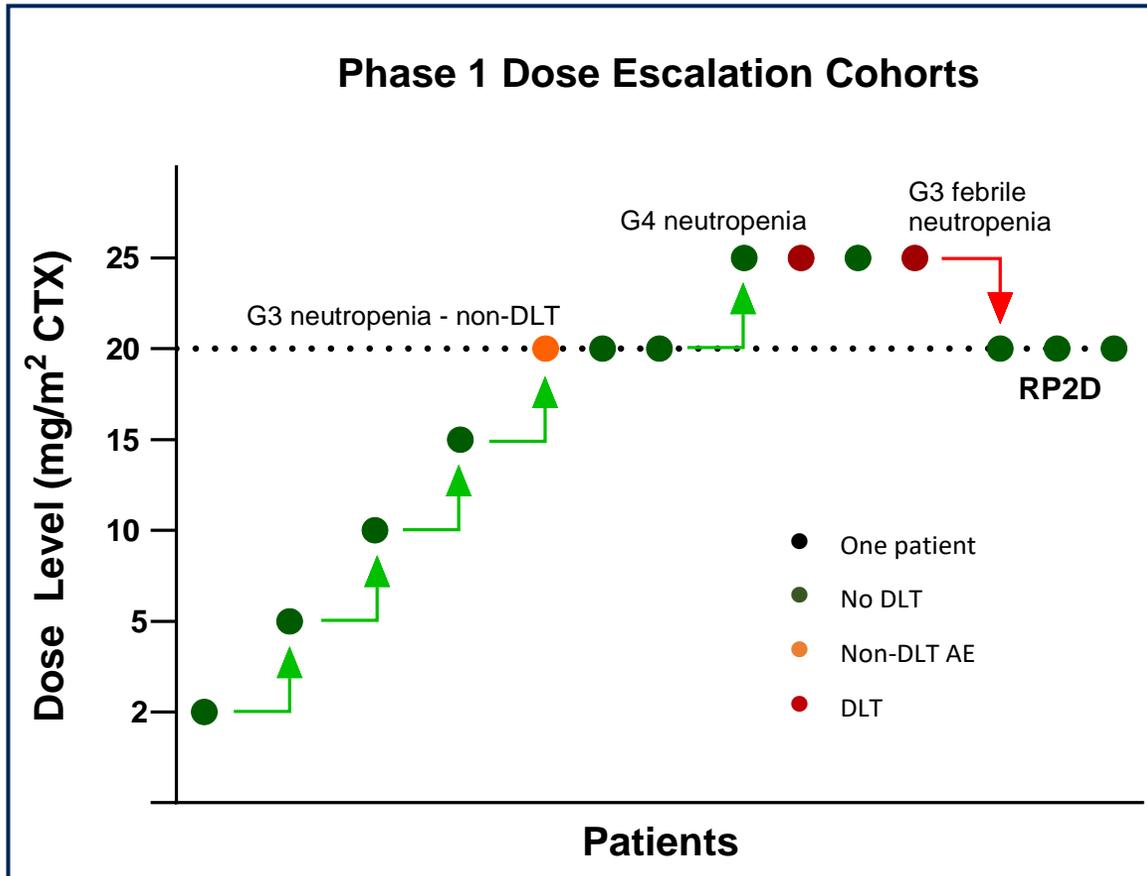


- DEP CTX or s-CTX IV on days 1, 8 & 15; n=10/group
- SCID mice; DU-145 human prostate xenograft

1. Iyer et al., *Drug Disc Today* 2006, 11:17-18):812-818
2. Kaminskis et al., *Nanomedicine* 2011, 6(6):1063-1084

Dendrimer cabazitaxel Phase 1/2 trial

- Phase 1 - **primary objective**: safety profile; MTD & DLTs; **secondary objectives**: preliminary efficacy, PK
- Single patient cohorts, followed by 3+3 escalation¹. Expansion cohorts in selected tumor types



- DEP CTX 3-weekly IV infusion
- no corticosteroid pre-medication
- no routine use of G-CSF

Phase 1 outcomes (n=14)

- DLTs: G4 neutropenia, G3 febrile neutropenia
- RP2D: 20 mg/m² cabazitaxel, Q3W

Phase 2 dose expansion (n=75)

Prostate
(n=25)

Ovary
(n=22)

Esophago-
gastric
(n=15)

Other
(n=13*)

* hepatobiliary, head & neck, lung, thymic carcinoma

1. Jones RH, Pinato DJ, Joshua A, et al. *Ann Oncol*, 2022;33(suppl_7):S616-S652

Phase 2 patient characteristics

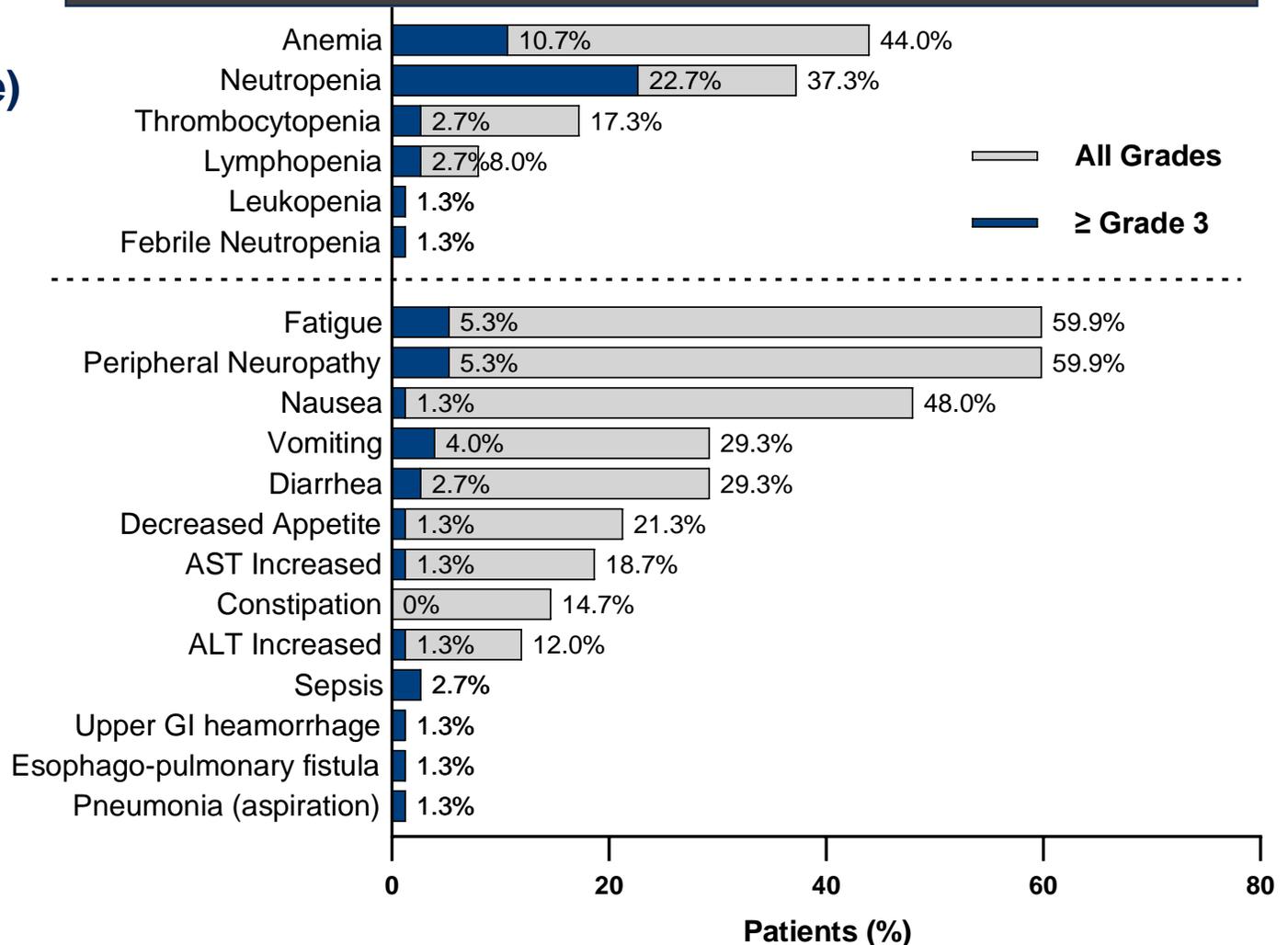
PATIENT BASELINE CHARACTERISTICS		PROSTATE	OVARIAN	EGC	HNSCC	HEPATO-BILIARY	OTHER*	TOTAL
Patients enrolled (n, %)		25 (33%)	22 (29%)	15 (20%)	7 (9%)	4 (5%)	2 (3%)	75 (100%)
Age (years)	Median (range)	73 (57-83)	62 (43-76)	61 (25 – 73)	60 (49-69)	65 (57-75)	73 (66-80)	65 (25-83)
Sex (n, %)	Male	25 (100%)	0 (100%)	10 (67%)	6 (86%)	2 (50%)	1 (50%)	44 (59%)
	Female	0 (0%)	22 (100%)	5 (33%)	1 (14%)	2 (50%)	1 (50%)	31 (41%)
ECOG PS	0	15 (60%)	12 (55%)	8 (53.3%)	4 (57%)	2 (50%)	0	41 (55%)
	1	10 (40%)	10 (45%)	7 (46.7%)	3 (43%)	2 (50%)	2 (100%)	34 (45%)
Prior lines of therapy	Median (range)	4 (2-9)	4 (1-11)	1 (1-3)	3 (2-4)	2 (1-4)	3 (2-4)	3 (1-11)
Prior systemic exposure (n, %)	Platinum	2 (8%)	22 (100%)	13 (87%)	7 (100%)	4 (100%)	2 (100%)	49 (65%)
	Taxane	24 (96%)	22 (100%)	3 (20%)	4 (57%)	0 (0%)	1 (50%)	54 (72%)
Prior surgery (n, %)	Any	7 (28%)	21 (95%)	6 (40%)	3 (43%)	4 (100%)	2 (100%)	43 (57%)
Radiotherapy (n, %)	Any	21 (84%)	7 (32%)	6 (60%)	6 (86%)	2 (50%)	1 (50%)	46 (61%)

*lung and thymic carcinoma

DEP CTX Phase 2 safety

- **G3/4 neutropenia 23% (16% in prostate)**
- **Febrile neutropenia 1% (none in prostate)**
- **G-CSF:**
 - primary prophylaxis: 0%
 - any: 9%
- **Most common symptomatic AEs:** fatigue, PSN, nausea; mostly mild/moderate
- **>90% of PSN was G1/2**
- **G3/4 non-heme TRAEs 21%**
- **No prominent hypersensitivity signal or anaphylaxis:** no routine steroid premedication
- **G1 alopecia 4% (3/75)**

Treatment-related AEs in ≥10% patients, or ≥ Grade 3 (n=75)



Pharmacokinetics

Phase 1 PK:

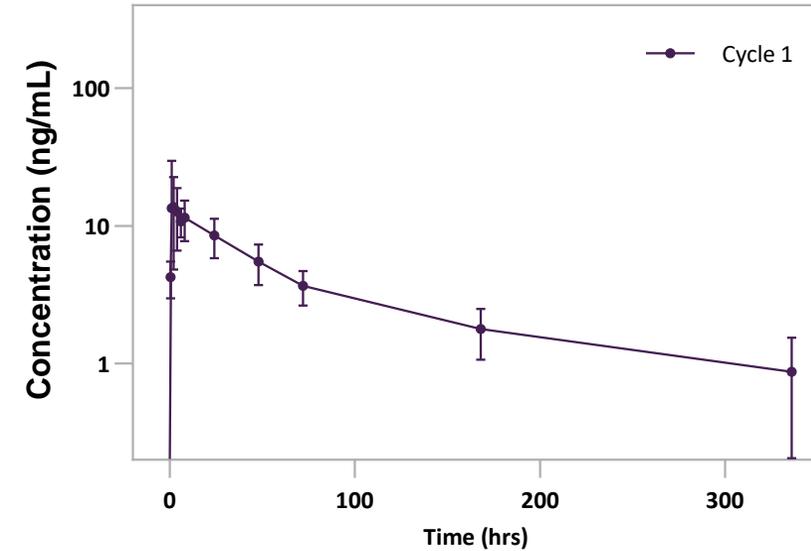
Linear PK parameters across dose range (2-25 mg/m² CTX)

No evidence of cycle-to-cycle accumulation

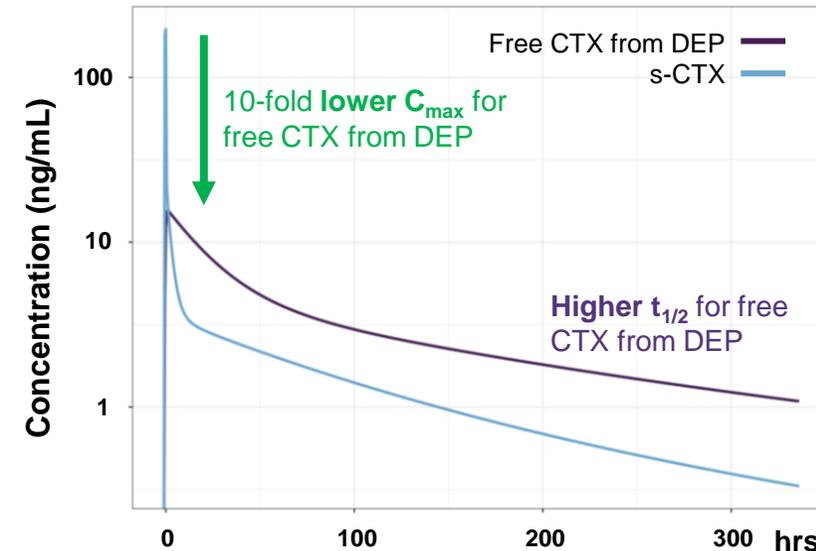
Slow-release depot

PK at RP2D	DEP CTX 20mg/m ²	
	Free CTX (mean)	Total CTX (mean)
C_{max} (ng/mL)	19.2	9,870
AUC_{inf} (ng.h/mL)	1,190	173,000
t_{1/2} (h)	~100	>100

DEP CTX Pharmacokinetics – Free CTX (mean ± SD)



Free CTX vs standard CTX[†]
– simulated population PK profiles



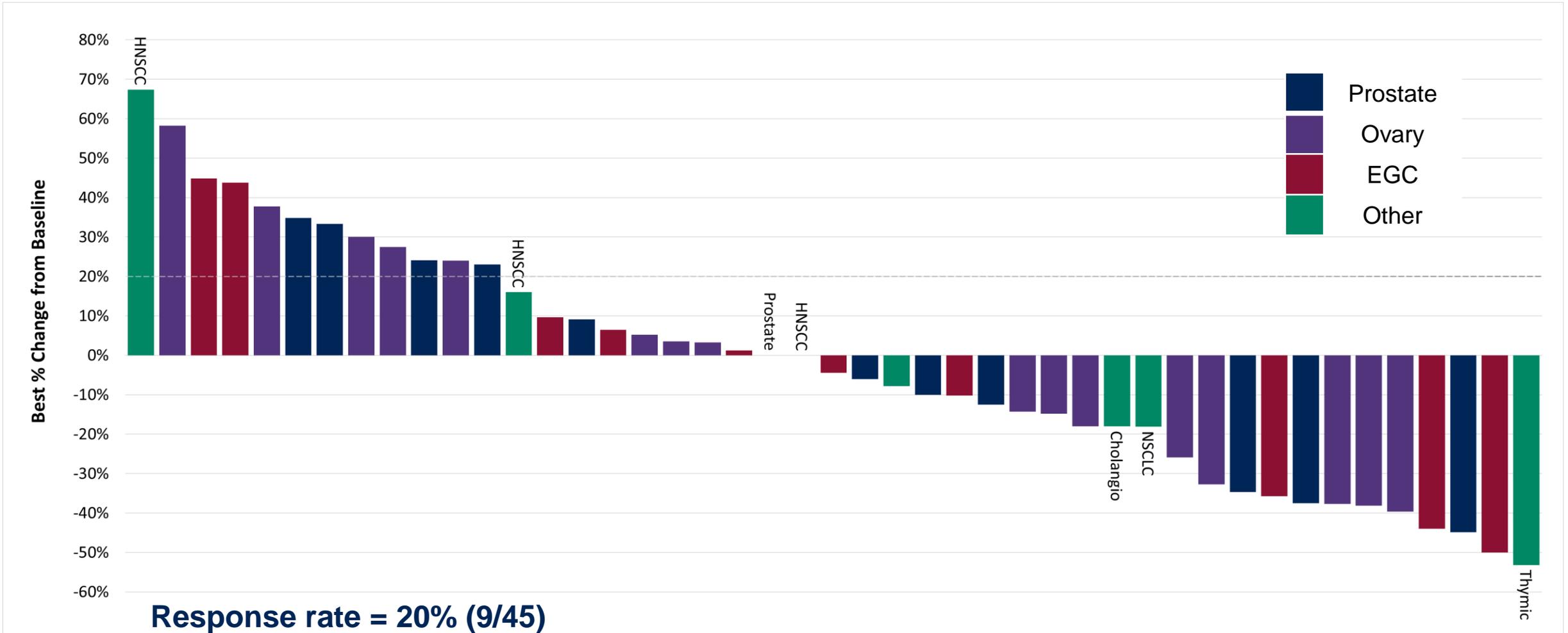
Phase 2 anti-tumor activity

	mCRPC (n = 25)	Ovary (n = 22)	EGC (n = 15)	HNSCC (n = 7)	Hepato- biliary (n = 4)	Other† (n = 2)	Total (n = 75)
Evaluable, n	17	18	10	3	1	2	51
RECIST measurable, n	12	17	10	3	1	2	45
ORR % [95% CI]	16.7% [2.1 - 48.4]	17.6% [3.8 - 43.4]	30.0% [6.7 - 65.2]	0.0% [0.0 - 70.8]	0.0% [0.0 - 97.5]	50.0% [1.3 - 98.7]	20.0% [9.6 - 34.6]
DCR % [95% CI]	70.6% [44.0 - 89.7]	66.7% [41.0 - 86.7]	80.0% [44.4 - 97.5]	33.3% [0.8 - 90.6]	100% [2.5 - 100.0]	100% [15.8 - 100.0]	70.6% [56.2 - 82.5]
Median PFS (mths) [95% CI]	4.4* [3.8 - 5.9]	3.1 [1.9 - 4.0]	4.0 [1.9 - 5.6]	1.7 [1.2 - 1.9]	0.8 [0.5 - 9.3]	6.3 [- ; -]	3.8 [2.1 - 4.1]
Median OS (mths) [95% CI]	14.7 [6.2 - 19.6]	Not reached [4.9 - -]	8.6 [4.5 - 12.0]	2.1 [1.5 - 15.1]	1.9 [0.6 - -]	9.0 [- ; -]	9.0 [7.0 - 15.1]

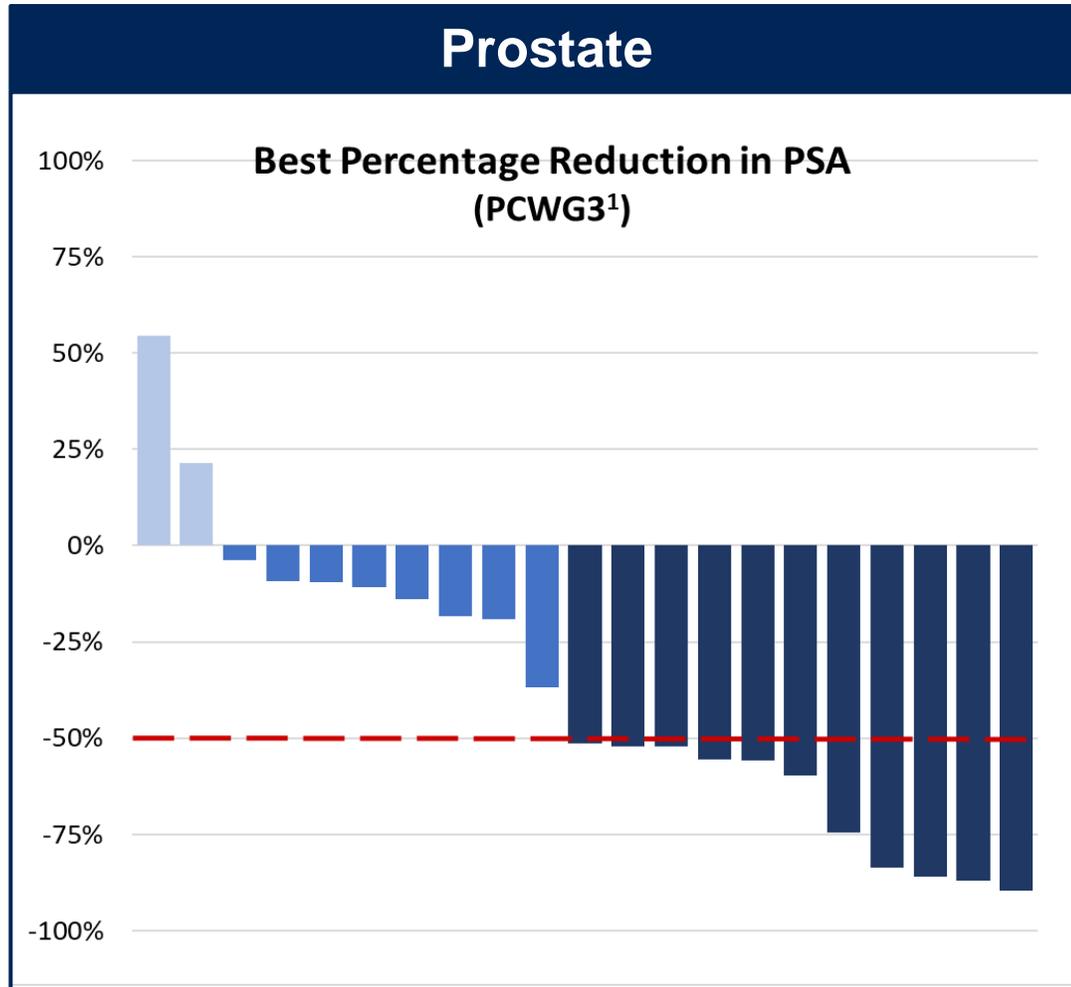
*Composite disease progression outcome: RECIST soft tumor / bone / PSA (RECIST v1.1, PCWG3)
 Evaluable: received ≥ 1 dose of DEP CTX and had a post-baseline scan at ≥8 weeks,
 or efficacy measurement for prostate patients.
 RECIST-measurable at baseline (ORR data)

HNSCC: Head & Neck Squamous Cell Cancers
 † Other cancers: thymic carcinoma, NSCLC

Phase 2 anti-tumor activity – RECIST



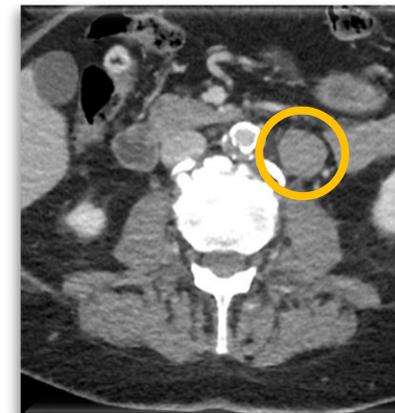
Phase 2 prostate cancer



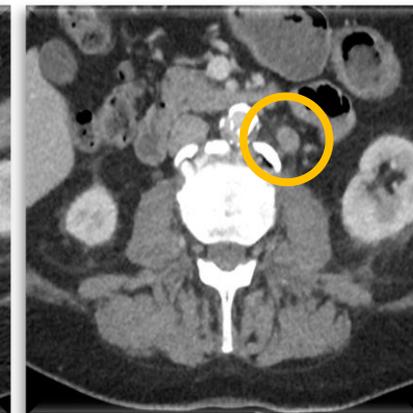
1. Scher H et al. *J Clin Oncol* 2016

- **PSA reduction in 91%**
 >50% reduction ('PSA50') in 52%

- **62% reduction abdominal LNs**
- **87% PSA reduction**



Baseline



On treatment

- **87% stable or improved bone disease**
- **Durable PRs and SDs up to 55 weeks**

Conclusions

- **Dendrimer cabazitaxel is safe and well tolerated:**
 - **no pre-medication** (due to lack of toxic excipients)
 - **potential for less severe myelosuppression** compared with standard CTX
 - **despite little use of G-CSF**
 - **no AEs related to dendrimer scaffold**
- **Clinical benefit even in patients previously exposed to taxanes**
- **DEP platform has potential to deliver other cytotoxics, targeted therapies & radioisotopes**
- **Further clinical development of DEP CTX is justified**

Acknowledgements

- All patients participating in the study, and their families
- All investigators and research personnel who conducted this trial
- Sponsor: Starpharma Pty Ltd

