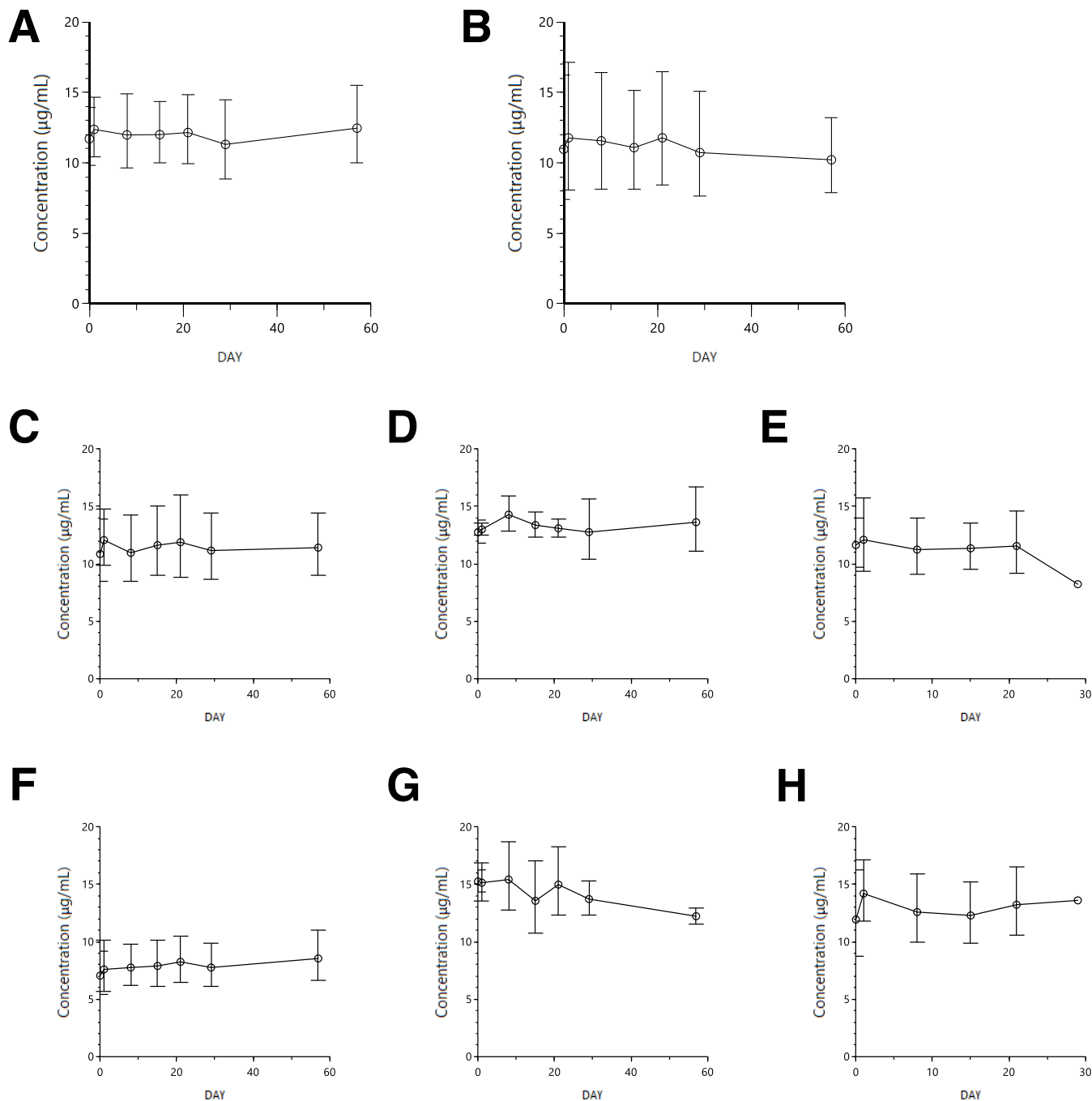
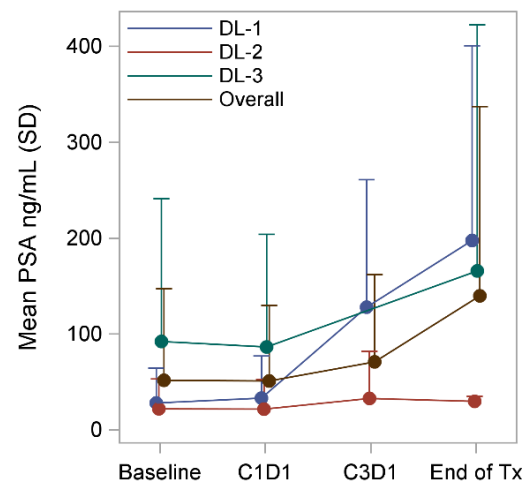
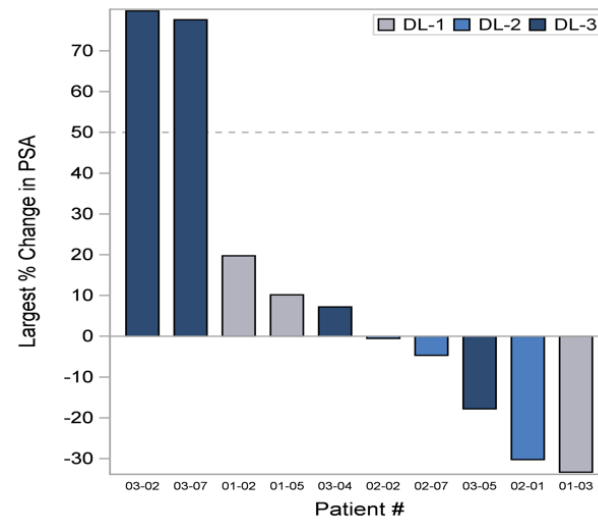




Supplementary Fig. S1: Enzalutamide PK studies.

(A-B) Trough enzalutamide (A) and N-desmethyl Enzalutamide (B) concentrations (geometric mean $\pm$ geometric standard deviation) over the period of study with venetoclax dosing starting immediately after the day 0 data point.

(C-H) Trough enzalutamide (C-E) and N-desmethyl enzalutamide (F-H) concentrations (geometric mean $\pm$ geometric standard deviation) over the period of study with venetoclax dosing starting immediately after the day 0 data point, by dose of venetoclax, 400 mg (C and F), 600 mg (D and G), or 800 mg (E and H).

A**B**

Supplementary Fig. S2. Measures of clinical efficacy of the enzalutamide/venetoclax combination treatment in mCRPC patients (A-B) Shown are PSA response summary (A) and waterfall plot (B).

Supplementary Table S1: Patient information (NCT03751436)*

Subject ID	Age (start of treatment)	Age (end of treatment)	Age (when patient passed)	Prior ARPI treatment	Consent	On study	Off treatment	Off study	Deceased/Alive
01-01-RP					ineligible				
01-02-RP	59	59	59	Abi x 10 mos	2-Aug-19	9-Aug-19	1-Nov-19	25-Jun-20	DECEASED 6/25/2020
01-03-RP	74	77	79	Enza x 2 mos	19-Aug-19	5-Sep-19	15-May-22	15-Aug-22	DECEASED 9/8/2024
01-04-RP					ineligible				
01-05-RP	73	73	74	Abi x 4 mos	30-Sep-19	7-Nov-19	28-Jan-20	31-May-21	DECEASED 6/2/2021
02-01-RP	67	68	70	No	18-Nov-19	5-Dec-19	5-Aug-20	13-Apr-22	DECEASED 5/5/2022
02-02-RP	69	69	70	Enza x 5 mos	30-Dec-19	2-Jan-20	30-Mar-20	3-Jun-21	DECEASED 6/3/2021
02-03-RP					ineligible				
02-04-RP					ineligible				
02-05-RP					ineligible				
02-06-RP					ineligible				
02-07-RP	76	77	79	Enza x 10 mos	25-Jun-20	30-Jun-20	15-Mar-21	16-Mar-22	DECEASED 11/2/2022
03-01-RP					ineligible				
03-02-RP	63	64	64	Abi x 11 mos	3-Jul-20	7-Jul-20	4-Sep-20	21-Jan-21	DECEASED 1/21/2021
03-03-RP					Withdrawn				
03-04-RP	75	75	77	Enza x 7 mos	3-Sep-21	8-Nov-21	5-Dec-21	11-Aug-23	DECEASED 8/11/2023
03-05-RP	63	63	x	Enza x 22 mos	12-Oct-21	11-Nov-21	5-Jan-22	5-Jan-23	ALIVE
03-06-RP					ineligible				
03-07-RP	74	74	x	Abi x 29 mos	2-May-22	3-May-22	17-Jul-22	18-May-23	ALIVE, still on Pluvicto
03-08-RP					ineligible				

*A total of 20 patients were screened and 10 eligible patients (marked in blue) were enrolled in the Enzalutamide and Venetoclax combination trial, who were put on 3 dose levels (DL) of venetoclax, i.e., DL1 at 400 mg/d (subjects 01-02-RP, 01-03-RP and 01-05-RP), DL2 at 600 mg/d (subjects 02-01-RP, 02-02-RP and 02-07-RP), and DL3 at 800 mg/d (subjects 03-02-RP, 03-04-RP, 03-05-RP and 03-07-RP).

Supplementary Table S2. Enzalutamide and N-desmethyl enzalutamide plasma PK parameters (geometric mean (geometric standard deviation)).

	ENZA		ENZAdm		MR	
Dose	C _{min} D0 [#]	C _{min} D1 [#]	C _{min} D0 [#]	C _{min} D1 [#]	D0	D1
(mg)	(µg/mL)	(µg/mL)	(µg/mL)	(µg/mL)		
400 (N=3)	10.8 (1.28)	12.1 (1.23)	7.04 (1.31)	7.59 (1.34)	0.65 (1.08)	0.63 (1.09)
600 (N=3)	12.7 (1.08)	13.0 (1.04)	15.2 (1.07)	15.1 (1.12)	1.20 (1.02)	1.17 (1.16)
800 (N=4)	11.6 (1.20)	12.1 (1.30)	11.9 (1.36)	14.2 (1.21)	1.03 (1.50)	1.17 (1.55)
Total (N=10)	11.7 (1.19)	12.4 (1.19)	11.0 (1.48)	11.8 (1.46)	0.94 (1.43)	0.95 (1.48)
P-value*	0.008		0.652		0.910	

[#]C_{min} D0 refers to the pre (pre 1st venetoclax) sample on day 1 while C_{min} D1 is the 24 h sample relative to C_{min} D0.

*Wilcoxon exact sign test (two-tailed, paired), comparing D0 and D1 values for enzalutamide (ENZA), metabolite (ENZAdm), and metabolic ratio (MR), respectively, not corrected for multiple testing.