Clinical trial results:
A Phase 3, Randomized, Study of Neoadjuvant and Adjuvant Nivolumab Plus Bempegaldesleukin (NKTR-214), Versus Nivolumab Alone Versus Standard of Care in Participants with Muscle-Invasive Bladder Cancer (MIBC) Who Are Cisplatin Ineligible

Summary

EudraCT number	2018-002676-40
Trial protocol	DE NL AT GR ES CZ PL FR BE GB IT
Global end of trial date	09 June 2023

Results information

Result version number	v1 (current)
This version publication date	14 June 2024
First version publication date	14 June 2024

Trial information

Trial identification

Sponsor protocol code	CA045-009

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

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	09 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the pCR rate of neoadjuvant bempeg+nivo to SOC (no neoadjuvant therapy) in all randomized subjects.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 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	Canada: 1
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Argentina: 22
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Mexico: 4
Worldwide total number of subjects	114
EEA total number of subjects	56

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)	25
From 65 to 84 years	88
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivolumab + Bempegaldesleukin

Arm description:

Bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.

Arm type	Experimental
Investigational medicinal product name	Bempegaldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection, Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bempegaldesleukin 0.006 mg/kg once every 3 weeks

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab 360 mg once every 3 weeks

Arm title	Arm B: Nivolumab

Arm description:

Nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab 360 mg once every 3 weeks

Arm title	Arm C: Standard of Care

Arm description:	
Standard of care therapy, with cystectomy alone, without neoadjuvant or adjuvant therapy.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care
Started	37	37	40
Completed	37	37	32
Not completed	0	0	8
Adverse event, serious fatal	-	-	1
Participant withdrew consent	-	-	1
Completed without radical cystectomy	-	-	5
Other reasons	-	-	1

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: Nivolumab + Bempegaldesleukin

Arm description:

Bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.

Arm type	Experimental
Investigational medicinal product name	Bempegaldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection, Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bempegaldesleukin 0.006 mg/kg once every 3 weeks

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details: Nivolumab 360 mg once every 3 weeks

Arm title	Arm B: Nivolumab
Arm description: Nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.	
Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: Nivolumab 360 mg once every 3 weeks	
Arm title	Arm C: Standard of Care
Arm description: Standard of care therapy, with cystectomy alone, without neoadjuvant or adjuvant therapy.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care
Started	37	37	32
Completed	15	13	32
Not completed	22	24	0
Adverse event, serious fatal	4	1	-
Disease progression	6	9	-
Participant withdrew consent	1	-	-
Study drug toxicity	4	6	-
Adverse event unrelated to study drug	1	5	-
Other reasons	5	3	-
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Nivolumab + Bempegaldesleukin
Reporting group description:	
Bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.	
Reporting group title	Arm B: Nivolumab
Reporting group description:	
Nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.	
Reporting group title	Arm C: Standard of Care
Reporting group description:	
Standard of care therapy, with cystectomy alone, without neoadjuvant or adjuvant therapy.	

Reporting group values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care
Number of subjects	37	37	40
Age categorical Units: Subjects			
Adults (18-64 years)	7	10	8
From 65-84 years	29	27	32
85 years and over	1	0	0
Age Continuous Units: Years			
median	73.0	72.0	74.5
standard deviation	± 8.8	± 7.5	± 8.4
Sex: Female, Male Units: Participants			
Female	6	7	9
Male	31	30	31
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	36	35	36
More than one race	0	0	0
Unknown or Not Reported	1	2	3

Reporting group values	Total		
Number of subjects	114		
Age categorical Units: Subjects			
Adults (18-64 years)	25		
From 65-84 years	88		
85 years and over	1		

Age Continuous Units: Years median standard deviation	 -		
Sex: Female, Male Units: Participants			
Female	22		
Male	92		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	107		
More than one race	0		
Unknown or Not Reported	6		

End points

End points reporting groups

Reporting group title	Arm A: Nivolumab + Bempegaldesleukin
Reporting group description:	
Bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.	
Reporting group title	Arm B: Nivolumab
Reporting group description:	
Nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.	
Reporting group title	Arm C: Standard of Care
Reporting group description:	
Standard of care therapy, with cystectomy alone, without neoadjuvant or adjuvant therapy.	
Reporting group title	Arm A: Nivolumab + Bempegaldesleukin
Reporting group description:	
Bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.	
Reporting group title	Arm B: Nivolumab
Reporting group description:	
Nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.	
Reporting group title	Arm C: Standard of Care
Reporting group description:	
Standard of care therapy, with cystectomy alone, without neoadjuvant or adjuvant therapy.	

Primary: Event Free Survival (EFS) - Nivolumab + Bempegaldesleukin Compared to Standard of Care

End point title	Event Free Survival (EFS) - Nivolumab + Bempegaldesleukin Compared to Standard of Care[1][2]
End point description:	
Event Free Survival (EFS) is defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on blinded independent committee review (BICR) assessments, or death due to any cause. Participants who did not have an EFS event will be censored on the date of their last evaluable tumor assessment (imaging or biopsy) or at the date of radical surgery whichever occur last. Participants who did not have any baseline tumor assessments (imaging or biopsy) and did not undergo radical cystectomy for other reason than worsening/progression of disease will be censored on their date of randomization. Participants who did not have any on study tumor assessments (imaging or biopsy) and did not die will be censored on their date of radical cystectomy (or randomization date if no radical cystectomy performed). "99999"=N/A	
End point type	Primary
End point timeframe:	
From randomization up to first EFS event (up to approximately 30 months)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary data only was planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data for the missing arm is included as a secondary endpoint.

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm C: Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	40		
Units: Months				
median (confidence interval 95%)	22.11 (8.21 to 99999)	15.18 (11.63 to 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Pathologic Complete Response (pCR) Rate- Nivolumab + Bempegaldesleukin Compared to Standard of Care

End point title	Pathologic Complete Response (pCR) Rate- Nivolumab + Bempegaldesleukin Compared to Standard of Care[3][4]

End point description:

Pathologic Complete Response (pCR) is defined as the percentage of randomized participants with absence of any cancer in pathology specimens after radical cystectomy, based on blinded independent pathology review (BIPR). Participants who do not undertake surgery will be counted as non-pCR.

End point type	Primary

End point timeframe:

From time of radical cystectomy up to 100 days after last treatment (up to approximately 17 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary data only was planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data for the missing arm is included as a secondary endpoint.

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm C: Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	40		
Units: Percentage of participants				
number (confidence interval 95%)	10.8 (3.0 to 25.4)	2.5 (0.1 to 13.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For those without documentation of death, OS will be censored on the last date the participant was known to be alive.

OS was not calculated for Arm A and Arm B because the number of events did not meet the threshold due to early study termination. In lieu of OS, time to death is reported as a Post-Hoc endpoint.

"99999"=N/A

End point type	Secondary

End point timeframe:

From randomization to study completion, up to approximately 40 months

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	37	40	
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	23.23 (14.36 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival (EFS) - Nivolumab Compared to Standard of Care

End point title	Event Free Survival (EFS) - Nivolumab Compared to Standard of Care[5]

End point description:

Event Free Survival (EFS) is defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on blinded independent committee review (BICR) assessments, or death due to any cause.

Participants who did not have an EFS event will be censored on the date of their last evaluable tumor assessment (imaging or biopsy) or at the date of radical surgery whichever occur last. Participants who did not have any baseline tumor assessments (imaging or biopsy) and did not undergo radical cystectomy for other reason than worsening/progression of disease will be censored on their date of randomization. Participants who did not have any on study tumor assessments (imaging or biopsy) and did not die will be censored on their date of radical cystectomy (or randomization date if no radical cystectomy performed).

"99999"=N/A

End point type	Secondary

End point timeframe:

From randomization up to first EFS event (up to approximately 30 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data for the missing arm is included as a primary endpoint.

End point values	Arm B: Nivolumab	Arm C: Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	40		
Units: Months				
median (confidence interval 95%)	99999 (10.84 to 99999)	15.18 (11.63 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Immune-Mediated Adverse Events (IMAEs)

End point title	The Number of Participants Experiencing Immune-Mediated Adverse Events (IMAEs)

End point description:

IMAEs are specific AEs that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator that meet the definition summarized below:
- those occurring within 100 days of the last dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component.

End point type	Secondary

End point timeframe:

from first dose to 100 days following last dose (up to approximately 20 months)

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	37	32	
Units: Participants	10	10	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation

End point title	The Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. Adverse events are graded on a scale from 1 to 5, with Grade 1 being mild and asymptomatic; Grade 2 is moderate requiring minimal, local or noninvasive intervention; Grade 3 is severe or medically significant but not immediately life-threatening; Grade 4 events are usually severe enough to require hospitalization; Grade 5 events are fatal.

End point type	Secondary

End point timeframe:

from first dose to 100 days following last dose (up to approximately 20 months)

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	37	32	
Units: Participants	8	8	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Adverse Events (AEs)

End point title	The Number of Participants Experiencing Adverse Events (AEs)

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. Adverse events are graded on a scale from 1 to 5, with Grade 1 being mild and asymptomatic; Grade 2 is moderate requiring minimal, local or noninvasive intervention; Grade 3 is severe or medically significant but not immediately life-threatening; Grade 4 events are usually severe enough to require hospitalization; Grade 5 events are fatal.

End point type	Secondary

End point timeframe:

from first dose to 100 days following last dose (up to approximately 20 months)

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	37	32	
Units: Participants	34	36	19	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Serious Adverse Events (SAEs)

End point title	The Number of Participants Experiencing Serious Adverse Events (SAEs)

End point description:

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization.

End point type	Secondary

End point timeframe:

from first dose to 100 days following last dose (up to approximately 20 months)

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	37	32	
Units: Participants	15	18	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Worst Grade Clinical Laboratory Values

End point title	Worst Grade Clinical Laboratory Values

End point description:

Clinical laboratory values by worst CTC grade are graded on a scale from 1 to 5, with Grade 1 being mild and asymptomatic; Grade 2 is moderate requiring minimal, local or noninvasive intervention; Grade 3 is severe or medically significant but not immediately life-threatening; Grade 4 events are usually severe enough to require hospitalization; Grade 5 events are fatal.

End point type	Secondary

End point timeframe:

From first dose to 100 days following last dose (up to approximately 20 months)

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	37	32	
Units: Participants				
Hemoglobin|Grade 0	5	5	0	

Platelet Count|Grade 0	35	34	5	
Leukocytes, Local Lab|Grade 0	33	35	6	
Lymphocytes (Absolute), Local Lab|Grade 0	23	12	0	
Absolute Neutrophil Count|Grade 0	31	36	0	
Alkaline Phosphate, Local Lab|Grade 0	24	30	2	
Aspartate Aminotransferase, Local Lab|Grade 0	31	30	2	
Alanine Aminotransferase, Local Lab|Grade 0	26	30	2	
Total Bilirubin, Local Lab|Grade 0	33	35	2	
Creatinine, Local Lab|Grade 0	11	13	5	
Hypernatremia|Grade 0	34	36	6	
Hyponatremia|Grade 0	24	29	5	
Hyperkalemia|Grade 0	24	25	6	
Hypokalemia|Grade 0	24	25	6	
Hypercalcemia|Grade 0	33	34	4	
Hypocalcemia|Grade 0	29	28	0	
Hemoglobin|Grade 1	23	23	2	
Platelet Count|Grade 1	1	3	1	
Leukocytes, Local Lab|Grade 1	2	2	0	
Lymphocytes (Absolute), Local Lab|Grade 1	4	6	0	
Absolute Neutrophil Count|Grade 1	4	1	0	
Alkaline Phosphate, Local Lab|Grade 1	10	7	0	
Aspartate Aminotransferase, Local Lab|Grade 1	5	6	0	
Alanine Aminotransferase, Local Lab|Grade 1	10	7	0	
Total Bilirubin, Local Lab|Grade 1	2	2	0	
Creatinine, Local Lab|Grade 1	10	14	1	
Hypernatremia|Grade 1	2	1	0	
Hyponatremia|Grade 1	12	7	1	
Hyperkalemia|Grade 1	7	9	0	
Hypokalemia|Grade 1	7	9	0	
Hypercalcemia|Grade 1	3	3	0	
Hypocalcemia|Grade 1	6	7	3	
Hemoglobin|Grade 2	7	8	3	
Platelet Count|Grade 2	0	0	0	
Leukocytes, Local Lab|Grade 2	0	0	0	
Lymphocytes (Absolute), Local Lab|Grade 2	0	6	0	
Absolute Neutrophil Count|Grade 2	0	0	0	
Alkaline Phosphate, Local Lab|Grade 2	2	0	0	
Aspartate Aminotransferase, Local Lab|Grade 2	0	1	0	
Alanine Aminotransferase, Local Lab|Grade 2	0	0	0	
Total Bilirubin, Local Lab|Grade 2	1	0	0	
Creatinine, Local Lab|Grade 2	12	9	0	
Hypernatremia|Grade 2	0	0	0	
Hyponatremia|Grade 2	0	0	0	
Hyperkalemia|Grade 2	4	3	0	
Hypokalemia|Grade 2	4	3	0	
Hypercalcemia|Grade 2	0	0	0	

Hypocalcemia|Grade 2	1	1	1	
Hemoglobin|Grade 3	1	1	1	
Platelet Count|Grade 3	0	0	0	
Leukocytes, Local Lab|Grade 3	1	0	0	
Lymphocytes (Absolute), Local Lab|Grade 3	3	2	0	
Absolute Neutrophil Count|Grade 3	0	0	0	
Alkaline Phosphate, Local Lab|Grade 3	0	0	0	
Aspartate Aminotransferase, Local Lab|Grade 3	0	0	0	
Alanine Aminotransferase, Local Lab|Grade 3	0	0	0	
Total Bilirubin, Local Lab|Grade 3	0	0	0	
Creatinine, Local Lab|Grade 3	3	1	0	
Hypernatremia|Grade 3	0	0	0	
Hyponatremia|Grade 3	0	1	0	
Hyperkalemia|Grade 3	1	0	0	
Hypokalemia|Grade 3	1	0	0	
Hypercalcemia|Grade 3	0	0	0	
Hypocalcemia|Grade 3	0	1	0	
Hemoglobin|Grade 4	0	0	0	
Platelet Count|Grade 4	0	0	0	
Leukocytes, Local Lab|Grade 4	0	0	0	
Lymphocytes (Absolute), Local Lab|Grade 4	0	0	0	
Absolute Neutrophil Count|Grade 4	1	0	0	
Alkaline Phosphate, Local Lab|Grade 4	0	0	0	
Aspartate Aminotransferase, Local Lab|Grade 4	0	0	0	
Alanine Aminotransferase, Local Lab|Grade 4	0	0	0	
Total Bilirubin, Local Lab|Grade 4	0	0	0	
Creatinine, Local Lab|Grade 4	0	0	0	
Hypernatremia|Grade 4	0	0	0	
Hyponatremia|Grade 4	0	0	0	
Hyperkalemia|Grade 4	0	0	0	
Hypokalemia|Grade 4	0	0	0	
Hypercalcemia|Grade 4	0	0	0	
Hypocalcemia|Grade 4	0	0	0	
Hemoglobin|Not Reported	1	0	26	
Platelet Count|Not Reported	1	0	26	
Leukocytes, Local Lab|Not Reported	1	0	26	
Lymphocytes (Absolute), Local Lab|Not Reported	7	11	32	
Absolute Neutrophil Count|Not Reported	1	0	32	
Alkaline Phosphate, Local Lab|Not Reported	1	0	30	
Aspartate Aminotransferase, Local Lab|Not Reported	1	0	30	
Alanine Aminotransferase, Local Lab|Not Reported	1	0	30	
Total Bilirubin, Local Lab|Not Reported	1	0	30	
Creatinine, Local Lab|Not Reported	1	0	26	
Hypernatremia|Not Reported	1	0	26	
Hyponatremia|Not Reported	1	0	26	

Hyperkalemia|Not Reported	1	0	26	
Hypokalemia|Not Reported	1	0	26	
Hypercalcemia|Not Reported	1	0	28	
Hypocalcemia|Not Reported	1	0	28	

Statistical analyses

No statistical analyses for this end point

Secondary: Pathologic Complete Response (pCR) Rate - Nivolumab Compared to Standard of Care

End point title	Pathologic Complete Response (pCR) Rate - Nivolumab Compared to Standard of Care[6]

End point description:

Pathologic Complete Response (pCR) is defined as the percentage of randomized participants with absence of any cancer in pathology specimens after radical cystectomy, based on blinded independent pathology review (BIPR). Participants who do not undertake surgery will be counted as non-pCR.

End point type	Secondary

End point timeframe:

From time of radical cystectomy up to 100 days after last treatment (up to approximately 17 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data for the missing arm is included as a primary endpoint.

End point values	Arm B: Nivolumab	Arm C: Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	40		
Units: Percentage of participants				
number (confidence interval 95%)	10.8 (3.0 to 25.4)	2.5 (0.1 to 13.2)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Time to Death

End point title	Time to Death

End point description:

The amount of time in months from when participants were randomized until death. Survival was reported as time to death instead of overall survival by Kaplan-Meier analysis due to the small number of events at the time of early study completion.

End point type	Post-hoc

End point timeframe:

From randomization to study completion, up to approximately 40 months

End point values	Arm A: Nivolumab + Bempegaldesleukin	Arm B: Nivolumab	Arm C: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	37	40	
Units: Months				
median (full range (min-max))	6.77 (3.2 to 18.4)	9.43 (1.8 to 20.1)	8.49 (1.6 to 23.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were assessed for all-cause mortality from randomization to study completion, up to approx. 40 months. Serious adverse events (SAEs) and AEs were assessed from first dose to 100 days following last dose, up to approx. 20 months.

Adverse event reporting additional description:

The number at risk for All-Cause Mortality, Serious Adverse Events, and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Arm A: Nivolumab + Bempegaldesleukin

Reporting group description:

Bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by bempegaldesleukin 0.006 mg/kg once every 3 weeks plus nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.

Reporting group title	Arm C: Standard of Care

Reporting group description:

Standard of care therapy, with cystectomy alone, without neoadjuvant or adjuvant therapy.

Reporting group title	Arm B: Nivolumab

Reporting group description:

Nivolumab 360 mg once every 3 weeks for 3 cycles as neoadjuvant therapy, followed by Radical Cystectomy, followed by nivolumab 360 mg once every 3 weeks up to an additional 12 cycles.

Serious adverse events	Arm A: Nivolumab + Bempegaldesleukin	Arm C: Standard of Care	Arm B: Nivolumab
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 37 (43.24%)	15 / 32 (46.88%)	22 / 37 (59.46%)
number of deaths (all causes)	8	11	6
number of deaths resulting from adverse events	5	3	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 37 (0.00%)	2 / 32 (6.25%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung disorder			

subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lipase increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site impaired healing			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound evisceration			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Vallecular cyst			

subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure acute			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Endocarditis noninfective			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Hypereosinophilic syndrome			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal barrier dysfunction			

subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal fistula			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rectal perforation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated nephritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			

subjects affected / exposed	2 / 37 (5.41%)	4 / 32 (12.50%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 37 (2.70%)	1 / 32 (3.13%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	4 / 37 (10.81%)	3 / 32 (9.38%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 32 (3.13%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A: Nivolumab + Bempegaldesleukin	Arm C: Standard of Care	Arm B: Nivolumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 37 (86.49%)	18 / 32 (56.25%)	29 / 37 (78.38%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 37 (2.70%)	1 / 32 (3.13%)	2 / 37 (5.41%)
occurrences (all)	1	1	2
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 37 (8.11%)	2 / 32 (6.25%)	4 / 37 (10.81%)
occurrences (all)	3	2	4
Hypertension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	6 / 37 (16.22%)
occurrences (all)	1	0	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 37 (24.32%)	1 / 32 (3.13%)	5 / 37 (13.51%)
occurrences (all)	9	1	5
Chills			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	8 / 37 (21.62%)	3 / 32 (9.38%)	6 / 37 (16.22%)
occurrences (all)	8	3	6
Influenza like illness			

subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	2 / 37 (5.41%)	1 / 32 (3.13%)	4 / 37 (10.81%)
occurrences (all)	2	1	4
Pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Peripheral swelling			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	10 / 37 (27.03%)	4 / 32 (12.50%)	3 / 37 (8.11%)
occurrences (all)	10	4	3
Xerosis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 37 (5.41%)	1 / 32 (3.13%)	1 / 37 (2.70%)
occurrences (all)	2	1	1
Dyspnoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	4 / 37 (10.81%)
occurrences (all)	1	0	4
Cough			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 32 (6.25%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Anxiety			

subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Product issues			
Device occlusion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Investigations			
Amylase increased			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	3 / 37 (8.11%)
occurrences (all)	2	0	3
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	3	0	2
Weight increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Weight decreased			
subjects affected / exposed	4 / 37 (10.81%)	2 / 32 (6.25%)	7 / 37 (18.92%)
occurrences (all)	4	2	7
Lipase increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	4 / 37 (10.81%)
occurrences (all)	1	0	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences (all)	3	0	1
Blood creatinine increased			
subjects affected / exposed	5 / 37 (13.51%)	2 / 32 (6.25%)	4 / 37 (10.81%)
occurrences (all)	5	2	4
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Procedural pain			
subjects affected / exposed	0 / 37 (0.00%)	2 / 32 (6.25%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Cardiac disorders			

Bradycardia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	3	0	2
Dizziness			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 37 (10.81%)	2 / 32 (6.25%)	7 / 37 (18.92%)
occurrences (all)	4	2	7
Eosinophilia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Hyperleukocytosis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 37 (0.00%)	3 / 32 (9.38%)	1 / 37 (2.70%)
occurrences (all)	0	3	1
Abdominal pain upper			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Constipation			
subjects affected / exposed	4 / 37 (10.81%)	4 / 32 (12.50%)	7 / 37 (18.92%)
occurrences (all)	4	4	7
Diarrhoea			
subjects affected / exposed	8 / 37 (21.62%)	0 / 32 (0.00%)	3 / 37 (8.11%)
occurrences (all)	8	0	3

Nausea			
subjects affected / exposed	4 / 37 (10.81%)	3 / 32 (9.38%)	2 / 37 (5.41%)
occurrences (all)	4	3	2
Oesophagitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)	2 / 32 (6.25%)	0 / 37 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)	4 / 32 (12.50%)	4 / 37 (10.81%)
occurrences (all)	1	4	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 37 (10.81%)	0 / 32 (0.00%)	4 / 37 (10.81%)
occurrences (all)	4	0	4
Pruritus			
subjects affected / exposed	13 / 37 (35.14%)	0 / 32 (0.00%)	6 / 37 (16.22%)
occurrences (all)	13	0	6
Dry skin			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	3	0	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 37 (5.41%)	1 / 32 (3.13%)	4 / 37 (10.81%)
occurrences (all)	2	1	4
Dysuria			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Hypothyroidism			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	5 / 37 (13.51%)
occurrences (all)	3	0	5
Musculoskeletal and connective tissue			

disorders			
Flank pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	1 / 37 (2.70%)	1 / 32 (3.13%)	2 / 37 (5.41%)
occurrences (all)	1	1	2
Arthritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Arthralgia			
subjects affected / exposed	3 / 37 (8.11%)	0 / 32 (0.00%)	4 / 37 (10.81%)
occurrences (all)	3	0	4
Groin pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	2 / 37 (5.41%)
occurrences (all)	2	0	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 37 (13.51%)	2 / 32 (6.25%)	7 / 37 (18.92%)
occurrences (all)	5	2	7
Cystitis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
COVID-19			
subjects affected / exposed	1 / 37 (2.70%)	1 / 32 (3.13%)	2 / 37 (5.41%)
occurrences (all)	1	1	2
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 32 (9.38%)	1 / 37 (2.70%)
occurrences (all)	1	3	1
Hyponatraemia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 32 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Hypokalaemia			

subjects affected / exposed	1 / 37 (2.70%)	2 / 32 (6.25%)	2 / 37 (5.41%)
occurrences (all)	1	2	2
Hyperglycaemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 32 (6.25%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Decreased appetite			
subjects affected / exposed	4 / 37 (10.81%)	2 / 32 (6.25%)	2 / 37 (5.41%)
occurrences (all)	4	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2019	- Modifications made to align with BMS policy updates - Added nivolumab and NKTR-214 program updates - Correction to Section 5.1.4: added missing paragraph regarding adjudicated events - Appendix 3 updated (Adverse Events) - Appendix 4 updated (WOCBP) - Appendix 9 added (Country Specific Requirements)
05 March 2020	- Revised to align with most recent language for BMS program updates - Modifications made to align with NKTR-214 program and IB updates - Appendix 2 updated (Study Governance Considerations) - Appendix 6 updated (Management Algorithms) - Appendix 7 added (CVA Management Algorithm)
26 August 2021	- Revised to include participants with high-risk urothelial carcinoma (UC) of the bladder with N1 disease and muscleinvasive bladder cancer (MIBC), addition of nivolumab + bempegaldesleukin vs nivolumab secondary endpoint comparisons, and the updated alpha allocation for the pathologic complete response (pCR) and event free survival (EFS) primary endpoints. - Modifications made to align with Bempegaldesleukin and Nivolumab program standards. - Align with changes to safety assessments including safety management algorithms, guidance for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status, and coronavirus disease 2019 (COVID-19) vaccine.
10 June 2022	- Participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy on protocol for the remainder of their treatment duration. New enrollment in this study has been stopped. - Imaging will be performed per local standard of care; blinded independent central review is discontinued. All study treatment decisions including progression and recurrence will be based on the investigator's assessment of tumor images. - The efficacy endpoints of pathologic complete response, event-free survival, and overall survival, as well as safety and tolerability for each treatment arm, will be summarized descriptively in all randomized participants. Secondary and exploratory objectives except for safety and biomarker parameters will not be required. No further efficacy data will be collected/analyzed. - For each randomized participant, the maximum duration of the study is 62 weeks plus 100 days of safety follow-up. - Participants currently in survival follow-up will discontinue from the study following one recurrence update and survival status update.

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.

BMS and Nektar jointly terminated this clinical development program. Discontinued survival follow-up and stopping submission of local labs to vendors, imaging to the BICR vendor, and PROs have resulted in confounded and incomplete trial results.

Notes: