Clinical trial results:
A randomized, double blind, placebo controlled phase II trial to evaluate the safety and efficacy of recMAGE-A3 + AS15 ASCI in patients with MAGE-A3 positive muscle invasive bladder cancer after cystectomy

Summary

EudraCT number	2010-024355-85
Trial protocol	DE NL ES IT CZ
Global end of trial date	09 December 2016

Results information

Result version number	v1 (current)
This version publication date	13 December 2017
First version publication date	13 December 2017
Summary attachment (see zip file)	Magnolia_synopsis (SYNOPSIS_MAGNOLIA_final.pdf)

Trial information

Trial identification

Sponsor protocol code	2010-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01435356
WHO universal trial number (UTN)	-
Other trial identifiers	NTR Number: NTR2846, EAU-RF: 2010-01

Notes:

Sponsors

Sponsor organisation name	EAU RF
Sponsor organisation address	Mr. E.N. van Kleffensstraat 5, Arnhem, Netherlands, 6842 CV
Public contact	Raymond G. Schipper, PhD, EAU RF, +31 263890677, researchfoundation@uroweb.org
Scientific contact	Wim P.J. Witjes, MD, PhD, EAU RF, +31 263890677, researchfoundation@uroweb.org

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	07 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2016
Global end of trial reached?	Yes
Global end of trial date	09 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this Phase II study is to evaluate the clinical efficacy in terms of Disease Free Survival of recMAGE-A3 + AS 15 ASCI versus placebo in the overall population.

Protection of trial subjects:

Potential risks for recMAGE-A3 + AS15 ASCI were identified during safety evaluation of MAGE-A3 antigen and the AS15 adjuvant in preclinical studies and studies in humans.
The first one was the general theoretical concern of acquiring a vaccine induced autoimmune disease after immunization with a product containing Adjuvant Systems (AS). Potential immune-mediated diseases (pIMDs) were specified in the protocol and needed to be reported in the same (expedited) way as SAEs.
Second, a potential developmental risk identified from preclinical embryo-foetal developmental toxicity studies in rats and rabbits with CpG 7909 from Pfizer Pharmaceutical Group (manufacturer of CpG 7909). CpG 7909 is one of the immunostimulatory components of GSK Biologicals' proprietary AS15 Adjuvant System. Any possible risk associated with CpG 7909 exposure in humans is currently unknown, although GSK non-clinical data currently available on AS15 alone and in combination with different antigens shows no adverse reproductive, developmental or fertility effects. Pregnancy was an exclusion criterion to participate in this study. In addition, all women of childbearing potential needed to have a negative pregnancy test before participating in the study, and be using effective contraception during study treatment.

Background therapy:

None

Evidence for comparator:

Currently, the standard treatment for localized muscle invasive bladder cancer is radical cystectomy.

- Many patients with muscle invasive bladder cancer will relapse after cystectomy

The 10-year disease-specific and overall survival of patients with organ confined (defined as < pT3a) is 72.9% and 49.1%, rapidly decreasing to 33.3% and 22.8% for non-organ confined disease (13). There is thus a clear medical need for an additional anti-tumoral treatment in this population.

- There is not enough evidence in favour of the routine use of adjuvant chemotherapy

From scientific evidence so far available, it is unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior or if the two approaches are equivalent with respect to the end-point overall survival. There is no additional effective treatment for the patient population at high risk of relapse receiving adjuvant chemotherapy and this represents a significant unmet medical need.

- MAGE-A3 is a factor of poor prognosis

The interest in recMAGE-A3 ASCI treatment is further reinforced by the possible link between MAGE-A3 expression and shorter survival

- MAGE-A3 is tumor-specific, recMAGE-A3 + AS15 ASCI highly tolerated and shows promising Phase II results

Taking into account the tumor-specificity of MAGE-A3, the high tolerability of recMAGE-A3 + AS15 and the promising results from the Phase II clinical trials in melanoma and lungcancer, EAU RF proposes to initiate a randomized, placebo-controlled clinical Phase II trial with recombinant MAGE-A3 (recMAGE-A3) combined with the AS15 adjuvant in patients with muscle invasive bladder cancer with MAGE-A3 expression after cystectomy.

This trial will assess whether adjuvant treatment with recMAGE-A3 + AS 15 ASCI after cystectomy is

safe and effective and improves outcome of MAGE-A3 positive patients after cystectomy.

Actual start date of recruitment	01 July 2011
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	Netherlands: 63
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Spain: 156
Country: Number of subjects enrolled	Czech Republic: 61
Country: Number of subjects enrolled	France: 48
Country: Number of subjects enrolled	Germany: 133
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	Russian Federation: 15
Worldwide total number of subjects	529
EEA total number of subjects	506

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)	199
From 65 to 84 years	328
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

From September 2011 to August 2014 529 patients were screened. Ten European countries participated with a total of 50 sites. As of 23 September 2014, the recruitment was put on hold. As of Protocol Amendment 4.0 , the recruitment was stopped and the study was unblinded.

Pre-assignment

Screening details:

Patients enter Screening S1 (pre-assignment period) during which it is checked whether the tumor tissue expresses the MAGE-A3 protein (=MAGE-A3 positive).
MAGE-A3 positive patients enter Screening S2 and in case they comply to all in/exclusioncriteria they can be randomised.

Pre-assignment period milestones

Number of subjects started	529
Number of subjects completed	205

Pre-assignment subject non-completion reasons

Reason: Number of subjects	not MAGE-A3 positive: 243
Reason: Number of subjects	no FFPE sample taken: 81

Period 1

Period 1 title	Screening S2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Screening S2 patients

Arm description:

Patients who were MAGE-A3 positive (at S1) underwent Screening S2. In case they were eligible they were randomised

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Screening S2 patients
Started	205
Completed	83
Not completed	122
Consent withdrawn by subject	29
Eligibility criteria not fulfilled	91
Lost to follow-up	2

Period 2

Period 2 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As of Protocol Amendment 4.0 , the recruitment was stopped and the study was unblinded

Arms

Are arms mutually exclusive?	Yes
Arm title	recMAGE-A3 +AS15

Arm description:

recombinant antigen ProtD-MAGE-A3/His (recMAGE-A3) and the GSK proprietary immunological adjuvant AS15

Arm type	Experimental
Investigational medicinal product name	recombinant antigen ProtD-MAGE-A3/His (recMAGE-A3) + AS15
Investigational medicinal product code	
Other name	recMAGE-A3 + AS15
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

recMAGE-A3 + AS 15 ASCI was administered by using a sterile two vial set comprising:
- One vial with the lyophilized preparation containing 300 µg recMAGE-A3 antigen plus 420 µg of CpG7909 (a part of the adjuvant system AS15),
- One vial with liquid adjuvant diluent AS01B (containing liposomes), along with 50 µg of MPL combined with 50 µg of QS21 in phosphate buffered saline), making up the remainder of the adjuvant system AS15.

The final recMAGE-A3 + AS15 ASCI for administration was obtained by reconstitution of the lyophilized preparation with the adjuvant diluent. A recMAGE-A3 + AS15 ASCI dose consisted of 0.5 ml.
A standard dose of recMAGE-A3 (300 ug) + AS15, or of placebo, was administered every 3 weeks from Visit 1 to Visit 5 and every 12 weeks from Visit 6 to Visit 13

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The placebo consisted of sucrose reconstituted with a 1/500 dilution of SB62 oil-inwater emulsion (pH = 6.8) in a total volume of 0.5 ml. It was administered by using a sterile two-vial set comprising:
- One vial with the lyophilized sucrose preparation,
- One vial with the diluted oil-in-water emulsion diluent.

0.5 ml of sucrose reconstituted in a diluted oil-in-water emulsion was administered every 3 weeks from Visit 1 to Visit 5 and every 12 weeks from Visit 6 to Visit 13

Number of subjects in period 2	recMAGE-A3 +AS15	Placebo
Started	52	31
Completed	48	29
Not completed	4	2
ineligible, incorrectly randomised, not treated	4	2

Period 3	
Period 3 title	Treated
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	recMAGE-A3 + AS15

Arm description:

recMAGE-A3 + AS15

Arm type	Experimental
Investigational medicinal product name	recombinant antigen ProtD-MAGE-A3/His (recMAGE-A3) + AS15
Investigational medicinal product code	
Other name	recMAGE-A3 + AS15
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

recMAGE-A3 + AS 15 ASCI was administered by using a sterile two vial set comprising:
- One vial with the lyophilized preparation containing 300 µg recMAGE-A3 antigen plus 420 µg of CpG7909 (a part of the adjuvant system AS15),
- One vial with liquid adjuvant diluent AS01B (containing liposomes), along with 50 µg of MPL combined with 50 µg of QS21 in phosphate buffered saline), making up the remainder of the adjuvant system AS15.

The final recMAGE-A3 + AS15 ASCI for administration was obtained by reconstitution of the lyophilized preparation with the adjuvant diluent. A recMAGE-A3 + AS15 ASCI dose consisted of 0.5 ml.
A standard dose of recMAGE-A3 (300 ug) + AS15, or of placebo, was administered every 3 weeks from Visit 1 to Visit 5 and every 12 weeks from Visit 6 to Visit 13

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The placebo consisted of sucrose reconstituted with a 1/500 dilution of SB62 oil-inwater emulsion (pH = 6.8) in a total volume of 0.5 ml. It was administered by using a sterile two-vial set comprising:
• One vial with the lyophilized sucrose preparation,
• One vial with the diluted oil-in-water emulsion diluent.

0.5 ml of sucrose reconstituted in a diluted oil-in-water emulsion was administered every 3 weeks from Visit 1 to Visit 5 and every 12 weeks from Visit 6 to Visit 13

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the number of randomized patients. Baseline data was not available for 6 patients who were incorrectly randomized and not treated. Baseline data provided for treated patients.

Number of subjects in period 3[2]	recMAGE-A3 + AS15	Placebo
Started	48	29
Completed	16	5
Not completed	32	24
Consent withdrawn by subject	6	1
Adverse event, non-fatal	3	-
study discontinuation (amendment 4)	5	11
patient moved to another city	1	1
Lack of efficacy	17	10
Protocol deviation	-	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number enrolled in this trial is the number of patients who entered Screening S1 (pre-assignment period, n=529) during which it was checked whether the tumor tissue expressed the MAGE-A3 protein (=MAGE-A3 positive).
Only MAGE-A3 positive patients (n=205) entered Screening S2 and in case they complied to all in/exclusioncriteria they were randomised (n=83).

Baseline characteristics

Reporting groups	
Reporting group title	recMAGE-A3 + AS15
Reporting group description: recMAGE-A3 + AS15	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	recMAGE-A3 + AS15	Placebo	Total
Number of subjects	48	29	77
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age at Screening S1			
Units: years			
arithmetic mean	65.7	65.5	
standard deviation	± 8.4	± 9.6	-
Gender categorical Units: Subjects			
Female	8	8	16
Male	40	21	61
T-category			
T-category of bladder cancer at diagnosis			
Units: Subjects			
T2	22	13	35
T3	21	13	34
T4	5	3	8
N-category			
N-category of bladder cancer at diagnosis			
Units: Subjects			
N0	36	22	58
N1	7	4	11
N2	5	3	8
M-category			
M-category of bladder cancer at diagnosis			
Units: Subjects			

M0	48	29	77
dominant histopathological type			
Dominant histopathological type of bladder tumor			
Units: Subjects			
transitional (urothelial) cell carcinoma	43	29	72
squamous cell carcinoma	3	0	3
adenocarcinoma	1	0	1
not available	1	0	1
tumor size			
macrosopic tumor size of primary tumor			
Units: centimeter			
arithmetic mean	3.4	3.2	
standard deviation	± 2.5	± 2.3	-

End points

End points reporting groups

Reporting group title	Screening S2 patients
Reporting group description:	
Patients who were MAGE-A3 positive (at S1) underwent Screening S2. In case they were eligible they were randomised	
Reporting group title	recMAGE-A3 +AS15
Reporting group description:	
recombinant antigen ProtD-MAGE-A3/His (recMAGE-A3) and the GSK proprietary immunological adjuvant AS15	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	recMAGE-A3 + AS15
Reporting group description:	
recMAGE-A3 + AS15	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Primary: disease free survival

End point title	disease free survival[1]
End point description:	
Disease-free Survival (DFS) was defined as the time from randomization to either the date of first recurrence of the disease or the date of death (whatever the cause), whichever occurred first. Types of recurrence considered as an event included loco-regional and distant metastases. In addition, any death occurring without prior documentation of tumor recurrence was considered as an event (and was not censored in the statistical analysis) as this approach is less prone to introduce bias.	
End point type	Primary
End point timeframe:	
Disease-free Survival (DFS) was defined as the time from randomization to either the date of first recurrence of the disease or the date of death (whatever the cause), whichever occurred first.	

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: Following amendment 4, the primary and secondary endpoints were not assessed as planned. All clinical data collected in the study were analysed descriptively. No formal statistical analysis were performed.

End point values	recMAGE-A3 + AS15	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	29		
Units: months				
least squares mean (confidence interval 95%)	27.5 (22.7 to 32.3)	19.8 (15.7 to 23.9)		

Attachments (see zip file)	Disease free survival/Magnolia DFS KM curve.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Overall Survival was defined as the interval from randomization to the date of death, irrespective of the cause of death; patients still alive were censored at the date of the last assessment.

End point values	recMAGE-A3 + AS15	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	29		
Units: months				
least squares mean (confidence interval 95%)	35.5 (32.1 to 39.9)	24.1 (21 to 27.2)		

Attachments (see zip file)	Overall survival/Magnolia OS KM curve.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Distant metastasis-free survival

End point title	Distant metastasis-free survival

End point description:

Distant metastasis-free survival (DMFS) was defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurred first. Patients alive and without distant metastasis were censored at the date of last assessment.

End point type	Secondary

End point timeframe:

Distant metastasis-free survival (DMFS) was defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurred first.

End point values	recMAGE-A3 + AS15	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	29		
Units: months				
least squares mean (confidence interval 95%)	31.5 (27.2 to 35.9)	21.4 (17.5 to 25.2)		

Attachments (see zip file)	Distant Metastasis-free survival/Magnolia DMFS KM curve.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs occurring within the period beginning at the first administration of study treatment and ending 30 days after the last administration of study treatment were recorded.

Adverse event reporting additional description:

All AEs either observed by the investigator or one of his clinical collaborators or reported by the patient spontaneously or in response to a direct question were evaluated by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	recMAGE-A3 + AS15

Reporting group description:

recMAGE-A3 + AS15

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	recMAGE-A3 + AS15	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 48 (27.08%)	5 / 29 (17.24%)	
number of deaths (all causes)	6	5	
number of deaths resulting from adverse events	0	0	
Investigations			
Diagnostic procedure	Additional description: RADIOGRAPHIC EVIDENCE OF CENTRAL TUMOR RENAL PELVIS LEFT		
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 48 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			

subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Femoral artery aneurysm			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
femoral artery occlusion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
massive progression of lymphadenopathy			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			

subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urethral stenosis			
subjects affected / exposed	2 / 48 (4.17%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	4 / 48 (8.33%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	recMAGE-A3 + AS15	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 48 (79.17%)	21 / 29 (72.41%)	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	29 / 48 (60.42%)	12 / 29 (41.38%)	
occurrences (all)	187	23	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	11 / 48 (22.92%)	6 / 29 (20.69%)	
occurrences (all)	13	8	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	8 / 48 (16.67%)	3 / 29 (10.34%)	
occurrences (all)	11	7	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	5 / 48 (10.42%)	5 / 29 (17.24%)	
occurrences (all)	6	7	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	9 / 48 (18.75%)	4 / 29 (13.79%)	
occurrences (all)	13	6	
Infections and infestations			

infections and infestations subjects affected / exposed occurrences (all)	15 / 48 (31.25%) 28	11 / 29 (37.93%) 21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2011	1) Broadening the time frame of inclusion criterion no. 3 for giving consent: Consent can be given before or after cystectomy since this is not a study-specific procedure. However, (optional) urine collection should be done before cystectomy 2) Additional inclusion criterion no. 10: The patient should be affiliated to health insurance or benefit of such an insurance 3) Additional exclusion criterion no. 14: Adults under legal supervision 4) Additional example to exclusion criterion no. 12: patients taking anticoagulant treatment or having a coagulation disorder 5) Additional condition of the tumor stage of the remaining tissue in the bladder in case tumor tissue derived during a TUR will be sent to the central laboratory for testing: when the bladder tumor is removed during a TUR preceding the cystectomy and the stage of the remaining tissue in the bladder is T0 or T1, the tumor tissue derived during the TUR may be sent to the central laboratory for testing 6) Clarification of the text: either images with or images without contrast material are required 7) Clarification of the nature of the gene profiling tests during recurrence: participation in the part of the study during recurrence is optional. Therefore gene profiling during recurrence should be labelled optional, not mandatory 8) Correction of typo: the hazard ratio of disease free survival of recMAGE-A3 + AS 15 ASCI treated patients will be taken against placebo treated patients
15 May 2012	1) Compliance with the Declaration of Helsinki 3§ and ICH GCP 4.3 and ICH GCP 5.13.4: the treating physician (investigator) is responsible for the medical care of the individual trial subject and the coding system in blinded trials should include a mechanism that permits rapid unblinding 2) Correction biopsy technique for (recurrent) tumour tissue samples in which MAGE A3 expression can be tested: MAGE A3 expression can only be tested in samples from resected tissue

06 January 2014	1) Change in exclusion criterion no. 2: Treatment with neo-adjuvant and adjuvant chemotherapy is allowed. Neo-adjuvant- and adjuvant chemotherapy treated subjects will be studied as subpopulations. 2) Broadening the time frame between cystectomy and randomization, from 9 to13 weeks (for patients not scheduled to receive adjuvant chemotherapy) or from 9 to 35 weeks (for patients receiving adjuvant chemotherapy). 3) Additional condition of the tumor tissue to be sent to the central laboratory for testing: As an alternative to the cystectomy specimen, the conditions are widened for a tumor sample collected during the TUR to be sent to the laboratory for testing. 4) Additional research in Translational Research: We also intend to characterize the tumor microenvironment and lymphocyte infiltration in the primary tumor and its recurrence lesions 5) Change in timing of the treatment/observation phase: The total duration of the study will be 7-8 years, starting with a recruitment phase of 4-5 years. 6) Correction of expected events: Expected events after interim analysis are 155. 7) Adaptation of text on potential immune-mediated diseases (pIMD) 8) Change of term "transitional cell carcinoma of bladder urothelium" into "urothelial carcinoma of the bladder" 9) Correction of typo, addition of "or": Plant extracts or anticancer treatments, including but not exclusively, chemotherapeutic or immunomodulating agents and radiotherapy. 10) Correction of reference to Figure 3
28 October 2014	Upon release and analysis of the MAGRIT trial results, the rationale of the MAGNOLIA study has been changed. As of 23 September 2014, the recruitment was put on hold. As of Protocol Amendment 4.0: - The recruitment will be stopped and the study population will be unblinded. - For patients randomized to the placebo group, no further protocol visits will be performed except for the concluding visit and no further doses will be administered - As it cannot be excluded that one or more patients may benefit from this treatment on an individual basis, patients receiving active treatment will be offered the option to continue the administration of the study treatment until the last dose is administered or until recurrence, whichever comes first, or until the patient or the investigator decides to stop the study treatment. Therefore, the study will continue only with patients from the active treatment group who will decide to stay in the study. Treatment will not be possible anymore after 30 November 2016. - During the treatment period, safety monitoring will continue as initially foreseen during the treatment period - The primary and secondary objectives will not be assessed as planned. All clinical data collected in the study will be analysed descriptively. Sections of the protocol impacted by amendment 4.0 include the Study Synopsis (Section 1), the Introduction and Rationale (Section 2), the Study Objectives & End Points (Section 3), the Design of the Study (Section 4), Patient Selection Criteria (Section 5), Investigational Products and Administration (Section 6), the Study Assessments and Procedures (Section 7), the Adverse Events and Serious Adverse Events (Section 8), the Patient Completion and Withdrawal (Section 9) and the Statistical Considerations (Section 10). In addition a typo was corrected in section 6.1.2 and in section 8.3 Table 8 was updated.

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.

Trial's recruitment was prematurely stopped, the number of patients participating was limited and the recMAGE-A3+AS15 patients were given the opportunity to continue treatment following amendment 4, whereas placebo patients needed to stop treatment.

Notes: