



## Clinical trial results:

### Altered tumor oxygenation by Metformin, a potential step in overcoming radiotherapy resistance in locally advanced cervical cancer.

#### Summary

EudraCT number	2018-004119-36
Trial protocol	NO
Global end of trial date	01 November 2024

#### Results information

Result version number	v1 (current)
This version publication date	15 February 2026
First version publication date	15 February 2026

#### Trial information

##### Trial identification

Sponsor protocol code	METOXY-LACC
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04275713
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Oslo University Hospital
Sponsor organisation address	Ullernchausseen 70, Oslo, Norway, 0379
Public contact	Trial Manager, Oslo University Hospital, UXKJUH@ous-hf.no
Scientific contact	Trial Manager, Oslo University Hospital, UXKJUH@ous-hf.no

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	06 October 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2024
Global end of trial reached?	Yes
Global end of trial date	01 November 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The overall study objective is to investigate whether metformin can induce molecular changes, cell death and/or improved oxygenation in the tumor tissue, especially in hypoxic areas, and thereby improve tumor response with acceptable added acute toxicity.

Protection of trial subjects:

Routine care with weekly visits at the out-patient clinic for management of side effects and toxicity.

Background therapy:

Pelvic radiotherapy and weekly chemotherapy (cisplatin) followed by cervical brachytherapy.

Evidence for comparator:

Tumor hypoxia is a prognostic factor, associated with poor radiotherapy response representing a valid, interventional target. This clinical trial investigated if the antidiabetic drug metformin, could decrease hypoxia according to established biomarkers. Metformin inhibits complex 1 of the mitochondrial respiratory chain, which results in reduced cellular oxidative phosphorylation. The subsequent reduction in cellular oxygen consumption has been shown to decrease tumor hypoxia in cervical cancer xenografts by making more oxygen available in initially hypoxic tumor areas. Moreover, metformin may improve tumor oxygenation by selectively killing hypoxic cells through the suppression of the mammalian target of rapamycin (mTOR) pathway and modulation of the unfolded protein response (UPR), both important for cell survival under hypoxic conditions.

Actual start date of recruitment	22 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	31
From 65 to 84 years	10
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from Oslo University Hospital between May 2020 and July 2024.

### Pre-assignment

Screening details:

Patients with newly diagnosed cervical cancer were screened after the initial diagnostic work-up, at the first visit to the Gynecologic outpatient clinic. Female patients  $\geq 18$  years of age with ECOG performance status 0–1 and histologically confirmed cervical cancer FIGO2018 stage IB2-IVa, planned for curative chemoradiotherapy were eligible.

### Pre-assignment period milestones

Number of subjects started	41
Number of subjects completed	41

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Intervention

Arm description:

Metformine 850 mg two times daily from one week before the start of radiotherapy and throughout the treatment course.

Arm type	Experimental
Investigational medicinal product name	metformin
Investigational medicinal product code	A10B A02
Other name	Glucophage
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets taken orally 850 mg two times daily

<b>Arm title</b>	Control
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Arm description:

Patients receiving standard treatment

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	Intervention	Control
Started	18	23
Completed	18	23

## Baseline characteristics

### Reporting groups

Reporting group title	Intervention
Reporting group description: Metformine 850 mg two times daily from one week before the start of radiotherapy and throughout the treatment course.	
Reporting group title	Control
Reporting group description: Patients receiving standard treatment	

Reporting group values	Intervention	Control	Total
Number of subjects	18	23	41
Age categorical			
Units: Subjects			
36-73	18	23	41
Age continuous			
Age at inclusion from the patients hospital chart			
Units: years			
median	54	51	
full range (min-max)	36 to 73	31 to 72	-
Gender categorical			
The study included females only			
Units: Subjects			
Female	18	23	41
FIGO 2018 Stage			
Stage at diagnosis			
Units: Subjects			
1b3	2	3	5
II	9	9	18
III-IVa	7	11	18
Age			
Age at diagnosis			
Units: years			
median	54	51	
full range (min-max)	36 to 73	31 to 72	-

### Subject analysis sets

Subject analysis set title	Primary endpoint
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All randomized participants with a signed informed consent form who have received allocated treatment, completed biopsy at baseline and after one week of study participation without major protocol deviations.	
Subject analysis set title	Safety
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized participants with assigned informed consent who have received allocated treatment	
Subject analysis set title	Secondary endpoints

Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

All randomized participants with assigned informed consent who had received allocated treatment and completed MRI at base line and after one week of participation without major protocol deviation.

Reporting group values	Primary endpoint	Safety	Secondary endpoints
Number of subjects	40	41	41
Age categorical			
Units: Subjects			
36-73	40	41	41
Age continuous			
Age at inclusion from the patients hospital chart			
Units: years			
median	51		
full range (min-max)	36 to 73		
Gender categorical			
The study included females only			
Units: Subjects			
Female	40	41	41
FIGO 2018 Stage			
Stage at diagnosis			
Units: Subjects			
1b3	5	5	
II	18	18	
III-IVa	17	18	
Age			
Age at diagnosis			
Units: years			
median	53	53	53
full range (min-max)	31 to 73	31 to 73	31 to 73

## End points

### End points reporting groups

Reporting group title	Intervention
Reporting group description: Metformine 850 mg two times daily from one week before the start of radiotherapy and throughout the treatment course.	
Reporting group title	Control
Reporting group description: Patients receiving standard treatment	
Subject analysis set title	Primary endpoint
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All randomized participants with a signed informed consent form who have received allocated treatment, completed biopsy at baseline and after one week of study participation without major protocol deviations.	
Subject analysis set title	Safety
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized participants with assigned informed consent who have received allocated treatment	
Subject analysis set title	Secondary endpoints
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All randomized participants with assigned informed consent who have received allocated treatment and completed MRI at baseline and after one week of participation without major protocol deviation.	

### Primary: Change in hypoxia related gene expression signature in tumour biopsies

End point title	Change in hypoxia related gene expression signature in tumour biopsies
End point description:	
End point type	Primary
End point timeframe: Change in hypoxia related gene expression signature in tumour biopsies from baseline assessed after one week	

End point values	Intervention	Control	Primary endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	18	22	40	
Units: Arbitrary unit				
arithmetic mean (standard deviation)	2.3 (± 7.4)	2.2 (± 7.5)	2.2 (± 7.3)	

### Statistical analyses

Statistical analysis title	Change in hypoxia gene signature between arms
Statistical analysis description: Change in hypoxia gene signature between arms	



Comparison groups	Intervention v Control
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	t-test, 2-sided

### Secondary: Change in MRI parameters

End point title	Change in MRI parameters
End point description:	
Change in tumour volume	
End point type	Secondary
End point timeframe:	
Change in MRI volume from baseline to time of first brachytherapy	

End point values	Intervention	Control	Secondary endpoints	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	18	23	41	
Units: percent volume/volume				
arithmetic mean (standard deviation)	-90 (± 14.5)	-81.8 (± 19.1)	-85.4 (± 17.5)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in volume - baseline to first brachytherapy
Statistical analysis description:	
Change in volume (%) - baseline to first brachytherapy	
Comparison groups	Control v Intervention
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Wilcoxon (Mann-Whitney)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of treatment to last follow-up (3-4 months after last radiotherapy treatment).

Adverse event reporting additional description:

Only AE Grade 3 or above, except renal toxicity (all grades).

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	Intervention arm
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Reporting group description:

Patients receiving chemoradiotherapy and metformin

Reporting group title	Control group
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Reporting group description:

Patients receiving standard treatment (chemoradiotherapy).

Serious adverse events	Intervention arm	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 18 (22.22%)	8 / 23 (34.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Fatigue	Additional description: Hospitalization due to fatigue		
subjects affected / exposed	1 / 18 (5.56%)	3 / 23 (13.04%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea	Additional description: Diarrhoea and abdominal pain		
subjects affected / exposed	3 / 18 (16.67%)	5 / 23 (21.74%)	
occurrences causally related to treatment / all	4 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Intervention arm	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 18 (44.44%)	5 / 23 (21.74%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 18 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 18 (22.22%)	5 / 23 (21.74%)	
occurrences (all)	5	5	
Skin and subcutaneous tissue disorders			
Urticaria	Additional description: Skin rash		
subjects affected / exposed	1 / 18 (5.56%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal dysfunction	Additional description: Increase in S-Creatinine above reference level		
subjects affected / exposed	1 / 18 (5.56%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2023	Updated sample size calculations and up-dated allocation sequence accordingly.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/40105683>