Clinical trial results:
METIMMOX: COLORECTAL CANCER METASTASIS – SHAPING ANTI-TUMOR IMMUNITY BY OXALIPLATIN

Summary

EudraCT number	2017-001845-29
Trial protocol	NO
Global end of trial date	15 March 2024

Results information

Result version number	v1 (current)
This version publication date	09 February 2025
First version publication date	09 February 2025
Summary attachment (see zip file)	First-line oxaliplatin-based chemotherapy and nivolumab for metastatic microsatellite-stable colorectal cancer-the randomised METIMMOX trial (Ree-2024-First-line oxaliplatin-based chemothe.pdf)

Trial information

Trial identification

Sponsor protocol code	CA209-9M8

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03388190
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Akershus University Hospital
Sponsor organisation address	Sykehusveien 25, Lørenskog, Norway, 1478
Public contact	Karin Vassbakk, Akershus University Hospital, karin.anne.vassbakk@ahus.no
Scientific contact	Karin Vassbakk, Akershus University Hospital, karin.anne.vassbakk@ahus.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	15 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2024
Global end of trial reached?	Yes
Global end of trial date	15 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: To determine progression-free survival, in terms of failure of treatment strategy, of sequential treatment with the Nordic FLOX regimen and nivolumab compared with the standard-of-care Nordic FLOX regimen in previously untreated microsatellite-stable metastatic colorectal cancer.

Protection of trial subjects:

Subjects will be evaluated for safety and tolerability if they have received any study drug. Toxicity assessments will be continuous during the treatment phase and formally recorded at each new therapy cycle, and every 8 weeks during planned breaks from active study therapy, and should be done in person. Once subjects reach the survival follow-up phase, either in-person or documented telephone calls to assess the subject’s status are acceptable.
AE and laboratory values will be graded according to CTCAE v4.0. The start and stop time of the study therapy infusions will be documented. Additional measures, including non-study required laboratory tests, will be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (e.g., suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via local laboratories until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible. Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Background therapy:

Administration of the FLOX regimen will be according to the schedule that was used in the NORDIC-VII Study [Tveit et al., 2012], which in recent years has also been implemented in clinical practice.

Evidence for comparator:

The concept referred to as immunogenic cell death (ICD) essentially implies cytotoxic damage of tumor cells by either radiation or systemic therapies and the resulting priming of tumor-targeting T lymphocytes via capture and presentation of shed tumor antigens by dendritic cells [Galluzzi et al., 2015]. Preclinical studies have highlighted oxaliplatin as an ICD-inducing agent [Tesniere et al., 2010; Zitvogel et al., 2010]. In mouse models, oxaliplatin has been shown to sensitize CRC and other adenocarcinomas to ICB therapy via enhanced tumor infiltration of cytotoxic T lymphocytes [Gou et al., 2014; Pfirschke et al., 2016]. Increasing clinical evidence also supports the notion that oxaliplatin is able to induce ICD [Pol et al., 2015] and thereby invoke efficacious anti-tumor immunity.

Actual start date of recruitment	01 March 2018
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: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	38
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The 80 patients were enrolled between 29 May 2018 and 22 October 2021 from Akershus University Hospital, Oslo University Hospital and Sørlandet Hospital in the South-Eastern Region of Norway, as well as Haukeland University Hospital in the Western Region of Norway and St. Olavs Hospital in the Central Region of Norway.

Pre-assignment

Screening details:

Essential study inclusion criteria were age ≥18 years, measurable infradiaphragmatic (liver, peritoneal and/or nodal)
metastatic manifestation(s) according to RECIST 1.1, and ECOG performance status 0-1. In addition, CRP <60 mg/L was required at study entry.

Period 1

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

Blinding implementation details:

Tumour assessments were based on blinded independent central review according to RECIST 1.1 as the primary method and the consensus guidelines for assessment of response to immune-modulating therapies (iRECIST) as the subsidiary method, by means of CT scans repeated every 8 weeks throughout the study participation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control arm

Arm description:

The control arm patients were assigned to eight cycles of the FLOX regimen Q2W (oxaliplatin 85 mg/m2 day 1 and bolus 5-fluorouracil 500 mg/m2 and folinic acid 100 mg days 1–2)

Arm type	Active comparator
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

85 mg/m2 (over 30–60 minutes) on day 1; bolus (over <5 minutes)

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

500 mg/m2 and 30 minutes later bolus (over <10 minutes)

Arm title	Experimental arm

Arm description:

Experimental arm patients were scheduled for two cycles of FLOX Q2W before two cycles of nivolumab (240 mg flat dose) Q2W in an
alternating schedule to a total of eight cycles.

Arm type	Experimental

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

85 mg/m2 (over 30–60 minutes) on day 1; bolus (over <5 minutes)

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

240 mg flat dose Q2W

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

500 mg/m2 and 30 minutes later bolus (over <10 minutes)

Number of subjects in period 1	Control arm	Experimental arm
Started	38	38
Completed	31	36
Not completed	7	2
Consent withdrawn by subject	1	-
Adverse event, non-fatal	4	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Control arm
Reporting group description:	
The control arm patients were assigned to eight cycles of the FLOX regimen Q2W (oxaliplatin 85 mg/m2 day 1 and bolus 5-fluorouracil 500 mg/m2 and folinic acid 100 mg days 1–2)	
Reporting group title	Experimental arm
Reporting group description:	
Experimental arm patients were scheduled for two cycles of FLOX Q2W before two cycles of nivolumab (240 mg flat dose) Q2W in an alternating schedule to a total of eight cycles.	

Reporting group values	Control arm	Experimental arm	Total
Number of subjects	38	38	76
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	65.0	60.5	
full range (min-max)	38 to 79	43 to 80	-
Gender categorical			
Units: Subjects			
Female	15	20	35
Male	23	18	41
Eastern Cooperative Oncology Performance status			
Units: Subjects			
Status 0	21	23	44
Status 1	17	15	32
Primary tumor sidedness			
Units: Subjects			
Right	11	11	22
Left or rectum	27	27	54
RAS/BRAF status			
Units: Subjects			
Wildtype	9	12	21
Mutant	29	26	55
Number of metastatic sites			
Units: Subjects			

1-2	22	24	46
>2	16	14	30
Involved liver Units: Subjects			
No	6	7	13
Yes	32	31	63

End points

End points reporting groups

Reporting group title	Control arm
Reporting group description:	
The control arm patients were assigned to eight cycles of the FLOX regimen Q2W (oxaliplatin 85 mg/m2 day 1 and bolus 5-fluorouracil 500 mg/m2 and folinic acid 100 mg days 1–2)	
Reporting group title	Experimental arm
Reporting group description:	
Experimental arm patients were scheduled for two cycles of FLOX Q2W before two cycles of nivolumab (240 mg flat dose) Q2W in an alternating schedule to a total of eight cycles.	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe:	
Within 2 years of active treatment and follow-up.	

End point values	Control arm	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: 76				
median (confidence interval 95%)				
Median PFS	9.2 (6.3 to 12.7)	9.2 (4.5 to 15.0)		

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	Control arm v Experimental arm
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Logrank

Secondary: Safety

End point title	Safety

End point description:

End point type	Secondary

End point timeframe:

Within the study period, and up to 12 months after treatment termination.

End point values	Control arm	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: 76				
Any grade 3 event	25	37		
Any grade 4 event	10	11		

Statistical analyses

Statistical analysis title	Safety
Comparison groups	Control arm v Experimental arm
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Chi-squared

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Within the study period and up to two years after treatment termination

End point values	Control arm	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: 76				
median (confidence interval 95%)				
Overall survival	14.6 (10.6 to 23.2)	20.7 (15.9 to 24.9)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Control arm v Experimental arm
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Logrank

Secondary: Objective response

End point title	Objective response

End point description:

End point type	Secondary

End point timeframe:

Within the study period

End point values	Control arm	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	36		
Units: 67				
Objective response	20	17		

Statistical analyses

Statistical analysis title	Objective response
Comparison groups	Control arm v Experimental arm
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded for the time of study participation, and up to one year after treatment termination.

Adverse event reporting additional description:

2 patients died of adverse events before receiving nivolumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Control arm

Reporting group description:

The control arm patients were assigned to eight cycles of the FLOX regimen Q2W (oxaliplatin 85 mg/m2 day 1 and bolus 5-fluorouracil 500 mg/m2 and folinic acid 100 mg days 1–2)

Reporting group title	Experimental arm

Reporting group description:

Experimental arm patients were scheduled for two cycles of FLOX Q2W before two cycles of nivolumab (240 mg flat dose) Q2W in an
alternating schedule to a total of eight cycles.

Serious adverse events	Control arm	Experimental arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 38 (92.11%)	33 / 38 (86.84%)	
number of deaths (all causes)	33	34	
number of deaths resulting from adverse events	0	2	
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 38 (2.63%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 38 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Dehydration			
subjects affected / exposed	1 / 38 (2.63%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Fatigue			
subjects affected / exposed	4 / 38 (10.53%)	3 / 38 (7.89%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 38 (2.63%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 38 (2.63%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 38 (2.63%)	7 / 38 (18.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	22 / 38 (57.89%)	15 / 38 (39.47%)	
occurrences causally related to treatment / all	22 / 22	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	4 / 38 (10.53%)	7 / 38 (18.42%)	
occurrences causally related to treatment / all	0 / 4	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	2 / 38 (5.26%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Arthritis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 38 (0.00%)	4 / 38 (10.53%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rash			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	3 / 38 (7.89%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 38 (7.89%)	4 / 38 (10.53%)	
occurrences causally related to treatment / all	3 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 38 (2.63%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 38 (2.63%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			

subjects affected / exposed	5 / 38 (13.16%)	5 / 38 (13.16%)	
occurrences causally related to treatment / all	5 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
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: 1 %

Non-serious adverse events	Control arm	Experimental arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 38 (0.00%)	2 / 38 (5.26%)	
Hepatobiliary disorders			
Hepatic enzyme increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38664577

http://www.ncbi.nlm.nih.gov/pubmed/36229579

http://www.ncbi.nlm.nih.gov/pubmed/38952672