



## Clinical trial results:

**A multicenter, randomized phase II trial of vinflunine/gemcitabine versus carboplatin /gemcitabine as first line treatment in patients with metastatic urothelial carcinoma unfit for cisplatin based chemotherapy due to impaired renal function.**

### Summary

EudraCT number	2013-002417-35
Trial protocol	SE DK FI
Global end of trial date	07 October 2021

### Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022
Summary attachment (see zip file)	Published article VINGEM (Holmsten et al VINGEM EJC 2019.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	NUCOGI-VINGEM
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02665039
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Department of Oncology, Karolinska University Hospital
Sponsor organisation address	Karolinska vägen 6, Stockholm, Sweden, 171 76
Public contact	MD, Prof Anders Ullén, Department of Oncology, Karolinska University Hospital, +46 851770000, anders.ullen@regionstockholm.se
Scientific contact	MD, Prof Anders Ullén, Department of Oncology, Karolinska University Hospital, +46 851770000, anders.ullen@regionstockholm.se

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	30 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2018
Global end of trial reached?	Yes
Global end of trial date	07 October 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To compare the progression free survival (FPS) of vinflunine/gemcitabine versus carboplatin/gemcitabine in patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract unfit for cisplatin based chemotherapy due to impaired renal function.

Protection of trial subjects:

AEs were graded after every treatment cycle in accordance with NCI CTCAE. Early safety reports to the Swedish Medical Products Agency (Årlig säkerhetsrapport för icke kommersiellt sponsrad klinisk läkemedelsprövning (DSUR)). Reporting of SAE and SUSAR according to the protocol and GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Denmark: 34
Country: Number of subjects enrolled	Finland: 1
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	9
From 65 to 84 years	53



## Subject disposition

### Recruitment

Recruitment details:

Between April 2014 and February 2018, 62 patients were randomised, at 11 centres associated with the Nordic Urothelial Cancer Oncology Group (NUCOG) in Denmark, Finland and Sweden.

### Pre-assignment

Screening details:

185 patients were pre-screened and 62 patients included. The reasons for excluded subjects during the screening process were: patients which (18 patients), did not meet the study criterias (81 patients) and other reasons not specified (24 patients)

### Pre-assignment period milestones

Number of subjects started	62
Number of subjects completed	62

### 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>	Vinflunine + gemcitabine

Arm description:

Experimental: Vinflunine + gemcitabine

Vinflunine will be given intravenously once every 21 days, starting at a dose of:

280 mg/m<sup>2</sup> in patients with GFR 40-60 ml/min

250 mg/m<sup>2</sup> in patients aged >80 years and/or GFR 30-40 ml/min

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

Arm type	Experimental
Investigational medicinal product name	vinflunine + gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Experimental: Vinflunine + gemcitabine

Vinflunine will be given intravenously once every 21 days, starting at a dose of:

280 mg/m<sup>2</sup> in patients with GFR 40-60 ml/min

250 mg/m<sup>2</sup> in patients aged >80 years and/or GFR 30-40 ml/min

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

<b>Arm title</b>	Carboplatin + gemcitabine
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Arm description:

Active Comparator: Carboplatin + gemcitabine

Carboplatin will be given intravenously once every 21 days, starting at a dose of AUC 4.5

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

Arm type	Active comparator
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Investigational medicinal product name	carboplatin + gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Active Comparator: Carboplatin + gemcitabine

Carboplatin will be given intravenously once every 21 days, starting at a dose of AUC 4.5

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

<b>Number of subjects in period 1</b>	Vinflunine + gemcitabine	Carboplatin + gemcitabine
Started	32	30
Completed	32	30

## Baseline characteristics

### Reporting groups

Reporting group title	Vinflunine + gemcitabine
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Reporting group description:

Experimental: Vinflunine + gemcitabine

Vinflunine will be given intravenously once every 21 days, starting at a dose of:

280 mg/m<sup>2</sup> in patients with GFR 40-60 ml/min

250 mg/m<sup>2</sup> in patients aged >80 years and/or GFR 30-40 ml/min

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

Reporting group title	Carboplatin + gemcitabine
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Reporting group description:

Active Comparator: Carboplatin + gemcitabine

Carboplatin will be given intravenously once every 21 days, starting at a dose of AUC 4.5

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

Reporting group values	Vinflunine + gemcitabine	Carboplatin + gemcitabine	Total
Number of subjects	32	30	62
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
Age continuous Units: years			
median	71	74	
full range (min-max)	50 to 84	43 to 82	-
Gender categorical Units: Subjects			
Female	8	10	18
Male	24	20	44

## End points

### End points reporting groups

Reporting group title	Vinflunine + gemcitabine
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Reporting group description:

Experimental: Vinflunine + gemcitabine

Vinflunine will be given intravenously once every 21 days, starting at a dose of:

280 mg/m<sup>2</sup> in patients with GFR 40-60 ml/min

250 mg/m<sup>2</sup> in patients aged >80 years and/or GFR 30-40 ml/min

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

Reporting group title	Carboplatin + gemcitabine
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Reporting group description:

Active Comparator: Carboplatin + gemcitabine

Carboplatin will be given intravenously once every 21 days, starting at a dose of AUC 4.5

Gemcitabine will be given intravenously on day 1 and day 8 of every 21 day cycle, starting at a dose of 1000 mg/m<sup>2</sup>

### Primary: progression-free survival

End point title	progression-free survival
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End point description:

End point type	Primary
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End point timeframe:

Time from randomisation to radiological disease progression or death.

End point values	Vinflunine + gemcitabine	Carboplatin + gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	30		
Units: months				
median (confidence interval 95%)	6.2 (4.4 to 8.3)	6.3 (4.2 to 7.8)		

### Statistical analyses

Statistical analysis title	log-rank test
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Statistical analysis description:

PFS was compared between the treatment arms using the log-rank test at a significance level of 5%.

Comparison groups	Vinflunine + gemcitabine v Carboplatin + gemcitabine
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Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.28
Variability estimate	Standard deviation

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were reported after every treatment cycle (i.e. every third week).

Adverse event reporting additional description:

Serious adverse events defined as according to the protocol: results in death, life-threatening, results in persistent disability, requires hospitalisation, is a congenital anomaly or birth defect, medically important event.

Non-serious adverse events defined as AE grade I-II according to NCI CTCAE (Table 3 in the article Holmsten et al)

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	4.0
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### Reporting groups

Reporting group title	Vinflunine + gemcitabine
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Reporting group description: -

Reporting group title	carboplatin + gemcitabine
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Reporting group description: -

<b>Serious adverse events</b>	Vinflunine + gemcitabine	carboplatin + gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 29 (89.66%)	16 / 30 (53.33%)	
number of deaths (all causes)	24	21	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac other			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 29 (17.24%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trombocytemia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tromboembolic event			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fall			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	4 / 29 (13.79%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ileus</b>			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Colon perforation</b>			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Diarrhoea</b>			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vomiting</b>			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
Urinary tract obstruction			
subjects affected / exposed	3 / 29 (10.34%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Endocrine disorders</b>			
Hyper/hypoglycemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal cord compression subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Febrile neutropenia subjects affected / exposed	9 / 29 (31.03%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	9 / 9	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Fever and infection subjects affected / exposed	18 / 29 (62.07%)	9 / 30 (30.00%)	
occurrences causally related to treatment / all	9 / 18	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
Dehydration subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
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>	Vinflunine + gemcitabine	carboplatin + gemcitabine	
Total subjects affected by non-serious adverse events subjects affected / exposed	29 / 29 (100.00%)	30 / 30 (100.00%)	
<b>Nervous system disorders</b>			
Peripheral neuropathy subjects affected / exposed	5 / 29 (17.24%)	6 / 30 (20.00%)	
occurrences (all)	5	6	
<b>Blood and lymphatic system disorders</b>			
Anaemia subjects affected / exposed	13 / 29 (44.83%)	12 / 30 (40.00%)	
occurrences (all)	13	12	
Neutropenia subjects affected / exposed	0 / 29 (0.00%)	12 / 30 (40.00%)	
occurrences (all)	0	12	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	9 / 29 (31.03%) 9	3 / 30 (10.00%) 3	
Thrombocytopenia with active bleeding subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	2 / 30 (6.67%) 2	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	24 / 29 (82.76%) 24	20 / 30 (66.67%) 20	
Infusion site reaction subjects affected / exposed occurrences (all)	7 / 29 (24.14%) 7	3 / 30 (10.00%) 3	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	15 / 29 (51.72%) 15	6 / 30 (20.00%) 6	
Abdominal pain subjects affected / exposed occurrences (all)	8 / 29 (27.59%) 8	3 / 30 (10.00%) 3	
Nausea subjects affected / exposed occurrences (all)	12 / 29 (41.38%) 12	9 / 30 (30.00%) 9	
Vomiting subjects affected / exposed occurrences (all)	9 / 29 (31.03%) 9	2 / 30 (6.67%) 2	
Stomatitis/mucositis subjects affected / exposed occurrences (all)	13 / 29 (44.83%) 13	8 / 30 (26.67%) 8	
Diarrhoea subjects affected / exposed occurrences (all)	7 / 29 (24.14%) 7	3 / 30 (10.00%) 3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	1 / 30 (3.33%) 1	

<p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>15 / 29 (51.72%)</p> <p>15</p>	<p>3 / 30 (10.00%)</p> <p>3</p>	
<p>Oedema limbs</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 29 (10.34%)</p> <p>3</p>	<p>1 / 30 (3.33%)</p> <p>1</p>	
<p>Skin reactions, pruritus, rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 29 (13.79%)</p> <p>4</p>	<p>3 / 30 (10.00%)</p> <p>3</p>	
<p>Renal and urinary disorders</p> <p>Renal toxicity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 29 (13.79%)</p> <p>4</p>	<p>2 / 30 (6.67%)</p> <p>2</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 29 (17.24%)</p> <p>5</p>	<p>7 / 30 (23.33%)</p> <p>7</p>	
<p>Infections and infestations</p> <p>Fever</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 29 (20.69%)</p> <p>6</p> <p>4 / 29 (13.79%)</p> <p>4</p>	<p>3 / 30 (10.00%)</p> <p>3</p> <p>3 / 30 (10.00%)</p> <p>3</p>	
<p>Metabolism and nutrition disorders</p> <p>Weight loss</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 29 (37.93%)</p> <p>11</p>	<p>7 / 30 (23.33%)</p> <p>7</p>	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2016	In 2016, owing to slow accrual rate, an amendment was approved to decrease the required number of patients to 60, from initial 120 patients.

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/31648851>