Clinical trial results:
A Phase 3, Randomized, Double-blind Trial of Nivolumab in Combination with Intravesical BCG versus Standard of Care BCG Alone in Participants with High-risk Non-muscle Invasive Bladder Cancer That Is Persistent or Recurrent After Treatment with BCG

Summary

EudraCT number	2019-002567-96
Trial protocol	FR ES NL GR SE GB DE AT IT
Global end of trial date	31 October 2023

Results information

Result version number	v1 (current)
This version publication date	24 October 2024
First version publication date	24 October 2024

Trial information

Trial identification

Sponsor protocol code	CA209-7G8

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	Chaussée 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	31 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the EFS per PRC of nivolumab plus BCG vs BCG alone in all randomized participants

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 subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2019
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	Greece: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Russian Federation: 2
Worldwide total number of subjects	12
EEA total number of subjects	7

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)	5
From 65 to 84 years	6
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

12 subjects randomized and treated

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Nivolumab 480 mg intravenous (IV) every 4 weeks (Q4W) for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

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

Dosage and administration details:

10mg/mL

Investigational medicinal product name	BCG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

BCG dose should be prepared and administered according to the package insert

Arm title	Arm B

Arm description:

Nivolumab-placebo IV Q4W for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

480mg

Number of subjects in period 1	Arm A	Arm B
Started	8	4
Completed	8	4

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Nivolumab 480 mg intravenous (IV) every 4 weeks (Q4W) for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months	
Reporting group title	Arm B
Reporting group description:	
Nivolumab-placebo IV Q4W for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months	

Reporting group values	Arm A	Arm B	Total
Number of subjects	8	4	12
Age categorical Units: Subjects			
Adults (18-64 years)	4	1	5
From 65-84 years	4	2	6
85 years and over	0	1	1
Age Continuous Units: Years			
arithmetic mean	61.1	73.0	
standard deviation	± 9.8	± 15.3	-
Sex: Female, Male Units: Participants			
Female	1	1	2
Male	7	3	10
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	7	4	11
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	5	1	6
Unknown or Not Reported	2	1	3

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Nivolumab 480 mg intravenous (IV) every 4 weeks (Q4W) for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

Reporting group title	Arm B

Reporting group description:

Nivolumab-placebo IV Q4W for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

Primary: Event Free Survival

End point title	Event Free Survival[1]

End point description:

The time between the date of randomization and the date of first documented event or death due to any cause, whichever occurs first. Events include recurrence of disease (TaHG, T1, or CIS) and progression of disease.

Here "9999" = NA

End point type	Primary

End point timeframe:

Approximately 44 Months and 1 Week

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: No statistical Analysis done for this endpoint

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

The time between the date of randomization and the date of death due to any cause. For participants still alive, OS is censored at the last date the participant is known to be alive.

Here "9999" = NA

End point type	Secondary

End point timeframe:

Approximately 44 months and 1 week

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

the time between the date of the first CR to the date of first documented recurrence, progression, or death due to any cause.

Here "9999" = NA

End point type	Secondary

End point timeframe:

Approximately 44 months and 1 week

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Worsening-Free Survival

End point title	Worsening-Free Survival

End point description:

The time from randomization to progression to muscle-invasive disease (ie, T2), cystectomy, systemic chemotherapy, radiotherapy, or death from any cause.

Here "9999" = NA

End point type	Secondary

End point timeframe:

Approximately 44 months and 1 week

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: All-causality adverse events

End point title	All-causality adverse events

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

24.6 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Subjects				
Grade 1	1	2		
Grade 2	4	1		
Grade 3	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: All-causality adverse events leading to discontinuation

End point title	All-causality adverse events leading to discontinuation

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting

medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

24.6 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Subjects				
Any Grade	1	3		
Grade 3-4	0	0		
Grade 5	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Drug-related adverse events

End point title	Drug-related adverse events

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

24.6 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Subjects				
Grade 1	1	1		
Grade 2	4	1		
Grade 3	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate at 13 Weeks

End point title	Complete Response Rate at 13 Weeks

End point description:

CRR is defined as the proportion of participants with CIS (+/- TaHG/T1) per PRC at randomization who are disease free at the first disease assessment (Week 13)

Here "9999" = NA

End point type	Secondary

End point timeframe:

13 Weeks

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Percentage of Participants				
arithmetic mean (standard deviation)	9999 (± 9999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events: (From first dose to last dose + 100 days): Approximately 44 months and 1 week

All-Cause mortality (From randomization to end of study): Approximately 44 months and 1 week

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all Randomized Participants. The number at Risk for 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	26.1

Reporting groups

Reporting group title	Arm B

Reporting group description:

Nivolumab-placebo IV Q4W for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

Reporting group title	Arm A

Reporting group description:

Nivolumab 480 mg intravenous (IV) every 4 weeks (Q4W) for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

Serious adverse events	Arm B	Arm A	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm B	Arm A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 8 (62.50%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	4	
Perineal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Sputum discoloured			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cortisol decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	3	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Dyschezia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Umbilical hernia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Nail disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	4	
Dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rash			

subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Urinary tract disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Nocturia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Immune-mediated cystitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Dysuria			
subjects affected / exposed	1 / 4 (25.00%)	3 / 8 (37.50%)	
occurrences (all)	2	5	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			

Polyarthritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	3 / 4 (75.00%)	3 / 8 (37.50%)	
occurrences (all)	5	5	
Cystitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2021	As of May 2021, the CA2097G8 study enrollment was significantly behind the projected target enrollment, at 5% since first patient first visit; therefore, the study will be unable to meet its scientific objectives. As such, the primary reason for this protocol amendment is to implement the decision to close participant enrollment to the study as of 02-Jun-2021. Details of closure of the study, with provision for participants currently on treatment to continue. Clarification that all pharmacokinetic (PK), biomarker, patient-reported outcomes, and health care resource utilization assessments are no longer applicable per Protocol Amendment 01. Clarification that study-related efficacy assessment and Pathology Review Committee are no longer applicable per Protocol Amendment 01. Sites should continue efficacy assessment as per local standards of care.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported