SYNOPSIS

NAME OF SPONSOR European Association of Urology Research Foundation (EAU RF) **NAME OF FINISHED PRODUCT** recMAGE-A3 + AS15 ASCI **NAME OF ACTIVE INGREDIENT(S)** N/A	**EudraCT nr.** 2010-024355-85 EAU RF protocol 2010-01	**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of Study	A randomized, double blind, placebo controlled phase II trial to evaluate the safety and efficacy of recMAGE-A3 + AS15 CI in patieNts with MAGE-A3 pOsitive muscLe Invasive blAdder cancer after cystectomy A European Association of Urology Research Foundation Randomized Phase II Clinical Trial		
Investigator(s)	Prof. Peter Mulders (Principal investigator) — Radboud UMC, Nijmegen, The Netherlands Prof. Axel Heidenreich — Universitätsklinikum der RWTH, Aachen, Germany; Universitätsklinikum Köln, Köln, Germany Prof. Marc Colombel — Hôpital Edouard Herriot, Lyon, France Prof. Luis Martínez-Piñeiro — Hospital Infanta Sofia, Madrid, Spain Prof. Renzo Colombo — University Vita Salute San Raffaele Hospital, Milan, Italy Prof. Fred Witjes — Radboud UMC, Nijmegen, The Netherlands Prof. Piotr Radziszewski — Medical University Warsaw, Poland Prof. Marko Babjuk — Hospital Motol, Praha, Czech Republic Prof. Pavel Yakovlev — Kiev Municipal Oncology Hospital, Kiev, Ukraine Ass. Prof. Christian Surcel — Fundeni Clinical Institute, Bucharest, Romania Prof. Igor Korneyev — Pavlov First Saint Petersburg State Medical University, St. Petersburg, Russia		
Study centre(s)	50 sites from 10 European Countries		
Publication	N/A		
Study period	From: 24-11-2011 To: 09-12-2016	Phase of development	Phase II
Objectives	<u>Primary Objective</u> To evaluate the clinical efficacy in terms of Disease Free Survival of recMAGE-A3 + AS 15 ASCI versus placebo in the overall population. <u>Secondary Objectives</u> • 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 survival (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. • 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: • Disease-free Survival (DFS) • 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: • Disease-free Survival (DFS). • Overall survival. • Disease-free specific survival (DFSS) • Distant metastasis-free survival (DMFS). iv) To characterize the tumor microenvironment and lymphocyte infiltration in the primary tumor and its recurrence lesions
Methodology	Prospective, multi-centre, randomized, placebo-controlled, double-blind, two-arm study in parallel groups
Number of patients	The target was 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, either directly after recovery from surgery, or after recovery from adjuvant chemotherapy. Enrolment in this study was competitive. A total of 84 patients were randomized, 77 patients received at least one study treatment administration (48 patients recMAGE-A3+AS15 treated and 29 placebo-treated).
Diagnosis and main criteria for inclusion	Histologically confirmed (after cystectomy or if needed transurethral resection) urothelial carcinoma of the bladder which is MAGE-A3 positive. 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
Test product, dose and mode of administration Duration of treatment	The double-blind treatment scheme consisted of 5 doses recMAGE-A3 + AS15 ASCI or placebo administered by intramuscular injection 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.
Criteria for evaluation	The efficacy analysis was performed including all patients who were randomized and who received at least one Study Treatment Administration. Primary efficacy variable: • Disease Free Survival Secondary efficacy variables: • Overall survival • Disease-free survival (DFS) • Disease-free specific survival (DFSS) • Distant metastasis-free survival (DMFS) Safety: • White blood cell count, Neutrophils, Platelets, Lymphocytes, Hemoglobin • Creatinine • Serum bilirubin, Aspartate transaminase (ASAT), Alanine transaminase (ALAT), Alkaline phosphatase • (Serious) Adverse events
Statistical methods	This was a clinical study to evaluate the clinical efficacy in terms of Disease Free Survival of recMAGE-A3 + AS 15 ASCI versus placebo in the overall population. Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements as well as safety observations and

	measurements. If it was deemed to be useful, summaries were done in addition for each stratum (T category, Neo-adjuvant Chemotherapy vs. Adjuvant Chemo¬therapy vs. no chemotherapy, the number of peri-operative chemotherapy cycles received, N category, gender and centre) separately. Number of valid observations and summary statistics (mean, standard deviation, median, maximum, minimum) were presented for continuous variables. Absolute and relative frequencies were tabulated for categorical data. In addition to the p-value for the testing procedure the corresponding confidence intervals have been computed. The comparison was done on the two-sided 5%-level.
Protocol amendment 4.0	Upon release and analysis of the MAGRIT trial results in 2014 showing the lack of a treatment effect in the primary, secondary and exploratory analyses and failure to identify a root cause for the lack of efficacy, GSK Biologicals decided to stop further development of recMAGE-A3 + AS15 as a standalone treatment for cancer patients (date of decision; 17 June 2014). This decision was not motivated by any safety concern as confirmed by all Independent Data Monitoring Committees (IDMCs) overlooking the ASCI trials. This decision implied that MAGE-A3 +AS15 CI would not be available for future treatment of bladder cancer patients which warranted a substantial amendment (4.0) of the MAGNOLIA study. As of the Protocol Amendment 4.0, the recruitment was stopped and the study population was unblinded. For patients randomized to the placebo group, no further protocol visits were performed except for the concluding visit and no further doses were administered. As it could not be excluded that one or more patients may benefit from this treatment on an individual basis, patients receiving active treatment were offered the option to continue the administration of the study treatment until the last dose was administered or until recurrence, or until the patient or the investigator decided to stop the study treatment. Therefore, the study continued with patients from the active treatment group who decided to stay in the study. During the treatment period, safety monitoring was continued as initially foreseen during the treatment period. The original primary and secondary objectives were not assessed as planned. All clinical data collected in the study were analysed descriptively. By default, for each biological sample already collected in the scope of this study and not tested yet, testing will only be done if a scientific rationale remains relevant despite the premature termination of the study. In that case, testing will be in compliance with the protocol and ICF signed by the patient. The immune response was not evaluated anymore as the immune response to IMP administration was confirmed in other ASCI trials, but did not show any correlation with the potential efficacy.

SUMMARY CONCLUSIONS

EFFICACY RESULTS

In the treated population (n = 77), the Disease Free Survival (DFS), Overall Survival, Disease Free Specific Survival (DFSS) and the Distant Metastases Free Survival (DMFS) were estimated using the Kaplan-Meier method with the following results (DFSS was equal to the DFS because all patients who died during the study had a prior documentation of progression):

	Randomized treatment	
	recMAGE-A3+AS15	**Placebo**
DFS/DFSS	27.5 months (95% CI, 22.7 – 32.3)	19.8 months (95% CI, 15.7–23.9)
Overall survival	35.5 months (95% CI, 32.1 – 38.8)	24.1 months (95% CI, 21.0–27.2)
DMFS	31.5 months (95% CI, 27.2 – 35.9)	21.4 months (95% CI, 17.5–25.2)

The results suggest an improving effect of recMAGE-A3+AS15 treatment on DFS/DFSS, overall survival and DMFS. However, as a) the study's recruitment was prematurely stopped and the number of participating patients was limited, b) patients in the placebo group stopped directly at the implementation of Protocol Amendment 4.0 (with subsequent shorter survival times) and c) data were only analysed descriptively, no final conclusions on efficacy can be drawn.

SAFETY RESULTS

The relative number of AEs per patient was higher in the recMAGE-A3+AS15 group compared to the Placebo group. In addition, a causal relationship to the study medication was suspected in more events in the recMAGE-A3+AS15 group than in the Placebo group. The majority of AEs with causal relationship were flu-like symptoms or local effects due to the injection with grade 1 or 2 severity.

There was no substantial difference between the recMAGE-A3+AS15 group and the Placebo group with respect to incidence and severity of the reported SAEs. There were 6 patients in the recMAGE-A3+AS15 group and 5 patients in the Placebo group who died during the study period because of disease recurrence or progression. Only in one patient progression and subsequent death were reported as a SAE because of the massiveness of the progression.

No SUSAR's have been reported in this trial.

CONCLUSION

This trial's recruitment was prematurely stopped and all clinical data collected in this study were analysed descriptively. For the evaluation of the efficacy and safety data it has to be taken into account that the number of participating patients was limited and the recMAGE-A3+AS15 patients were given the opportunity to continue treatment following Protocol Amendment 4.0, whereas placebo patients needed to stop treatment.

Therefore, no definitive conclusions on the safety and efficacy of recMAGE-A3+AS15 treatment in the studied patient population can be drawn.

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