PARIS 2022 ESMO congress

SAKK
WE BRING PROGRESS TO CANCER CARE

SAKK 08/14 - IMPROVE
Investigation of metformin in patients with metastatic castration-resistant prostate cancer (mCRPC) in combination with enzalutamide vs. enzalutamide alone

A randomized, open label, phase II trial

C. Rothermundt, R. Cathomas, K. Gysel, N. Fischer, R. Pereira Mestre, T. Hermanns, S. I. Rothschild, N. Mach, W. Mingrone, M. Ciriolo, B. Müller, A. Erdmann, C. Schär, C. Mamot, P. Bohanes, A. Omlin, S. Bastian, K. Ribi, S. Gillessen

St. Gallen, Switzerland
September 11, 2022

Declaration of Interests

Christian Rothermundt

Consulting or Advisory Role (Payment to Institution)

Bayer (Schweiz) AG, Bristol-Myers Squibb, Ipsen, MSD Oncology, Pfizer

Consulting or Advisory Role (Payment to me)

Merck (Schweiz) AG

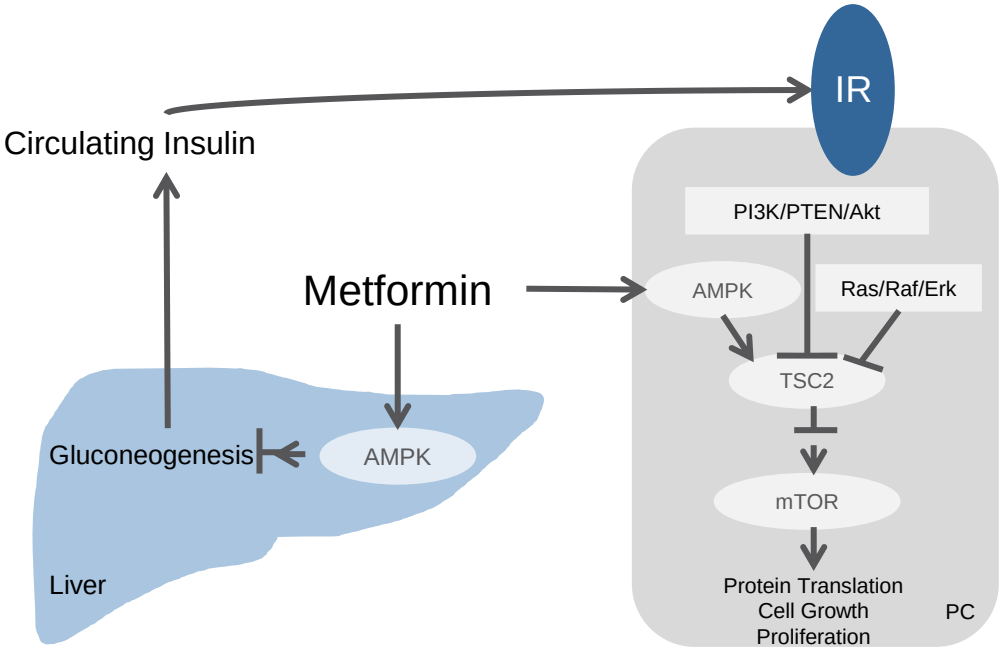
Travel Expenses (Payment to me)

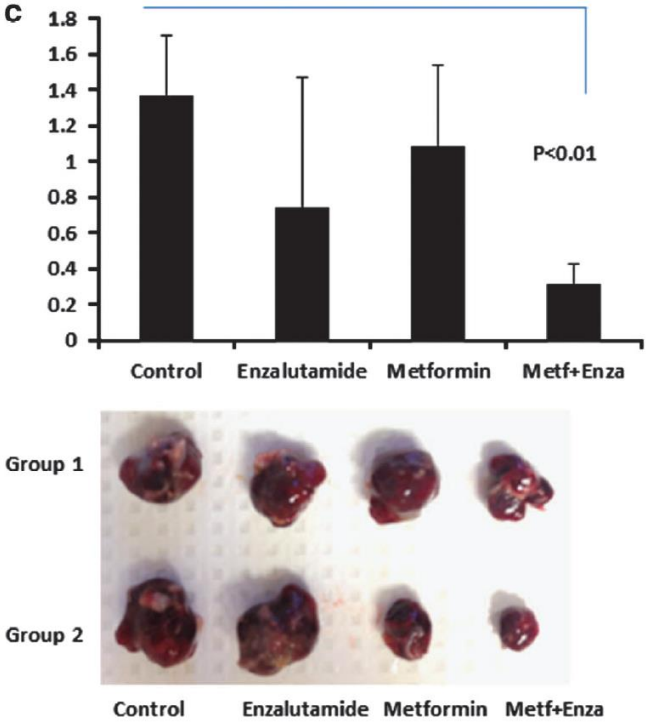
PharmaMar

Research Funding (Payment to Institution)

Astellas Pharma AG

Pre-clinical Rationale

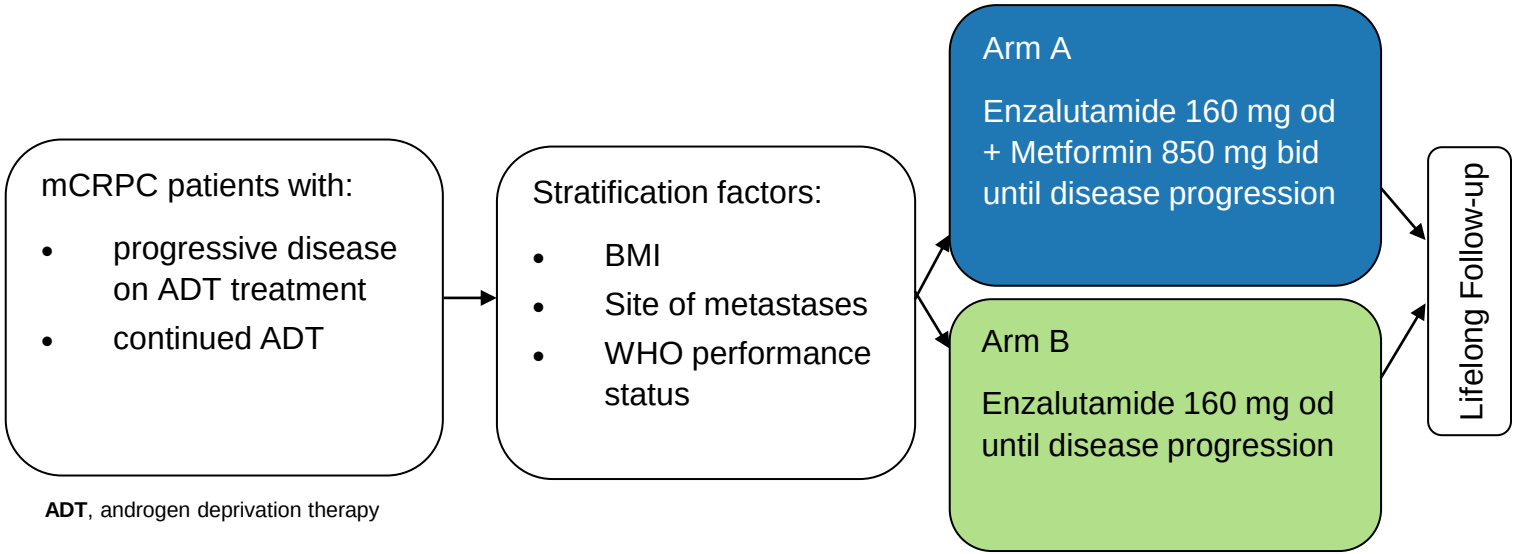




Nguyen HG et al. Oncogene. 2014 Sep 4;33(36):4521-30.
Goodwin PJ et al. J Clin Oncol. 2009 Jul 10;27(20):3271-3.

IR, Insulin Receptor; **PC**, Prostate Cancer Cell; **AMPK**, AMP-activated protein kinase; **mTOR**, mammalian target of rapamycin; **PI3K**, phosphoinositide 3-kinase; **PTEN**, phosphatase and tensin homolog; **Akt**, v-akt murine thymoma viral oncogene homolog; **Erk**, extracellular signal-regulated kinase; **TSC2**, tuberous sclerosis complex tumor suppressor gene 2

Trial Design



ADT, androgen deprivation therapy

Primary Endpoint

Disease Control Rate (DCR) at 15 months:

complete response (CR) or partial response (PR) achieved for at least one assessment within the first 15 months (±6 weeks) of trial treatment, or

stable disease (SD) maintained during treatment for at least 15 months (±6 weeks) after treatment start.

Patients with no assessment within 15 months (±6 weeks) or with SD and last evaluation before 15 months (±6 weeks) were considered:

- failures for DC at 15 months, if they had no following assessment or if they progressed at the following assessment after 15 months (±6 weeks)
- successes for DC at 15 months, if they did not progress at the following assessment after 15 months (±6 weeks) of trial treatment.

Sample Size Calculation:

- Null hypothesis: DCR at 15 months is equal for arm A and B
- Alternative hypothesis: DCR at 15 months is unequal for arm A and B
- Expected difference: 20%
- Type I error 10%, power 80%
- 168 evaluable patients needed

Progression defined by ONE of the following cases (according to PCWG2):

presence of radiographic progression AND symptomatic/clinical progression

presence of radiographic progression AND PSA progression

presence of symptomatic/clinical progression AND PSA progression

DCR, Disease Control Rate; **PCWG2**, Prostate Cancer Working Group 2; **CR**, complete response; **PR**, partial response; **SD**, stable disease; **PSA**, prostate specific antigen

Accrual & Baseline Characteristics

Accrual: from 06/2016 – 02/2021 in 16 sites in Switzerland

Baseline Characteristics	Enzalutamide + Metformin (N=84)	Enzalutamide alone (N=82)
Age (years)		
▪ median (min, max)	72.5 (53.0, 86.0)	71.0 (52.0, 86.0)
Time from first diagnosis (histologically confirmed) to randomization (months)		
▪ median (min, max)	47.2 (0.2, 265.1)	49.0 (7.9, 250.0)
Prostatectomy		
▪ Yes	30 (35.7%)	31 (37.8%)
Site of metastases		
▪ Non-visceral only	64 (76.2%)	60 (73.2%)
▪ Visceral +/- non-visceral	20 (23.8%)	22 (26.8%)

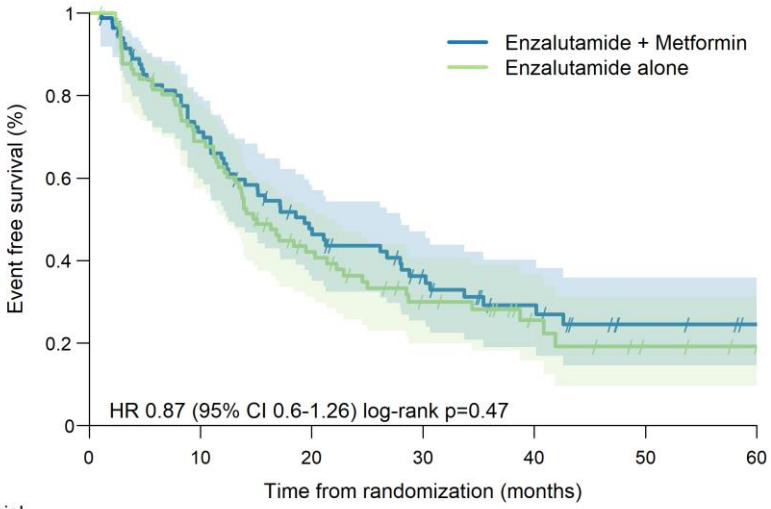
Results: DCR at 15 months

	Enzalutamide + Metformin (N=84)	Enzalutamide alone (N=82)	Total (N=166)
Variable	n (%)	n (%)	n (%)
DCR at 15 months			
▪ No	40 (47.6%)	36 (43.9%)	76 (45.8%)
▪ Yes	44 (52.4%)	46 (56.1%)	90 (54.2%)
Disease control category			
▪ CR	10 (11.9%)	8 (9.8%)	18 (10.8%)
▪ PR	9 (10.7%)	11 (13.4%)	20 (12.0%)
▪ SD for at least 15 months	25 (29.8%)	27 (32.9%)	52 (31.3%)

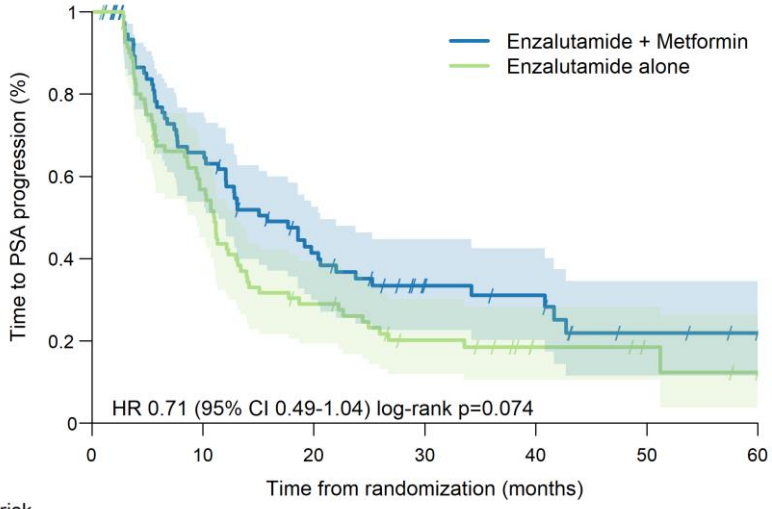
DCR at 15 months:

- Enzalutamide + Metformin: 52.4% (90%CI: 42.9%-61.8%)
- Enzalutamide alone: 56.1% (90%CI: 46.4%-65.4%)
- Fisher's exact test: p-value = 0.644

Results: Event Free Survival & Time to PSA Progression



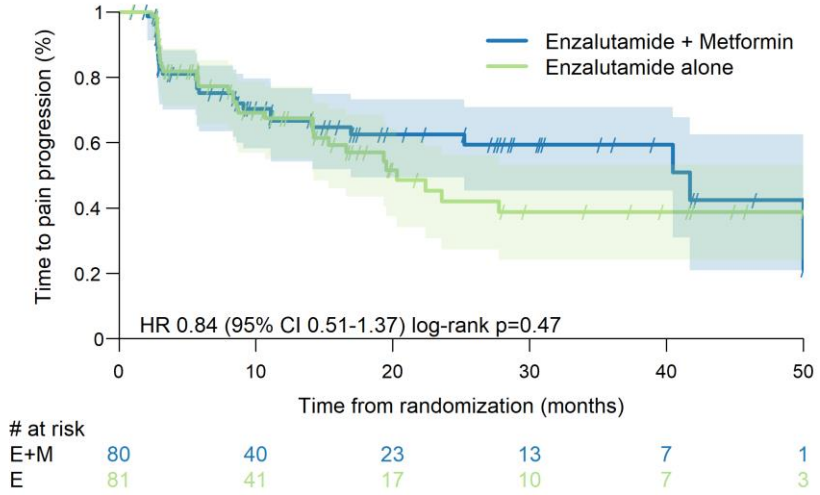
# at risk							
E+M	84	56	35	22	13	5	2
E	82	55	30	17	8	3	1



# at risk							
E+M	84	48	27	14	11	4	2
E	82	43	21	12	5	3	1

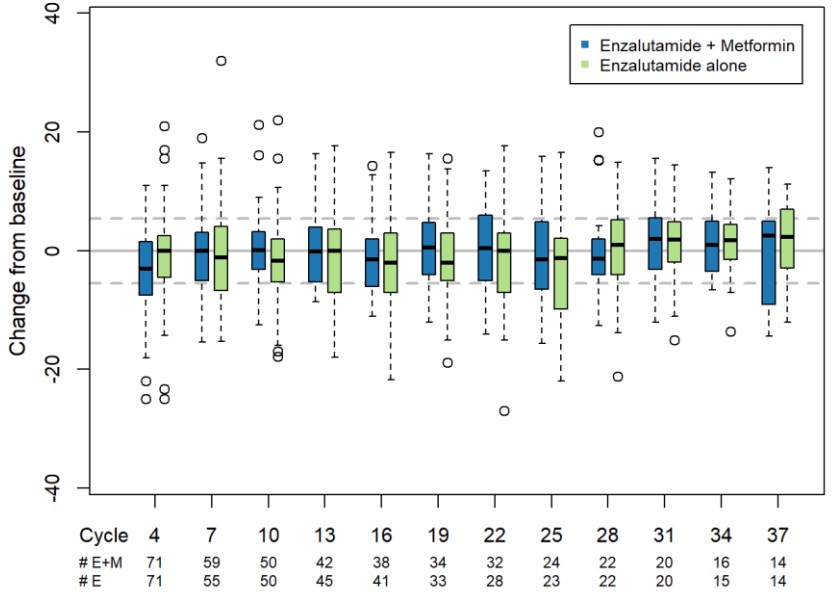
Results: Time to Pain Progression & Quality of Life

Pain progression according to the short version of the Brief Pain Inventory



Pain progression = Mean pain increases by at least 2 points compared to baseline
Scale of pain: 0-10

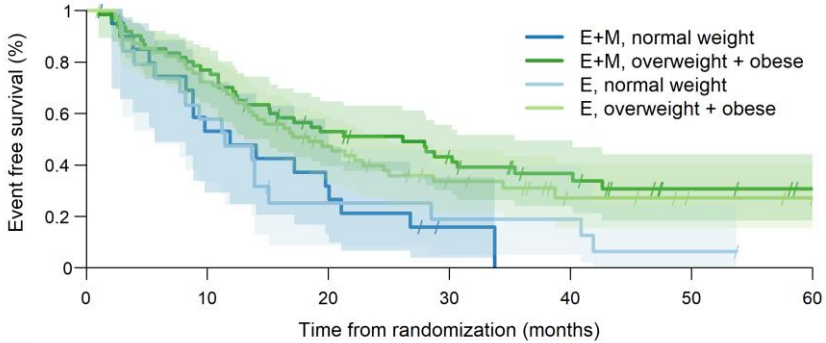
NCCN-Functional Assessment of Cancer Therapy Prostate Symptom Index-17 (FPSI-17)



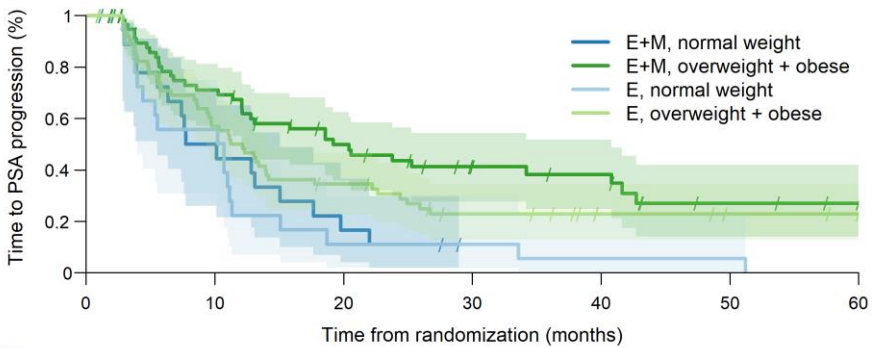
Subgroup Analyses

	Enzalutamide + Metformin (N=84)	Enzalutamide alone (N=82)	Total (N=166)
	n (%)	n (%)	n (%)
BMI			
▪ normal	21 (25.0%)	19 (23.2%)	40 (24.1%)
▪ overweight	43 (51.2%)	45 (54.9%)	88 (53.0%)
▪ obese	20 (23.8%)	18 (22.0%)	38 (22.9%)

BMI, Body Mass Index; [kg/m^2]; < 18.5, underweight; 18.5 – 24.9, normal weight; 25.0 – 29.9, overweight; > 30, obese



# at risk							
E+M, n	21	10	6	1	0	0	0
E+M, o+o	63	46	29	21	13	5	2
E, n	19	11	4	3	3	1	0
E, o+o	63	44	26	14	5	2	1



# at risk							
E+M, n	21	9	3	0	0	0	0
E+M, o+o	63	39	24	14	11	4	2
E, n	19	10	2	2	1	1	0
E, o+o	63	33	19	10	4	2	1

Treatment related Adverse Events (TRAE)

	Enzalutamide + Metformin (N = 85)			Enzalutamide alone (N = 84)		
TRAE Grade 3 – 5	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
▪ Acute coronary syndrome	1 (1.2%)					
▪ Anxiety				1 (1.2%)		
▪ Cardiac arrest			1 (1.2%)			
▪ Fatigue	1 (1.2%)			3 (3.6%)		
▪ Fracture	1 (1.2%)					
▪ Hyperkalaemia	1 (1.2%)					
▪ Hyponatraemia	1 (1.2%)					
▪ Insomnia				1 (1.2%)		
▪ Myocardial infarction	1 (1.2%)			1 (1.2%)		
▪ Nausea	1 (1.2%)					
▪ Neutrophil count decreased	1 (1.2%)					
▪ Platelet count decreased		1 (1.2%)				
▪ Syncope				1 (1.2%)		
▪ Vasovagal reaction				1 (1.2%)		
▪ Weight loss	1 (1.2%)					
▪ White blood cell decreased	1 (1.2%)					

Some other important TRAEs of Grade 1-2:

- Abdominal pain
- Bloating
- Constipation
- Cramp abdominal
- Diarrhoea
- Flatulence

Summary

- This is the first randomized study to investigate Enzalutamide + Metformin in mCRPC.
- The study is negative for the primary endpoint, DCR at 15 months.
- Metformin may have a modest effect on PSA dynamics and symptom control.
- Unplanned subgroup analyses suggest better outcomes for overweight and obese patients compared to normal weight patients.
- Larger studies are needed for confirmation.

Acknowledgements

- The patients and their families
- Investigators and study teams

Funding

- Astellas Pharma AG
- Swiss Cancer Research

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org