



Clinical trial results:

A prospective, single arm, multicenter, phase II-trial to assess safety and efficacy of preoperative RAdiation therapy before radical CystEctomy combined with ImmunoTherapy in locally advanced urothelial carcinoma of the bladder

Summary

EudraCT number	2018-001823-38
Trial protocol	DE
Global end of trial date	12 October 2023

Results information

Result version number	v1 (current)
This version publication date	10 August 2025
First version publication date	10 August 2025

Trial information

Trial identification

Sponsor protocol code	AB65/18
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03529890
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technische Universität München, Fakultät für Medizin
Sponsor organisation address	Ismaninger Strasse 22, Munich, Germany, 81675
Public contact	Prof. Dr. Margitta Retz, Technische Universität München, Fakultät für Medizin, heidrun.rexer@meckkevidence.de
Scientific contact	Prof. Dr. Margitta Retz, Technische Universität München, Fakultät für Medizin, heidrun.rexer@meckkevidence.de

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	08 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2023
Global end of trial reached?	Yes
Global end of trial date	12 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Rate of patients with completed treatment consisting of radio-immunotherapy and radical cystectomy at the end of week 15

Protection of trial subjects:

Standard of Care

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 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	Germany: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	13
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

01-Jan-2019 until 06-Dec-2021

Pre-assignment

Screening details:

Key eligibility criteria were locally advanced urothelial bladder cancer in patients unfit for or refusing cisplatin-based neoadjuvant therapy. However patients needed to be fit for radical cystectomy.

38 subjects were screened, 33 entered into the trial. Reasons for exclusions were metastatic disease or unresectable disease in baseline imaging

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Trial
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Arm description:

As no randomization occurred, all subjects are included in this arm.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-936558-01
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab 240 mg was given intravenously every two weeks for a total of 4 cycles. A deviation from time frame of ± 3 business days per administration was allowed.

Number of subjects in period 1	Overall Trial
Started	33
Completed	31
Not completed	2
Adverse event, serious fatal	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
Reporting group description: -	

Reporting group values	Overall Trial	Total	
Number of subjects	33	33	
Age categorical			
Units: Subjects			
Adults (18-64 years)	13	13	
From 65-84 years	20	20	
Age continuous			
Units: years			
median	69.0		
full range (min-max)	38 to 78	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	20	20	
Smoking Status			
Units: Subjects			
Never-Smoker	8	8	
Former Smoker	15	15	
Current Smoker	10	10	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS includes all subjects who have received at least one study treatment and have completed a post treatment radiographic response assessment.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all participating subjects regardless of trial progress

Reporting group values	Full Analysis Set	Safety Set	
Number of subjects	31	33	
Age categorical			
Units: Subjects			
Adults (18-64 years)	12		
From 65-84 years	19		
Age continuous			
Units: years			
median	69.0		
full range (min-max)	38 to 78		

Gender categorical Units: Subjects			
Female	13		
Male	18		
Smoking Status Units: Subjects			
Never-Smoker			
Former Smoker			
Current Smoker			

End points

End points reporting groups

Reporting group title	Overall Trial
Reporting group description: As no randomization occurred, all subjects are included in this arm.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The FAS includes all subjects who have received at least one study treatment and have completed a post treatment radiographic response assessment.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: Included all participating subjects regardless of trial progress	

Primary: Feasibility

End point title	Feasibility
End point description: Feasibility is defined as the ratio of subjects with complete treatment (radio-immunotherapy & radical cystectomy) at end of week 15. Complete treatment consists of at least administrations of Nivolumab and at least 23 of 28 radiation fractions.	
End point type	Primary
End point timeframe: 15 weeks after study inclusion	

End point values	Overall Trial	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31 ^[1]	31 ^[2]		
Units: Treatment Completion ratio				
number (confidence interval 95%)	0.87 (0.75 to 0.98)	0.87 (0.75 to 0.98)		

Notes:

[1] - Analysis was carried out solely in the full analysis Set

[2] - Analysis was performed in the FAS

Statistical analyses

Statistical analysis title	Feasibility analysis
Statistical analysis description: For the primary endpoint, an exact test for single proportions was performed to reject the null hypothesis of $\geq 22.5\%$ of treatment-related delay in surgery at week 15. If the resulting p-value is less than 5%, the study is considered successful. The analysis of the primary endpoint and efficacy endpoints is based on the Full Analysis Set (FAS).	
Comparison groups	Overall Trial v Full Analysis Set

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Exact test for single proportions
Parameter estimate	Proportion
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	0.98

Secondary: Disease free survival (DFS)

End point title	Disease free survival (DFS)
End point description:	
Disease free survival (DFS) defined by local recurrence or distant metastasis or death in R0 resected patients during 1 year follow up starting at the date of cystectomy	
End point type	Secondary
End point timeframe:	
1 year follow up starting at the date of cystectomy	

End point values	Overall Trial	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26 ^[3]	26		
Units: Days				
median (full range (min-max))	337 (38 to 379)	337 (38 to 379)		

Notes:

[3] - R0-resected Patients were included in the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: OS

End point title	OS
End point description:	
Time to death by any cause during 1 year follow up (overall survival (OS)) starting at the date of cystectomy	
End point type	Secondary
End point timeframe:	
1 year follow up (overall survival (OS)) starting at the date of cystectomy	

End point values	Overall Trial	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	31		
Units: Days				
median (standard deviation)	358 (\pm 49.4)	358 (\pm 49.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological overall response rate

End point title	Radiological overall response rate
End point description: Radiological overall response rate after radio-immunotherapy before radical cystectomy (complete remission, partial remission, stable disease, progressive disease)	
End point type	Secondary
End point timeframe: After completion of neoadjuvant treatment prior to cystectomy.	

End point values	Overall Trial	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	31		
Units: Subjects				
Complete Response	5	5		
Partial Response	17	17		
Stable Disease	8	8		
Progressive Disease	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological Response (ypT0 - Rate)

End point title	Pathological Response (ypT0 - Rate)
End point description: Rate of patients achieving complete pathological response in cystectomy specimen	
End point type	Secondary

End point timeframe:

After cystectomy

End point values	Overall Trial	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	31		
Units: Subjects	12	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical Margin Status

End point title Surgical Margin Status

End point description:

End point type Secondary

End point timeframe:

After Cystectomy

End point values	Overall Trial	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	31		
Units: Subjects				
R0	28	28		
R1	2	2		
R2	0	0		
Rx	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Toxicity of preoperative radio-immunotherapy

End point title Acute Toxicity of preoperative radio-immunotherapy

End point description:

Acute toxicity of preoperative radio-immunotherapy followed by radical cystectomy until 3 months after end of therapy according to CTCAE v4.

Following typical side effects of surgery will be excluded from analysis:

o Paralytic ileus < 10d post-surgery defined as absence of bowel movements, not needing surgical intervention

- o Reactive diarrhea < 14d post-surgery
- o Bacterial colonization of urine or urinary tract infections < 14d post-surgery which may need antibiotic treatment, but are not systemic (indication for systemic infection: fever > 38,2°C or sepsis criteria)
- o Asymptomatic hydronephrosis without significant serum creatinine elevation < 6 weeks post-surgery

End point type	Secondary
End point timeframe:	
Beginning of treatment until 3 months post radical cystectomy	

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Subjects				
Subjects affected	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of immune related toxicities

End point title	Rate of immune related toxicities
End point description:	
- Rate of immune related toxicities: Immune mediated pneumonitis, colitis, hepatitis, hypophysitis, adrenal insufficiency, hypo-/hyperthyroidism, diabetes (type 1), nephritis, immune mediated skin reactions	
End point type	Secondary
End point timeframe:	
Complete trial participation timeframe.	

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Subjects				
Immune-mediated pneumonitis	1			
colitis	1			
hepatitis	2			
hypophysitis	0			
adrenal insufficiency	0			
hypo-/hyperthyroidism,	5			
diabetes (type 1)	0			
nephritis	0			
immune mediated skin reactions	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Late toxicity

End point title	Late toxicity
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End point description:

End point type	Secondary
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End point timeframe:

1 year follow-up following radical cystectomy

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Affected Subjects				
Subjects affected	23			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

01.01.2019 - 09.03.2023

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCTAE
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Dictionary version	4.0
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Reporting groups

Reporting group title	Safety Set
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Reporting group description:

All patients entered into the trial.

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 33 (96.97%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Incidental prostate cancer			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic Reaction	Additional description: Allergic reaction to unknown agent		
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-related Hepatitis			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Acidosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalemia	Additional description: Hyperkalemia requiring inpatient treatment.		
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19-Infection	Additional description: Covid-19 infection prolonging hospital stay		
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Bladder anastomotic leak			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteric anastomotic leak & Urinoma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flank Pain			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bleeding after fall with head injury			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fascial and wound dehiscence			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence with wound infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax	Additional description: Subject suffered a pneumothorax after attempted port implantation.		
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Recurrent bleeding out of the right nephrostomy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphocele			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Small intestinal anastomotic leak			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected peritoneal hematoma			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prolapse of urostomy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial Infarction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Worsening of general condition			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal anastomotic leak & mechanical Ileus			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
High output ileostomy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Sigma-Diverticulitis with covered perforation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-related Colitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Tumor progression associated Liver failure	Additional description: Subject presented with highly elevated Bilirubine and newly onset ascites. These findings were initially suspected to be caused by study treatment. However biopsy revealed diffuse liver metastases.		
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-related Hepatitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Herpes Zoster Infection & Erysipela			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Exanthema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-related Dermatitis			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Macrohematuria			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intercostal neuralgia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urosepsis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder Infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	21 / 33 (63.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 33 (96.97%)		
Vascular disorders			
Lymphocele			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	10		
Lymphedema			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Thromboembolic event			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	7		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pneumonitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	4		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	19		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	10		
Acidosis			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	13		
GGT increased			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	10		
Lymphocyte count decreased			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	18		
Platelet count decreased			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Hyperuricemia			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Alkaline phosphatase increased			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
White blood cell decreased			

subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	9		
Creatinine increased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	6		
Lipase increased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	6		
Hypoalbuminemia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Platelet count increased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypocalcemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypokalemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	4		
Hyponatremia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Small intestinal anastomotic leak			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Wound complication			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Urethral anastomotic leak			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Wound dehiscence</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 33 (6.06%)</p> <p>2</p> <p>2 / 33 (6.06%)</p> <p>3</p>		
<p>Cardiac disorders</p> <p>Atrial fibrillation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 33 (6.06%)</p> <p>2</p>		
<p>Nervous system disorders</p> <p>Paresthesia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neuralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Radiculitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 33 (12.12%)</p> <p>4</p> <p>2 / 33 (6.06%)</p> <p>2</p> <p>2 / 33 (6.06%)</p> <p>4</p> <p>2 / 33 (6.06%)</p> <p>5</p>		
<p>Blood and lymphatic system disorders</p> <p>Anemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>17 / 33 (51.52%)</p> <p>17</p>		
<p>Gastrointestinal disorders</p> <p>Diarrhea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p>	<p>16 / 33 (48.48%)</p> <p>23</p> <p>6 / 33 (18.18%)</p> <p>7</p> <p>6 / 33 (18.18%)</p> <p>6</p>		

subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Proctitis			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Ascites			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Ileus			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Mucositis oral			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	9		
Dry skin			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Hyperhidrosis			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Eczema			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Renal and urinary disorders			
Cystitis noninfective			

subjects affected / exposed	12 / 33 (36.36%)		
occurrences (all)	18		
Urinary tract obstruction			
subjects affected / exposed	12 / 33 (36.36%)		
occurrences (all)	24		
Urinary incontinence			
subjects affected / exposed	11 / 33 (33.33%)		
occurrences (all)	11		
Urinary tract pain			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	11		
Urinary frequency			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Hematuria			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Acute kidney injury			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Chronic kidney disease			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Urinary retention			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	8		
Hypothyroidism			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4		
Flank pain subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 8		
Pain in extremity subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 7		
Back pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	16 / 33 (48.48%) 36		
Bladder infection subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 6		
Lung infection subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Sepsis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Metabolism and nutrition disorders Arthritis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2018	Clarifications and amendments to protocol and ICF during the approval process per request of EC and PEI. Approval of the Amendment in concurrence with initial protocol approval.
25 January 2019	Clarifications and amendments to protocol and ICF during the approval process per request of EC and PEI prior to start of recruitment.
20 September 2019	<ul style="list-style-type: none">- Corrections and clarifications regarding deviation time of visits and radiological disease-assessments were implemented.- The timepoint for the planned interim safety analysis was clarified to account for speedy recruitment.- Several typing errors were corrected throughout the protocol.- Changes to the SmPC were implemented in the ICF
26 November 2019	<ul style="list-style-type: none">- A change of radiation dose constraints was implemented after independent safety monitoring identified a possible link between patients suffering from insufficiency of the ileo-ileal anastomosis and a higher radiation dose to the small bowel. The tolerated radiation dose to the small bowel was reduced in response.- An additional planned interim safety analysis to review the impact of the changes made in this amendment was implemented after completion of radio-immunotherapy in patient no. 22.- A version change of the SmPC was implemented in the protocol.
24 February 2021	<ul style="list-style-type: none">- Planned study duration was prolonged to account for slowed recruitment due to the covid pandemic.- Exclusion criterion regarding prior administration of chemotherapy was clarified- Inclusion criterion regarding eligibility for radical cystectomy was clarified to account for curative intention- Changes to the SmPC were implemented in the ICF
03 January 2022	- Changes to the SmPC were implemented in the ICF

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported