Clinical trial results:
PROMET - Multicenter, Randomized Phase II Trial of Salvage Radiotherapy +/- Metformin for Patients with Prostate Cancer after Prostatectomy

Summary

EudraCT number	2016-003599-39
Trial protocol	DE FR
Global end of trial date	28 February 2022

Results information

Result version number	v1 (current)
This version publication date	12 July 2023
First version publication date	12 July 2023

Trial information

Trial identification

Sponsor protocol code	SAKK08/15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02945813
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31389 91 91, sakkcc@sak.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31389 91 91, sakkcc@sak.ch

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to determine if SRT plus metformin is superior to SRT alone in the endpoint of time to progression after prostatectomy failure.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continous assessment of laboratory values and vital signs.

Background therapy:

Salvage radiotherapy (SRT): 70 Gy SRT* | SRT is started 4 weeks after the first dose of metformin (Arm A) / 4-6 weeks after randomization (Arm B) | Duration of SRT: 7 weeks

*The total radiotherapy dose (including boost dose) can be 72-74Gy in case of evidence of macroscopic local recurrence.

Evidence for comparator:

not applicable.

Actual start date of recruitment	24 October 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Switzerland: 54
Worldwide total number of subjects	109
EEA total number of subjects	55

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

111 of planned 170 patients at 17 sites in Switzerland (10 sites, 54 patients), Germany (3 sites, 9 patient), and France (4 sites, 48 patients) have been enrolled from October 2017 to November 2020.

Note: Two patients enrolled in France, did not receive RT after randomization and were not included in the analysis.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fullfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

SRT + Metformin

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	1,1-dimethylbiguanide hydrochloride
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

850 mg metformin p.o. (0-0-1) for 4 weeks, followed by 850 mg metformin p.o. b.i.d (1-0-1) for 48 weeks.

Arm title	Arm B

Arm description:

SRT

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Arm A	Arm B
Started	55	54
Completed	55	54

Period 2	
Period 2 title	Treatment phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

SRT + Metformin

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	1,1-dimethylbiguanide hydrochloride
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

850 mg metformin p.o. (0-0-1) for 4 weeks, followed by 850 mg metformin p.o. b.i.d (1-0-1) for 48 weeks.

Arm title	Arm B

Arm description:

SRT

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Arm A	Arm B
Started	55	54
Completed	55	51
Not completed	0	3
Major eligibility violations	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: SRT + Metformin	
Reporting group title	Arm B
Reporting group description: SRT	

Reporting group values	Arm A	Arm B	Total
Number of subjects	55	54	109
Age categorical Units: Subjects			
Adults (18-64 years)	26	24	50
From 65-84 years	29	30	59
Gender categorical Units: Subjects			
Female	0	0	0
Male	55	54	109

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: SRT + Metformin	
Reporting group title	Arm B
Reporting group description: SRT	
Reporting group title	Arm A
Reporting group description: SRT + Metformin	
Reporting group title	Arm B
Reporting group description: SRT	
Subject analysis set title	Arm A - FAS
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of Arm A	
Subject analysis set title	Arm B - FAS
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of Arm B (excluding three patients with major eligibility violations)	
Subject analysis set title	Arm A - PPS
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol set of Arm A (excluding 13 patients from the FAS due to RT interruption of >5 days [6 pts.] or MET interruption/discontinuation for >30 days [7 pts.])	
Subject analysis set title	Arm B - PPS
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol set of Arm B (excluding four patients from the FAS due to RT interruption of >5 days)	

Primary: PE | Time to progression (FAS)

End point title	PE | Time to progression (FAS)

End point description:

Biochemical progression [BP] defined as (1) Serum PSA value of 0.2 ng/mL or more above the post-radiotherapy nadir, (2) In case there is no PSA decline during trial treatment: Serum PSA value of 0.2 ng/mL or more above the PSA value at randomization. | The biochemical progression has to be confirmed by a second higher serum PSA value (at least 1 week apart, but no later than 4 weeks). The date of biochemical progression is the date of the first PSA rise of 0.2 ng/mL or more.
Clinical progression [CP] defined as either local or regional recurrence of the disease or the appearance of distant metastases. Secondary cancers are not considered as being a clinical progression.

No of events: Arm A = 9 [BP: 7 | CP: 2 | Death: 0] || Arm B = 7 [BP: 4 | CP: 3 | Death: 0]
Note: Dummy data ("999") entered for median TTP due to database restrictions. Median TTP was not reached.

End point type	Primary

End point timeframe:

From randomization until one of the following events, whichever comes first: (1) Biochemical progression [BP], (2) Clinical progression [CP] or (3) Death due to clinical progression [Death]

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Time To Progression (months)				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm B - FAS v Arm A - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.617
Method	Logrank

Statistical analysis title	HR without stratification factors (95% CI)
Statistical analysis description:	
Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing]) Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.	
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	3.46

Statistical analysis title	HR with stratification factors (95% CI)
Statistical analysis description:	
Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing]) Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.	
Comparison groups	Arm A - FAS v Arm B - FAS

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.94

Statistical analysis title	HR without stratification factors (1-sided 80% CI)

Statistical analysis description:

Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing])
Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.

Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.29
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	1.97

Statistical analysis title	HR with stratification factors (1-sided 80% CI)

Statistical analysis description:

Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing])
Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.

Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.25
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	2.05

Primary: PE | Time to progression (PPS)

End point title	PE | Time to progression (PPS)

End point description:

Biochemical progression [BP] defined as (1) Serum PSA value of 0.2 ng/mL or more above the postradiotherapy nadir, (2) In case there is no PSA decline during trial treatment: Serum PSA value of 0.2 ng/mL or more above the PSA value at randomization. | The biochemical progression has to be confirmed by a second higher serum PSA value (at least 1 week apart, but no later than 4 weeks). The date of biochemical progression is the date of the first PSA rise of 0.2 ng/mL or more.
Clinical progression [CP] defined as either local or regional recurrence of the disease or the appearance of distant metastases. Secondary cancers are not considered as being a clinical progression.

No of events: Arm A = 7 [BP: 5 | CP: 2 | Death: 0] || Arm B = 6 [BP: 3 | CP: 3 | Death: 0]
Note: Dummy data ("999") entered for median TTP due to database restrictions. Median TTP was not reached.

End point type	Primary

End point timeframe:

From randomization until one of the following events, whichever comes first: (1) Biochemical progression [BP], (2) Clinical progression [CP] or (3) Death due to clinical progression [Death]

End point values	Arm A - PPS	Arm B - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	47		
Units: Time to progression (months)				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm A - PPS v Arm B - PPS
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.519
Method	Logrank

Statistical analysis title	HR without stratification factors (95% CI)

Statistical analysis description:

Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing])
Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.

Comparison groups	Arm A - PPS v Arm B - PPS

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	4.26

Statistical analysis title	HR with stratification factors (95% CI)

Statistical analysis description:

Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing])
Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.

Comparison groups	Arm B - PPS v Arm A - PPS
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	5.58

Statistical analysis title	HR without stratification factors (1-sided 80% CI)

Statistical analysis description:

Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing])
Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.

Comparison groups	Arm A - PPS v Arm B - PPS
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.43
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	2.29

Statistical analysis title	HR with stratification factors (1-sided 80% CI)

Statistical analysis description:

Stratification factors (Gleason score [<8/≥8], resection margins [R0/R1], PSA at randomization [≤0.5 ng/ml/>0.5 ng/ml], ADT use [yes/no], Macroscopic local recurrence [yes/no/missing])
Macroscopic local recurrence is not used as stratification factor as it is often missing and very unbalanced.

Comparison groups	Arm A - PPS v Arm B - PPS
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.63
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	2.77

Secondary: SE | Progression-free survival

End point title	SE | Progression-free survival

End point description:

Biochemical progression [BP] and Clinical progression [CP] as defined for the primary endpoint.

No of events: Arm A = 10 [BP: 7 | CP: 2 | Death: 1] | Arm B = 7 [BP: 4 | CP: 3]
Note: Dummy data ("999") entered for median TTP due to database restrictions. Median TTP was not reached.

End point type	Secondary

End point timeframe:

From randomization until one of the following events, whichever comes first: (1) Biochemical progression [BP], (2) Clinical progression [CP] or (3) Death due to clinical progression [Death]

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Progression-free survival (months)				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm A - FAS v Arm B - FAS

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.475
Method	Logrank

Statistical analysis title	HR without stratification factors (95% CI)
Statistical analysis description:	
Stratification factors: see information provided for the primary analysis.	
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	3.73

Statistical analysis title	HR with stratification factors (95% CI)
Statistical analysis description:	
Stratification factors: see information provided for the primary analysis.	
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	4.45

Secondary: SE | Undetectable PSA under normal testosterone levels

End point title	SE | Undetectable PSA under normal testosterone levels
End point description:	
Undetectable PSA is defined as a serum PSA value of ≤ 0.05 ng/mL for at least two consecutive measurements after the last radiotherapy fraction and up to 18 months thereafter. To count as undetectable PSA under normal testosterone levels, the testosterone level has to be ≥ 50 ng/dL (i.e. a non-castrate testosterone level).	
End point type	Secondary

End point timeframe:

At at least two consecutive measurements after the last radiotherapy fraction and up to 18 months thereafter.

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Patients (%)				
number (confidence interval 95%)	58.2 (44.1 to 71.3)	70.6 (56.2 to 82.5)		

Statistical analyses

Statistical analysis title	Fisher's Exact Test
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.226
Method	Fisher exact

Secondary: SE | 50% PSA response

End point title	SE | 50% PSA response

End point description:

50% PSA response is defined as a ≥ 50% PSA decline after radiotherapy compared to the serum PSA level at randomization up to 12 months after last radiotherapy fraction.

End point type	Secondary

End point timeframe:

Up to 12 months after last radiotherapy fraction.

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Patients (%)				
number (confidence interval 95%)	81.8 (69.1 to 90.9)	88.2 (76.1 to 95.6)		

Statistical analyses

Statistical analysis title	Fisher's Exact Test
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.423
Method	Fisher exact

Secondary: SE | Best response

End point title	SE | Best response

End point description:

Best response is defined as the percentage of change in PSA from randomization to the maximum decline in PSA at any point after radiotherapy and up to 12 months after last radiotherapy fraction. If PSA after radiotherapy and up to 12 months after last radiotherapy fraction was always higher than PSA at randomization, the best response is defined as the percentage of change in PSA at randomization to the minimal PSA value after radiotherapy and up to 12 months after last radiotherapy fraction.

End point type	Secondary

End point timeframe:

Up to 12 months after last radiotherapy fraction.

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Best response (%)				
median (full range (min-max))	-91.3 (-100 to 120.4)	-91.7 (-100 to 56.8)		

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.64
Method	Wilcoxon (Mann-Whitney)

Secondary: SE | Clinical progression-free survival

End point title	SE | Clinical progression-free survival

End point description:

Clinical progression (as defined for the primary endpoint).

No of events: Arm A = 8 | Arm B = 4
Note: Dummy data ("999") entered for median clincial PFS due to database restrictions. Median clinical PFS was not reached.

End point type	Secondary

End point timeframe:

From randomization until clinical progression [CP] or death due to any cause.

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Time to clinical PFS (months)				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.243
Method	Logrank

Statistical analysis title	HR without stratification factors (95% CI)

Statistical analysis description:

Stratification factors: see information provided for the primary analysis.

Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	6.71

Statistical analysis title	HR with stratification factors (95% CI)

Statistical analysis description:	
Stratification factors: see information provided for the primary analysis.	
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	3.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	17.4

Secondary: SE | Time to further anti-cancer systemic therapy (TTFT)

End point title	SE | Time to further anti-cancer systemic therapy (TTFT)
End point description:	
No of events: Arm A = 6 | Arm B = 2 Note: Dummy data ("999") entered for median TTFT due to database restrictions. Median TTFT was not reached.	
End point type	Secondary
End point timeframe:	
From randomization until the start of any type of salvage systemic treatment.	

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: TTFT (months)				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.175
Method	Logrank

Statistical analysis title	HR without stratification factors (95% CI)

Statistical analysis description:	
Stratification factors: see information provided for the primary endpoint.	
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	2.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	14.29

Statistical analysis title	HR with stratification factors (95% CI)
Statistical analysis description:	
Stratification factors: see information provided for the primary endpoint.	
Comparison groups	Arm A - FAS v Arm B - FAS
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	12.85

Secondary: SE | Prostate cancer-specific survival (PCSS)	
End point title	SE | Prostate cancer-specific survival (PCSS)
End point description:	
End point type	Secondary
End point timeframe:	
From randomization to the date of death due to prostate cancer.	

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Death due to prostate cancer	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Overall survival (OS)

End point title	SE | Overall survival (OS)

End point description:

Until the time of this analysis one patient (0.9%) died. Therefore, only survival status is summarized.

End point type	Secondary

End point timeframe:

From randomization to the date of death from any cause.

End point values	Arm A - FAS	Arm B - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: Patients (%)				
number (not applicable)				
Alive	90.9	96.1		
Dead	1.8	0.0		
Lost to follow-up	7.3	3.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From registration and up to 28 days after end of treatment phase (week 52).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	Arm A
Reporting group description: SRT + Metformin	
Reporting group title	Arm B
Reporting group description: SRT	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 55 (3.64%)	3 / 54 (5.56%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased	Additional description: AST and ALT increased.		
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 55 (87.27%)	44 / 54 (81.48%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	6 / 55 (10.91%)	7 / 54 (12.96%)	
occurrences (all)	7	8	
Hypertension			
subjects affected / exposed	5 / 55 (9.09%)	3 / 54 (5.56%)	
occurrences (all)	5	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 55 (25.45%)	13 / 54 (24.07%)	
occurrences (all)	17	14	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 55 (12.73%)	1 / 54 (1.85%)	
occurrences (all)	9	1	
Anal haemorrhage			
subjects affected / exposed	3 / 55 (5.45%)	1 / 54 (1.85%)	
occurrences (all)	4	1	
Proctalgia			
subjects affected / exposed	3 / 55 (5.45%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Constipation			
subjects affected / exposed	4 / 55 (7.27%)	6 / 54 (11.11%)	
occurrences (all)	4	8	
Diarrhoea			
subjects affected / exposed	29 / 55 (52.73%)	13 / 54 (24.07%)	
occurrences (all)	43	15	
Flatulence			
subjects affected / exposed	4 / 55 (7.27%)	3 / 54 (5.56%)	
occurrences (all)	4	4	
Nausea			
subjects affected / exposed	5 / 55 (9.09%)	0 / 54 (0.00%)	
occurrences (all)	6	0	
Proctitis			
subjects affected / exposed	1 / 55 (1.82%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
Rectal haemorrhage			
subjects affected / exposed	4 / 55 (7.27%)	3 / 54 (5.56%)	
occurrences (all)	4	3	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	5 / 55 (9.09%)	7 / 54 (12.96%)	
occurrences (all)	5	8	
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	8 / 55 (14.55%)	5 / 54 (9.26%)	
occurrences (all)	8	5	

Dysuria			
subjects affected / exposed	5 / 55 (9.09%)	0 / 54 (0.00%)	
occurrences (all)	6	0	
Pollakiuria			
subjects affected / exposed	18 / 55 (32.73%)	17 / 54 (31.48%)	
occurrences (all)	21	20	
Urinary incontinence			
subjects affected / exposed	15 / 55 (27.27%)	11 / 54 (20.37%)	
occurrences (all)	16	13	
Micturition urgency			
subjects affected / exposed	7 / 55 (12.73%)	3 / 54 (5.56%)	
occurrences (all)	10	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2017	Clarifications and administrative changes requested by German authorities. Please note that version 2.0 has been submitted and approved exclusively in Germany.
17 January 2018	Clarifications and administrative changes requested during the initial submission of the protocol by the Swiss, French and German authorities.
02 September 2019	Allow inclusion of local recurrences detected on PET or MRI, adaption of definition of clinical progression for the primary endpoint, adaption of trial timelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to early closure of the trial, a time window of up to 12 months after radiotherapy instead of 18 months was considered. This has been adapted in the definition of the secondary endpoints undetectable PSA and 50% PSA response.

Notes: