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

Published: 28-07-2011
Last updated: 27-04-2024

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 ASCIversus placebo in the overall population.Secondary objectives are:• To evaluate overall survival in the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON39841

Source
ToetsingOnline

Brief title
MAGNOLIA

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
bladder cancer: malignant tumor of bladder, bladdercarcinoma

Research involving

Human

Sponsors and support

Primary sponsor: European Association of Urology
Source(s) of monetary or material Support: European Association of Urology,GlaxoSmithKline,GSK (Bio)

Intervention

Keyword: cystectomy, MAGE-A3 positive muscle invasive bladder cancer, recMAGEA3 + AS15 ASCI, safety and efficacy

Outcome measures

Primary outcome

Primary endpoint is Disease-free Survival (DFS):

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 occurs

first.

· Types of recurrence to be considered as an event include loco-regional and

distant metastases.

· In addition, any death occurring without prior documentation of tumor

recurrence will be considered as an event (and will not be censored in the

statistical analysis) as this approach is less prone to introduce bias.

· If no event has occurred by the time of the analysis, then the time to event

will be censored at the date of the last assessment of the patient in question.

· Any new primary cancer at another site, including transitional carcinoma of

the upper urinary tract, will not be considered as recurrence and should be

reported as a SAE.

Protocol Amendment 4: The primary and secondary objectives will not be assessed as planned. All clinical data collected in the study will be analysed descriptively.The immune response will not be evaluated anymore as the immune response to IP administration was confirmed in other ASCI trials, but did not show any correlation with the potential efficacy.

Secondary outcome

Secondary endpoints are:

· Overall Survival: Defined as the interval from randomization to the date of death, irrespective of the cause of death; patients still alive will be censored at the date of the last assessment.

· Disease-free specific survival (DFSS): Defined as the interval from randomization to the date of first recurrence of disease or date of death due to bladder carcinoma, whichever occurs first. Patients without recurrence or death are censored at the date of last assessment. Patients without recurrence who die from another cause are censored at the date of death.

· Distant metastasis-free survival (DMFS): Defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurs first. Patients alive and without distant metastasis are censored at the date of last assessment.

· (Serious) Adverse events.

· To evaluate impact of predictive gene signature on efficacy of treatment in terms of DFS and overall survival.

· To evaluate the immune response to the AS15 ASCI.

· To evaluate Gene expression profiles of the primary tumor by microarray.

Protocol Amendment 4: The primary and secondary objectives will not be assessed as planned. All clinical data collected in the study will be analysed descriptively.The immune response will not be evaluated anymore as the immune response to IP administration was confirmed in other ASCI trials, but did not show any correlation with the potential efficacy.

Study description

Background summary

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.
· 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 (34)
· MAGE-A3 is tumor-specific, recMAGE-A3 ASCI treatment 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 lung cancer, 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.

Study objective

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.
Secondary objectives are:
• To evaluate overall survival in the overall study population, in the subpopulations with and without use of neo-adjuvant chemotherapy and in the subpopulations with and without use of adjuvant chemotherapy
• To evaluate Disease-free (DFS) in the subpopulations with and without use of neo-adjuvant chemotherapy and in the subpopulations with and without use of adjuvant chemotherapy.
• To evaluate Disease-free specific survival (DFSS) in the overall study population, in the subpopulations with and without use of neo-adjuvant chemotherapy and in the subpopulations with and without use of adjuvant chemotherapy.
• To evaluate Distant metastasis-free survival (DMFS) in the overall study population, in the subpopulations with and without use of neo-adjuvant chemotherapy and in the subpopulations with and without use of adjuvant chemotherapy.
• To evaluate the safety of recMAGE-A3 + AS15 ASCI in the overall study population, in the subpopulations with and without use of neo-adjuvant chemotherapy and in the subpopulations with and without use of adjuvant chemotherapy.
• To evaluate the immune response to recMAGE-A3 + AS15 ASCI in the overall study population and in the subpopulations with and without use of neo-adjuvant chemotherapy and in the subpopulations with and without use of adjuvant chemotherapy.
• Translational research:
i) To identify a gene signature predictive to recMAGE-A3+AS15 ASCI in MIBC.
ii) To evaluate on exploratory basis a possible correlation between gene expression profile of the primary tumor and clinical efficacy of recMAGE-A3 + AS15 ASCI compared to placebo in terms of:
1. Disease-free Survival (DFS)
2. Overall survival
iii) To evaluate expression of genes in a previously identified gene signature and evaluate their correlation with clinical efficacy of recMAGE-A3 + AS15 ASCI compared to placebo in terms of:
1. Disease-free Survival (DFS).
2. Overall survival.
3. Disease-free specific survival (DFSS)
4. Distant metastasis-free survival (DMFS).
iv) To characterize the tumor microenvironment and lymphocyte infiltration in the primary tumor and its recurrence lesions

Protocol Amendment 4: The analysis of MAGRIT study results confirmed the absence of treatment effect in any of the primary, secondary, or exploratory analyses. Consequently, GSK Biologicals has decided to stop further development of recMAGE-A3 + AS15 as a standalone treatment for cancer patients. 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. Treatment will not be possible anymore after 30 November 2016.

Study design

This is a multicentre, prospective, randomized, placebo-controlled, parallel group, double-blind, trial to compare the efficacy and safety of recMAGEA3 + AS15 ASCI intramuscular injections with Placebo intramuscular injections.
The target will be to enrol 273 patients to be randomly assigned to 2 treatment schedules in a 2:1 ratio, 2 patients randomized for recMAGE-A3 + AS15 ASCI versus 1 patient randomized for placebo.
The treatment scheme consists of 5 doses administered at 3-week intervals followed by 8 doses administered at 3-month intervals for a total maximum duration of study treatment administration of 27 months. Data collection will be organised by Remote Date Entry on Electronic Case Report Forms (eCRF).
A total of 8-10 European countries will participate with an anticipated average of 6-8 centres each. Sites should be able to contribute at least 10-15 screened patients per year. Enrolment in this study is competitive.

Protocol Amendment 4: The analysis of MAGRIT study results confirmed the absence of treatment effect in any of the primary, secondary, or exploratory analyses. Consequently, GSK Biologicals has decided to stop further development of recMAGE-A3 + AS15 as a standalone treatment for cancer patients. 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. Treatment will not be possible anymore after 30 November 2016.

Intervention

Please refer to the section of study design.

Study burden and risks

Protocol: Given the situation of the patient who needs a cystectomy, the extra burdenand risks associated with participation in the study is considered minimal and acceptable. During the first 3 months in the study, the number of patient visits is higher. This is due to the need for administration of treatment every 3 weeks. Hereafter, the number of visits and treatments is equal to what patients with these criteria is offered when they are treated in the standard way, which is watchful waiting after cystectomy. Possible extra procedures in this study depend on local routine practices.
For example 3-monthly CT scans /MRI*s can be extra if 6-monthly imaging procedures are considered standard routine practice (during treatment phase only). Also laboratory assessments and the questionnaire on smoking habits can be considered as
extra.
Explanation: As described above 3-monthly scans can be extra if 6-monthly imaging procedure are considered standard routine which means that there will be 5 extra scans (compared to the guideline given by EAU). It also has to be taken into account that the standard of care concerning the frequency of scans varies from country to country as for example in Germany 3 monthly scans is standard of care. The treatment injections, laboratory assessments and the questionnaire on smoking habits can be considered as extra. We refer to the flowchart in the reply to question C1.4 of the CCMO, with indication of the 6 monthly scans as only standard routine practice, all other assessments are trial specific.
The risks related to the expected treatment outcome, quality and quantity of side effects of the study medication can be considered as
acceptable (see Section 2.5.3). Benefit for the patient is that the patient is followed according to the latest standards and guidelines of treatment of MIBC and the patient has a chance on early detection of recurrence of disease.

Contacts

Public
European Association of Urology

Mr. E.N. van Kleffensstraat 5
AA Arnhem 6803
NL
Scientific
European Association of Urology

Mr. E.N. van Kleffensstraat 5
AA Arnhem 6803
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Aged greater than or equal to 18 years at the time ICF is signed, either sex.;2. Histologically confirmed (after cystectomy or if needed transurethral resection) urothelial carcinoma of the bladder which is MAGE-A3 positive.;3. Written informed consent for tissue and (optional) urine sampling, MAGE-A3 expression analysis and gene profiling and optional translational research has been obtained from the patient prior to cystectomy, and written informed consent for the complete study has been obtained prior to the performance of any other protocol-specific procedure.;4. TNM classification at pathological examination of surgically removed specimen: Stage T2,3 N0 or N1 or N2 and M0 disease or Stage T4 N0 M0 disease. ;5. The patient is free of residual disease and free of metastasis, as confirmed by a negative baseline Computer Tomogram (CT scan) or Magnetic Resonance Imaging (MRI) of the pelvis, abdomen and chest no more than 13 weeks prior to randomization. Other examinations should be performed as clinically indicated.;6. Patient is fully recovered from surgery within 13 weeks following cystectomy. For patients who receive adjuvant chemotherapy, the patient is fully recovered within 3-6 weeks following chemotherapy.;7. The patient must have adequate bone-marrow reserve, defined as an absolute neutrophil count >= 1.0 x 109/L, and a platelet count >= 75 x 109/L, adequate renal function, defined as a serum creatinine <= 1.5 times the Upper Limit of Normal (ULN), and adequate hepatic function, defined as a Total bilirubin <= 1.5 times the ULN, and a Alanine transaminase (ALAT) and Aspartate Transaminase (ASAT) <= 2.5 times the ULN as assessed by standard laboratory criteria.;8. World Health Organization (WHO) performance status 0 - 1 at the time of randomization.;9. If the patient is female, she must be of non-childbearing potential, i.e. have a current tubal ligation, hysterectomy, ovariectomy or be post menopausal, or if she is of childbearing potential, she must practice adequate contraception for 30 days prior to administration of study treatment, have a negative pregnancy test and continue such precautions during all study treatment period and for 2 months after completion of the injection series.

Exclusion criteria

1. The patient has previous or concomitant malignancies at other sites except effectively treated non-melanoma skin cancer, cervical carcinoma in situ, incidental localised prostatic carcinoma or effectively treated malignancy that has been in remission for over 5 years.;2. The patient has received any anti cancer systemic treatment, including immunotherapy(local intravesical BCG is allowed), chemotherapy, except:;* For the treatment of previous malignancies as allowed by the protocol (i.e., nonmelanoma skin cancer, cervical carcinoma in situ, incidental localised prostatic carcinoma or effectively treated malignancy that has been in remission for over 5 years).
* For the treatment with neo-adjuvant chemotherapy for their muscle invasive bladder cancer
* For the treatment with adjuvant cisplatinum-based chemotherapy for their muscle invasive bladder cancer;3. The patient has received radiotherapy of the abdominal or pelvic region, within 6 months prior to randomization.;4. Women who are pregnant or breast feeding.;5. The patient has a known infection with human immunodeficiency virus (HIV) or chronic hepatitis B or C.;6. The patient has a history of allergic disease or reactions likely to be exacerbated by any component of the study investigational product.;7. The patient has any confirmed or suspected immunosuppressive or immunodeficient condition or potential immune-mediated diseases. Patients with vitiligo are not excluded to participate in the trial.;8. Patient has received a major organ allograft.;9. The patient requires concomitant treatment with systemic corticosteroids, or any other immunosuppressive agents. Note: the use of prednisone, or equivalent, < 0,125 mg/kg/day (absolute maximum 10 mg/day), or inhaled corticosteroids or topical steroids is permitted.;10. The patient has received any investigational or non-registered medicinal product other than the study medication within the 30 days preceding the first dose of study medication, or plans to receive such a drug during the study.;11. The patient has psychiatric or addictive disorders that may compromise his/her ability to give informed consent or to comply with the trial procedures.;12. The patient has other concurrent severe medical problems, unrelated to the malignancy, that would significantly limit full compliance with the study or expose the patient to unacceptable risk. For example, but not limited to: uncontrolled congestive heart failure or uncontrolled hypertension, unstable heart disease (coronary heart disease or myocardial infarction) or uncontrolled arrhythmia.;13. The patient uses alternative treatments eg. plantextracts.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-06-2012
Enrollment:	25
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	28-07-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-11-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-01-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	26-01-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-07-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-03-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-02-2014
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-11-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-024355-85-NL
CCMO	NL35466.000.11