Capivasertib in combination with enzalutamide for metastatic castration resistant prostate cancer: results from the randomized phase II RE-AKT trial

Supplementary Material

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A. List of sites and investigators

Site	Principal Investigator Name	Total Recruited
Royal Marsden Hospital, Sutton	Prof Johann de Bono	45
Beatson West of Scotland Cancer Centre	Rob Jones	2
Belfast City Hospital	Dr Suneil Jain	1
University College Hospital	Ursula McGovern	5
St James's University Hospital	Dr Christy Ralph	6
Southampton General Hospital	Dr Simon Crabb	8
Royal Preston Hospital	Dr Alison Birtle	2
Pilgrim Hospital	Dr Miguel Panades	3
Norfolk & Norwich Hospital	Dr Jenny Nobes	9
Queen Alexandra Hospital	Dr Joanna Gale	2
Clatterbridge Cancer Centre	Dr Zafir Malik	8
Mount Vernon Hospital	Prof Peter Hoskin	5
Derriford Hospital	Dr Peter Sankey	2
Western General Hospital	Dr Duncan McLaren	1
Nottingham City Hospital	Dr Eliot Chadwick	1

B. Eligibility criteria

Inclusion Criteria

1. Written informed consent.

2. Histological diagnosis of adenocarcinoma of the prostate and with tumour tissue accessible for research analyses for this trial (e.g. PTEN testing). Patients who have no histological diagnosis must be willing to undergo a biopsy to prove prostate adenocarcinoma.

3. Metastatic Castration-Resistant Prostate Cancer (mCRPC).

4. Progressed after 1 or 2 lines of taxane based chemotherapy.

5. Progressed after abiraterone (pre or post chemotherapy). Patients must have received at least 12 weeks of treatment with abiraterone.

6. Age ≥18 years.

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 – 2.

8. PSA ≥ 10ng/ml.

9. Documented willingness to use an effective means of contraception while participating in the study and for 12 months post last dose of treatment.

10. Documented ongoing castrate serum testosterone <50 ng/dL (<1.7 nmol/L).

11. Received prior castration by orchiectomy and/or ongoing Luteinizing Hormone-Releasing Hormone (LH-RH) agonist treatment.

12. Progression of disease by PSA utilizing PCWG2 criteria and at least another of the following criteria;

    a. Bone scan: disease progression as defined by at least 2 new lesions on bone scan.
    b. Soft tissue disease progression defined by modified RECIST 1.1.
    c. Clinical progression with worsening pain and the need for palliative radiotherapy for bone metastases.

Exclusion Criteria

1. Prior treatment with enzalutamide (MDV3100).

2. Prior treatment with PI3K, AKT, TOR kinase or mTOR inhibitors.

3. Surgery, chemotherapy, or other anti-cancer therapy within 4 weeks prior to trial entry / randomisation into the study (6 weeks for bicalutamide). Any other therapies for prostate cancer, other than GnRH analogue therapy, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (e.g., finasteride or dutasteride), must be discontinued at least 2 weeks before the first dose of study drug.

4. Participation in another clinical trial and any concurrent treatment with any investigational drug within 4 weeks prior to trial entry / randomisation.

5. Prior limited field radiotherapy within 2 weeks or wide field radiotherapy within 4 weeks of trial entry / randomisation.

6. History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumours, brain metastases, or alcoholism.

7. History of loss of consciousness or transient ischemic attack within the previous 12 months of trial entry / randomisation.

8. Known brain or leptomeningeal involvement.

9. Use of potent inhibitors or inducers of CYP3A4, CYP2C9, CYP2C19 and CYP2D6 substrates within 2 weeks before trial entry / randomisation (3 weeks for St John's Wort) must be avoided.

10. Clinically significant abnormalities of glucose metabolism as defined by any of the following:

    a. Diabetes mellitus type I.
    b. Fasting plasma glucose [fasting is defined as no calorific intake for at least 8 hours]: ≥ 7.0mmol/L (126 mg/dL) for those patients without a pre-existing diagnosis of Type 2 diabetes mellitus≥ 9.3 mmol/L (167mg/dL) for those patients with a pre-existing diagnosis of Type 2 diabetes mellitus
    c. Glycosylated haemoglobin (HbA1C) ≥8.0% (63.9 mmol/mol)
    d. Requirement for insulin for routine diabetic management and control
    e. Requirement for more than two oral hypoglycaemic medications for routine diabetic management and control

11. Inadequate organ and bone marrow function as evidenced by:
    a. Haemoglobin <85 g/L
    b. Absolute neutrophil count <1.0 x 109/L
    c. Platelet count < 75 x 109/L
    d. Albumin ≤25 g/L
    e. AST / SGOT and/or ALT / SGPT ≥ 2.5 x ULN (≥ 5 x ULN if liver metastases present)
    f. Total bilirubin ≥ 1.5 x ULN (except for patient with documented Gilbert's disease)
    g. Serum Creatinine > 1.5 x ULN

12. Inability or unwillingness to swallow oral medication.

13. Malabsorption syndrome or other condition that would interfere with enteral absorption.
14. Any of the following cardiac criteria;
    a. Mean resting corrected QT interval (QTcF) >470msec obtained from 3 consecutive ECGs taken within 5 minutes
    b. Any clinically important abnormalities in rhythm, conduction, or morphology of a resting ECG (e.g., complete left bundle branch block, third degree heart block)
    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT

syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval or with a potential for Torsades de pointes

d. Experience of any of the following procedures or conditions in the preceding six months:coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA ≥ Grade2
e. Uncontrolled hypotension defined as – systolic blood pressure (BP) <90mmHg and/or diastolic BP <50mmHg

15. Clinically significant history of liver disease consistent with Child-Pugh Class B or C, including viral or other hepatitis, current alcohol abuse, or cirrhosis.

16. Any other finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patients at high risk from treatment complications.

17. Need for chronic corticosteroid therapy of >10 mg of prednisolone or >0.5mg of dexamethasone per day or an equivalent dose of other anti-inflammatory corticosteroid. Patients in which corticosteroids cannot be stopped prior to entering the trial are allowed a maximum of 10mg of prednisolone per day or equivalent. In the case of corticosteroid discontinuation, a 2-week (14 days) washout is required with a mandatory PSA check prior to starting the trial. If the PSA has declined compared to the value obtained prior to stopping corticosteroids, patients will not be eligible for study. Patients can only enter the study with a confirmed PSA increase.

18. Malignancies other than prostate cancer within 5 years prior to trial entry / randomisation, except for adequately treated basal or squamous cell skin cancer.

19. Unresolved clinically significant toxicity from prior therapy except for alopecia and Grade 1 peripheral neuropathy.

20. Inability to comply with study and follow-up procedures.

21. Patients with predominately small cell or neuroendocrine differentiated prostate cancer are not eligible.

C. Supplementary Tables

Table C.1: Previous cancer treatment by treatment group

	Enzalutamide/ capivasertib N=50		Enzalutamide/ placebo N=50		Total N=100	
	n	**%**	**n**	**%**	**n**	**%**
Prostatectomy	5	10	7	14	12	12
Transurethral resection prostate	8	16	6	12	14	14
External beam radiotherapy	21	42	21	42	42	42
Brachytherapy	1	2	1	2	2	2
Palliative Radiotherapy	32	64	37	74	69	69
Abiraterone	50	100	50	100	100	100
Docetaxel	50	100	50	100	100	100
Cabazitaxel	21	42	21	42	42	42
Radium 223	9	18	19	38	28	28
Steroids	48	96	46	92	94	94
Dexamethasone	19	38	18	36	37	37
Prednisolone	29	58	28	56	57	57
Chemical castration	46	92	46	92	92	92
Antiandrogens	31	62	33	66	64	64
Bicalutamide	30	60	32	64	62	62
Flutamide	0	0	1	2	1	1
Other	1	2	0	0	1	1
Other hormonal treatments	10	20	8	16	18	18
Diethylstilbestrol	8	16	8	16	16	16
Onapristone	2	4	0	0	2	2
Targeted therapy	3	5	6	12	9	9
AZD3514	0	0	1	2	1	1
Custirsen	0	0	1	2	1	1
Dasatinib	0	0	1	2	1	1
Masitinib/placebo	0	0	1	2	1	1
Olaparib	1	2	2	4	3	3
Saracatinib/placebo	1	2	0	0	1	1
Tasquinimod /placebo	1	1	0	0	1	1
Biphosphonates	1	2	2	4	3	3
Other chemotherapy	0	0	3	6	3	3
Carboplatin	0	0	2	4	2	2
Pacitaxel	0	0	1	2	1	1
Other	3	5	6	12	9	9
Celecoxib	0	0	1	2	1	1
GM-CSF	0	0	1	2	1	1
Gvax	1	2	0	0	1	1
Lenalidomide	0	0	1	2	1	1
Pembrolizumab	1	2	1	2	2	2
Prostvac	0	0	1	2	1	1
Metformin (stampede trial)	1	1	1	2	2	2

Table C.2: Brief Pain Inventory scores, by treatment group

Variable	Time, weeks	Enzalutamide/capivasertib				Enzalutamide/placebo				P-value
		N	Median	Q1	Q3	N	Median	Q1	Q3	
Worst pain in last 24 hours	0	48	4.0	2.0	6.0	49	4.0	1.0	7.0	0.7
	12	32	3.0	0.0	6.0	29	4.0	2.0	7.0	0.4
	24	19	2.0	0.0	6.0	13	4.0	0.0	6.0	0.7
Least pain in last 24 hours	0	49	1.0	0.0	3.0	48	1.0	0.0	2.5	0.9
	12	32	1.0	0.0	3.0	29	1.0	0.0	3.0	0.9
	24	19	1.0	0.0	1.0	13	1.0	0.0	3.0	0.8
Average pain	0	48	3.0	0.5	5.0	49	3.0	1.0	5.0	0.8
	12	32	2.5	0.0	5.0	29	3.0	1.0	4.0	0.7
	24	19	1.0	0.0	4.0	13	2.0	0.0	4.0	0.9
Pain now	0	49	2.0	0.0	4.0	49	2.0	0.0	3.0	0.8
	12	32	2.0	0.0	3.0	29	2.0	0.0	3.0	0.6
	24	19	1.0	0.0	3.0	13	0.0	0.0	1.0	0.5
Mean severity score	0	48	2.8	0.8	4.5	48	2.4	0.9	4.4	0.7
	12	32	2.4	0.0	4.3	29	2.8	1.0	3.8	0.7
	24	19	1.0	0.0	3.8	13	1.5	0.3	3.0	0.8
Analgesic score	0	50	2.9	0.1	5.4	48	1.7	0.1	5.5	0.8
	12	31	2.3	0.0	5.4	29	2.7	0.0	4.4	0.7
	24	18	0.9	0.0	5.1	12	1.4	0.0	3.6	1.0

Table C.3: Antitumour activity (individual components) by $PTEN_{IHC}$ status and treatment group (evaluable population)

		Enzalutamide/capivasertib					Enzalutamide/placebo					Difference %R			
		N	R	%R	95%CI		N	R	%R	95%CI		Diff	90%CI		p-value
$PTEN_{IHC}$ Normal *(N=62)*	*RECIST 1.1 response*	23	4	17.4	(5.0	38.8)	27	4	14.8	(4.2	33.7)	2.6	(-14.6	19.8)	
	Confirmed PSA fall >=50%	24	7	29.2	(12.6	51.1)	28	7	25.0	(10.7	44.9)	4.2	(-16.2	24.5)	
	Confirmed CTC conversion	16	2	12.5	(1.6	38.3)	22	5	22.7	(7.8	45.4)	-10.2	(-30.3	9.8)	
	RECIST 1.1 or PSA response	24	8	33.3	(15.6	55.3)	30	7	23.3	(9.9	42.3)	10.0	(-10.3	30.3)	0.30
$PTEN_{IHC}$ Loss *(N=26)*	*RECIST 1.1 response*	9	0	0.0	(0.0	33.6)	8	1	12.5	(0.3	52.7)	-12.5	(-31.7	6.7)	
	Confirmed PSA fall >=50%	10	0	0.0	(0.0	30.8)	12	1	8.3	(0.2	38.5)	-8.3	(-21.5	4.8)	
	Confirmed CTC conversion	9	0	0.0	(0.0	33.6)	11	0	0.0	(0.0	28.5)	0.0	(0.0	0.0)	
	RECIST 1.1 or PSA response	11	0	0.0	(0.0	28.5)	11	1	9.1	(0.2	41.3)	-9.1	(-23.3	5.2)	0.48

N: number of patients
R: Number of responses
%R: Response Rate, 95%CI: 95% exact confidence interval for proportions; 90% CI: normal approximation for difference of proportions
P-value: 1-sided exact Fisher's test

Table C.4 Antitumor activity (measured by composite response) by treatment group (evaluable population) and $PTEN_{IHC}$ status and biopsy type (diagnostic or fresh)

Biopsy type	Composite response by PTENIHC status	Enzalutamide/capivasertib					Enzalutamide/placebo					Difference %			p-value
		N	R	%R	95%CI		N	R	%R	95%CI		Diff	90%CI		
Diagnostic *(N=67)*	$PTEN_{IHC}$ Normal *(N=49)*	23	8	34.8	(16.4	57.3)	26	6	23.1	(9.0	43.6)	0.1	(-0.1	0.3)	0.28
	$PTEN_{IHC}$ Loss *(N=18)*	8	0	0.0	(0.0	3.69)	10	1	10.0	(0.3	44.5)	-0.1	(-0.3	0.1)	0.56
Fresh *(N=21)*	$PTEN_{IHC}$ Normal (*N=13*)	6	1	16.7	(0.4	64.1)	7	2	28.6	(28.6	71.0)	-0.1	(-0.5	0.3)	0.56
	$PTEN_{IHC}$ Loss (*N=8*)	5	0	0.0	(0.0	52.2)	3	0	0.0	(0.0	70.8)	0.0	-	-	-

N: number of patients
R: Number of responses
%R: Response Rate, 95%CI: 95% exact confidence interval for proportions; 90% CI: normal approximation for difference of proportions
P-value: 1-sided exact Fisher's test

Table C.5: Secondary endpoints by $PTEN_{IHC}$ status and treatment

		$PTEN_{IHC}$ Loss		$PTEN_{IHC}$ Normal	
		ENZ/CAP	**ENZ/PLA**	**ENZ/CAP**	**ENZ/PLA**
Percentage change from baseline in PSA at 12 weeks	**N**	9	13	24	26
	Median	51.5%	59.1%	-30.2%	30.9%
	Q1 - Q3	-12.6% to 70.3%	-0.1% to 101.5%	-63.7% to 20.7%	-69.6% to 81.7%
	P-value1*	0.84		0.12	
	P-value2**	0.04			
Best percentage change from baseline in PSA while on treatment	**N**	10	12	23	26
	Median	34.3%	11.3%	-42.9%	-29.5%
	Q1 - Q3	-27.5% to 66.7%	-66.5% to 76.0%	-84.6% to 16.3%	-69.6% to 35.5%
	P-value1*	0.82		0.34	
	P-value2**	0.04			
Best percentage change from baseline in CTC while on treatment	**N**	11	14	23	30
	Median	-41.5%	-44.1%	-66.7%	-33.4%
	Q1 - Q3	-100% to -23.6%	-77.8% to 5.9%	-97.1% to 0%	-72.7% to 55%
	P-value1*	0.44		0.21	
	P-value2**	0.96			
Best percentage change from baseline in sum of target lesions while on treatment	**N**	5	5	15	10
	Median	4.2%	8.0%	-7.8%	-9.3%
	Q1 - Q3	0% to 27.0%	-14.0% to 11.3%	-35.3% to 5.0%	-40.0% to 33.9%
	P-value1*	0.69		0.68	
	P-value2**	0.26			

*P-value1 corresponds to a Mann-Whitney test comparing the median percentage change between treatment groups within each $PTEN_{IHC}$ status.

**P-value2 corresponds to a Mann-Whitney test comparing the median percentage change between each $PTEN_{IHC}$ status.

ENZ: enzalutamide, CAP: capivasertib, PLA: placebo

Table C.6: Serious Adverse Reactions reported in the trial

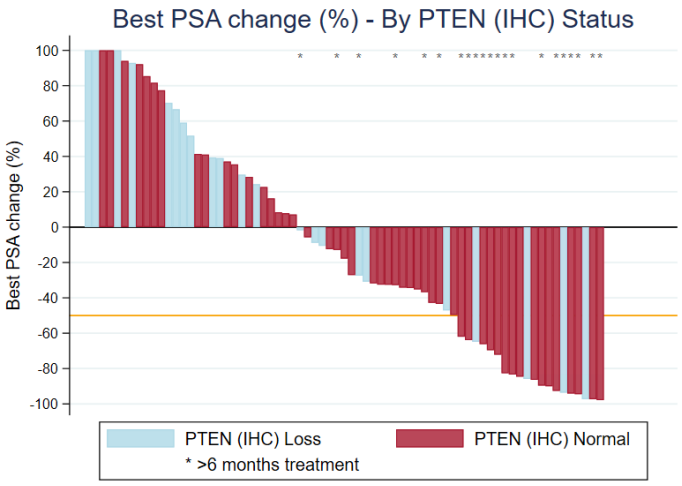
Patient	Type	Category	Randomised treatment	Time on treatment before event (months)	Severity	Summary of event	Outcome	Relationship to CAP/PLA	Relationship to ENZ
1	SAR	Hospitalisation	ENZ/CAP	0.7	2. Moderate	Diarrhoea(2): Shortness of breathing(1):	Recovered	Diarrhoea - Possibly related Shortness of breath - Unrelated	Diarrhoea – Unrelated Shortness of breath - Unrelated
2	SAR	Hospitalisation	ENZ/CAP	0.4	3. Severe	Lip swelling (Possible hypersensitive reaction)(1): Maculopapular rash(3):	Recovered	Probably related	Unrelated
3	SAR	Hospitalisation	ENZ/CAP	4.8	3. Severe	Diarrhoea(3):	Recovered	Possibly related	Unrelated
4	SAR	Hospitalisation	ENZ/CAP	2.1	3. Severe	Diarrhoea type 7(3):	Recovered	Possibly related	Unrelated
5	SUSAR	Hospitalisation	ENZ/CAP	6.9	3. Severe	Low sodium levels(3): Confusion(3):	Recovered	Possibly related	Possibly related
6	SUSAR	Hospitalisation	ENZ/CAP	1.2	3. Severe	Acute Kidney Injury(3):	Recovered	Possibly related	Unrelated
7	SUSAR	Other	ENZ/CAP	0.2	2. Moderate	Transient Ischemic Attack(2):	Recovered	Probably related	Unrelated
8	SUSAR	Life Threatening	ENZ/CAP	7.1	4. Life Threatening	Diarrhoea(4): Acute kidney injury(3): Infection (3):	Recovered	Possibly related	Unrelated
9	SUSAR	Hospitalisation	ENZ/CAP	15.8	3. Severe	Acute Kidney Injury(3): Urinary Tract Infection(3):	Recovered	Possibly related	Unrelated
10	SUSAR	Hospitalisation	ENZ/CAP	10.5	1. Mild	Non-neutropenic sepsis(1):	Recovered	Unrelated	Unrelated
11	SAR	Hospitalisation	ENZ/PLA	3.7	3. Severe	Left Hip Pain(3): Reduced Mobility(3): Skin rash over both feet(1):	Recovered	Left hip: Unrelated Rash: Probably related	Left hip: Unrelated Rash: Unlikely related
12	SUSAR	Hospitalisation	ENZ/PLA	37.3	3. Severe	Encephalitis - Unknown cause(3):	Recovered with Sequelae	Unlikely related	Unlikely related
13	SAR	Hospitalisation	ENZ/PLA	1.0	2. Moderate	Diarrhoea(2): Pleural Effusion(1):	Condition Improving	Diarrhoea: Possibly related Pleural effusion: Unrelated	Unrelated

SAR: Serious Adverse Reaction; SUSAR: Suspected Unexpected Serious Adverse Reactions. ENZ: enzalutamide, CAP: capivasertib, PLA: placebo

D. Supplementary Figures

Figure D.1: Best percentage change from baseline at any time during allocated treatment in a) PSA b) CTC and c) sum of target lesions, by $PTEN_{IHC}$ status

a



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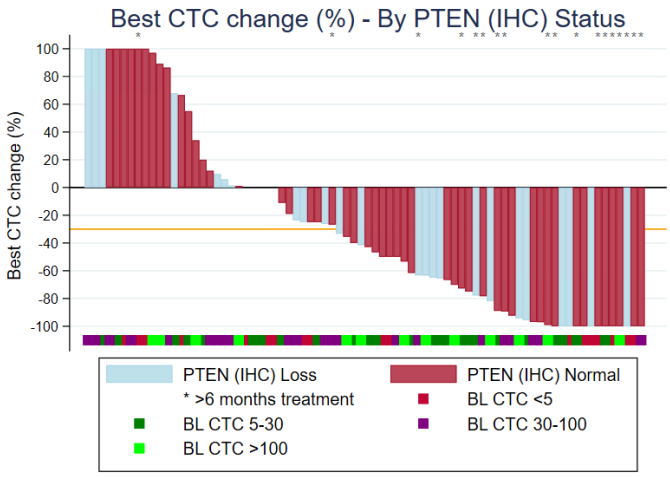


Note: BL CTC refers to baseline CTC

c

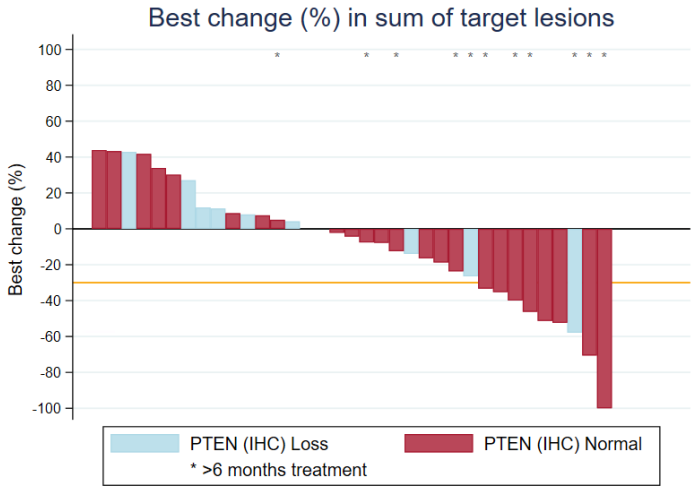
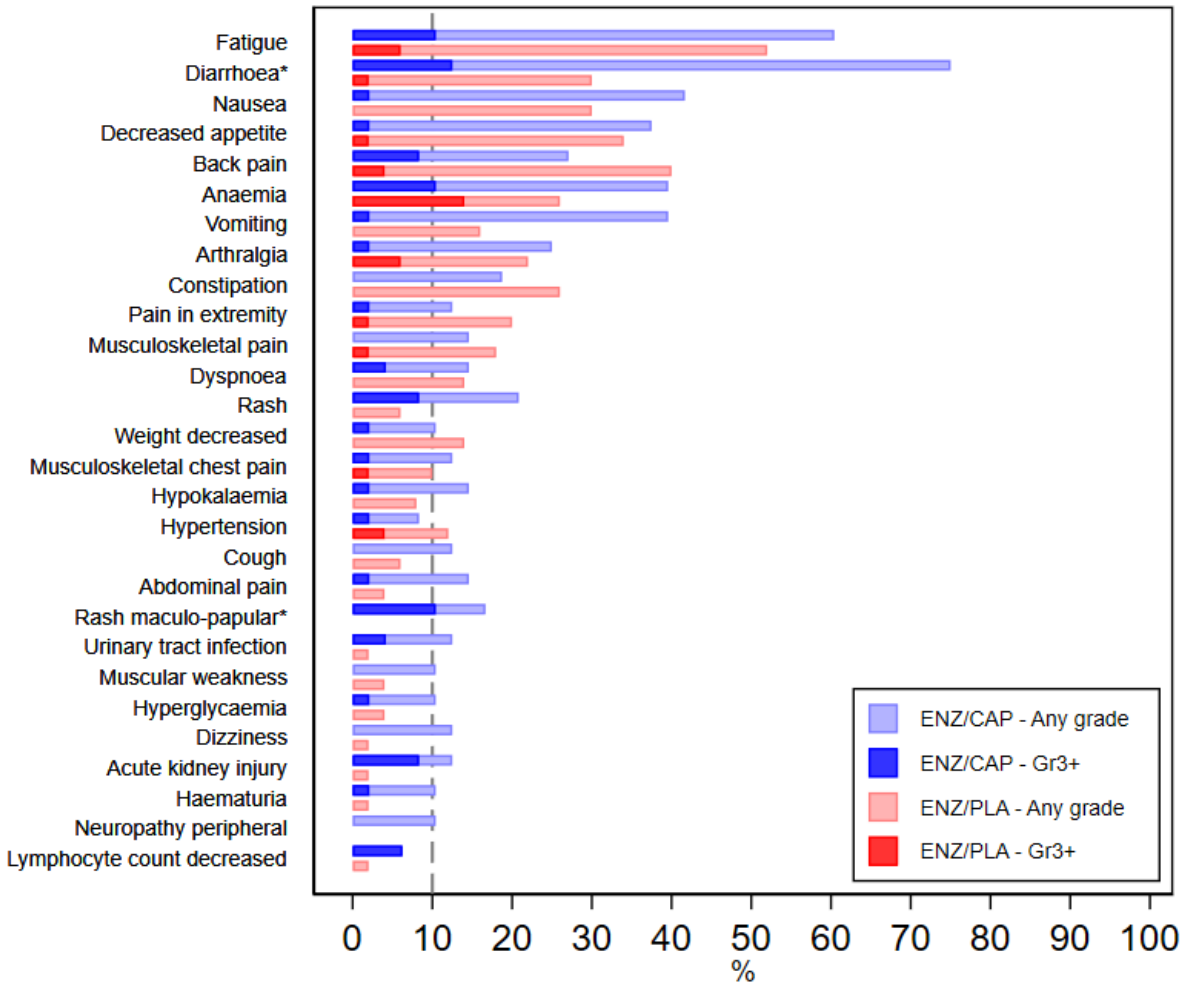


Figure D.2. – Treatment-emergent adverse events while on treatment

Adverse events (AE) were graded according to Common Terminology Criteria for Adverse Events version 4. Treatment-emergent refers to AE not present at baseline, or worsening form baseline. Only AE occurring in at least 10% of patients for any grade, or at least 5% for grade 3 or worse, are reported here.



*Statistically significant differences between groups found in the comparison of number of patients with these particular adverse events (any grade, $p<0.01$).