MAGE-A3 immunotherapeutic as adjuvant therapy for patients with resected, MAGE-A3-positive, stage III melanoma (DERMA): a double-blind, randomised, placebo-controlled, phase 3 trial

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Summary

Background Despite newly approved treatments, metastatic melanoma remains a life-threatening condition. We aimed to evaluate the efficacy of the MAGE-A3 immunotherapeutic in patients with stage IIIB or IIIC melanoma in the adjuvant setting.

Methods DERMA was a phase 3, double-blind, randomised, placebo-controlled trial done in 31 countries and 263 centres. Eligible patients were 18 years or older and had histologically proven, completely resected, stage IIIB or IIIC, MAGE-A3-positive cutaneous melanoma with macroscopic lymph node involvement and an Eastern Cooperative Oncology Group performance score of 0 or 1. Randomisation and treatment allocation at the investigator sites were done centrally via the internet. We randomly assigned patients (2:1) to receive up to 13 intramuscular injections of recombinant MAGE-A3 with AS15 immunostimulant (MAGE-A3 immunotherapeutic; 300 µg MAGE-A3 antigen plus 420 µg CpG 7909 reconstituted in AS01B to a total volume of 0·5 mL), or placebo, over a 27-month period: five doses at 3-weekly intervals, followed by eight doses at 12-weekly intervals. The co-primary outcomes were disease-free survival in the overall population and in patients with a potentially predictive gene signature (GS-positive) identified previously and validated here via an adaptive signature design. The final analyses included all patients who had received at least one dose of study treatment; analyses for efficacy were in the as-randomised population and for safety were in the as-treated population. This trial is registered with ClinicalTrials.gov, number NCT00796445.

Findings Between Dec 1, 2008, and Sept 19, 2011, 3914 patients were screened, 1391 randomly assigned, and 1345 started treatment (n=895 for MAGE-A3 and n=450 for placebo). At final analysis (data cutoff May 23, 2013), median follow-up was 28·0 months [IQR 23·3–35·5] in the MAGE-A3 group and 28·1 months [23·7–36·9] in the placebo group. Median disease-free survival was 11·0 months (95% CI 10·0–11·9) in the MAGE-A3 group and 11·2 months (8·6–14·1) in the placebo group (hazard ratio [HR] 1·01, 0·88–1·17, p=0·86). In the GS-positive population, median disease-free survival was 9·9 months (95% CI 5·7–17·6) in the MAGE-A3 group and 11·6 months (5·6–22·3) in the placebo group (HR 1·11, 0·83–1·49, p=0·48). Within the first 31 days of treatment, adverse events of grade 3 or worse were reported by 126 (14%) of 894 patients in the MAGE-A3 group and 56 (12%) of 450 patients in the placebo group, treatment-related adverse events of grade 3 or worse by 36 (4%) patients given MAGE-A3 *vs* six (1%) patients given placebo, and at least one serious adverse event by 14% of patients in both groups (129 patients given MAGE-A3 and 64 patients given placebo). The most common adverse events of grade 3 or worse were neoplasms (33 [4%] patients in the MAGE-A3 group *vs* 17 [4%] patients in the placebo group), general disorders and administration site conditions (25 [3%] for MAGE-A3 *vs* four [<1%] for placebo) and infections and infestations (17 [2%] for MAGE-A3 *vs* seven [2%] for placebo). No deaths were related to treatment.

Interpretation An antigen-specific immunotherapeutic alone was not efficacious in this clinical setting. Based on these findings, development of the MAGE-A3 immunotherapeutic for use in melanoma has been stopped.

Funding GlaxoSmithKline Biologicals SA.

Introduction

Melanoma is the most aggressive form of skin cancer and 5-year overall survival in patients with stage IIIB or IIIC disease is 35–60%.[1] Treatment is complete surgical resection, but patients with stage IIIB disease (macroscopic involvement of lymph nodes) are at high risk of

Research in context

Evidence before this study

We searched PubMed for studies published between inception and Nov 26, 2017, using the terms "melanoma AND (vaccine OR immunotherapeutic) AND clinical trials, phase 3" without any limitations for date or language. We found eight relevant studies in patients with resected melanoma (stages I to IV) who had received different types of immunotherapies or vaccines. None of the studies reported that treatment improved clinical outcome in the adjuvant setting.

Added value of this study

Both MAGRIT and DERMA provide conclusive evidence of the acceptable clinical safety profile of the MAGE-A3 immunotherapeutic, but treatment did not provide clinical benefit in either patient population. The clinical development of the MAGE-A3 immunotherapeutic for these indications has therefore been stopped. DERMA confirms a high rate of early disease recurrence among patients with resected stage IIIB or IIIC melanoma, and provides a large body of data on disease progression and clinical outcomes in the adjuvant setting of melanoma. We showed the feasibility of using an adaptive signature design for the validation of biomarkers in a registration study, and validated a gene signature with prognostic value.

Implications of all the available evidence

In line with the existing scientific literature, we have shown that antigen-specific immunotherapeutics alone are not efficacious in this clinical setting. The absence of treatment effect might be due to an inability to raise appropriate antitumour immune responses or the need to overcome tumour immune suppressive mechanisms (as shown with checkpoint inhibitors), or both. The targeting of other shared tumour antigens, together with MAGE-A3 antigen, might support the amplification of immune responses in patients receiving the treatment. Ideal target antigens for vaccination should combine different properties, such as tumour-specific expression, and the presence of a vast and high avidity specific T-cell repertoire.

relapse, which increases with the number of affected lymph nodes and capsular extension. Adjuvant therapies for patients with stage IIIB or IIIC melanoma, such as interferon alpha and pegylated interferon, improve relapse-free survival but do not affect overall survival substantially, with conflicting clinical results depending on the dose, duration, and target population investigated.[2,3] Adjuvant ipilimumab improves relapse-free survival and overall survival in patients with operable stage III melanoma compared with placebo, but more than half of patients have grade III–IV toxicities, and some die as a result of these events.[4] Two studies have changed the field of adjuvant treatment for melanoma. First, nivolumab as adjuvant treatment in patients with resected stage IIIB, IIIC, and IV melanoma resulted in significantly improved recurrence-free survival, and decreased severe toxicity compared with ipilimumab.[5] Second, the combined treatment of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) significantly decreased the risk of recurrence and death in patients with stage III melanoma with *BRAF*^{V600E} or *BRAF*^{V600K} mutations when compared with placebo alone.[6] The safety profile of dabrafenib plus trametinib in the adjuvant setting for patients with localised advanced disease was consistent with the safety of this combination in patients with metastatic disease.

The MAGE-A3 cancer-testis tumour antigen is expressed in up to 76% of melanomas, but the gene is silent in all normal human tissues, except placenta and testis.[7,8] The MAGE-A3 immunotherapeutic (GlaxoSmithKline, Rixensart, Belgium; GSK) comprises a recombinant MAGE-A3 protein given with the proprietary immunostimulant AS15 (GSK), and was designed to enhance both humoral and cell-mediated immune responses against MAGE-A3-expressing cells.[9] In a phase 2 proof-of-concept study[10] in patients with early progressive metastatic melanoma, five (7%) of 72 patients treated with MAGE-A3 immunotherapeutic had an objective clinical response, and ten (14%) patients achieved stable disease. This phase 2 study evaluated recombinant MAGE-A3 protein combined with two different immunostimulants, AS02$_B$ or AS15. Both immunostimulants had a similar safety profile, and four of the five objective responses were seen in the 37 patients who received AS15. On the basis of these results and those of previous preclinical and clinical studies,[11–13] AS15 was selected for further testing. These results in patients with melanoma, along with those of a randomised phase 2 study of the MAGE-A3 immunotherapeutic in patients with non-small-cell lung cancer (NSCLC),[14] were considered sufficient to commence a worldwide, multicentre, phase 3 study. An immune-related gene signature associated with clinical benefit after immunisation with the MAGE-A3 immunotherapeutic was found in the phase 2 proof-of-concept in patients with melanoma, and was retrospectively validated in the phase 2 study in patients with NSCLC.[10,14,15] Therefore, the DERMA study aimed to evaluate the clinical efficacy and prospectively validate the candidate gene signature to predict response to therapy in patients with stage III melanoma and macroscopic lymph node involvement treated with the MAGE-A3 immunotherapeutic.[16,17]

Methods

Study design and participants

The DERMA study was a double-blind, randomised, placebo-controlled phase 3 study done in 31 countries and 263 centres (appendix pp 4–13).

Eligible patients were older than 18 years of age and had histologically proven, stage IIIB or IIIC cutaneous

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See Online for appendix

For a **summary of the protocol** see https://www.gsk-clinicalstudyregister.com/search/?study_ids=111482

melanoma with macroscopic lymph node involvement defined according to the TNM staging system (sixth edition) and AJCC classification (2010); a performance status of 0 or 1, and adequate renal and hepatic function and bone-marrow reserve at the time of randomisation; and were surgically rendered disease-free no more than 9 weeks before randomisation and had fully recovered from the procedure before treatment. For patients undergoing elective regional dissection of their lymph nodes followed by lymphadenectomy, the date of the radical lymphadenectomy was the day the patient was regarded as free from disease. Macroscopic lymph-node involvement was defined as clinically detectable lymph node metastases confirmed by pathological examination following therapeutic lymphadenectomy; patient's lymph node metastasis had to show expression of the MAGE-A3 gene as per quantitative MAGE-A3 gene expression determined by RT-PCR analysis on formalin-fixed paraffin-embedded tissue. Patients with cancer of unknown primary were also eligible (operable macroscopic or gross regional lymph node metastasis; TxN1b-N2b-N3 M0).

Systemic treatment with an immunomodulator (ie, interferon or anti-cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4], or both) after a previous surgery was allowed, provided that there was a wash-out period of 30 days before randomisation. Previous radiotherapy was allowed if the treatment had been completed before the lymphadenectomy that qualified the patient for study participation.

Patients were excluded if they had mucosal or ocular melanoma, a history of in-transit metastases (N2c or N3), a history of autoimmune disease (excluding vitiligo), infection with HIV, another confirmed or suspected immunosuppressive or immunodeficient condition, previous or concomitant malignancies (except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, or effectively treated malignancy that had been in remission for over 5 years and was highly likely to have been cured), or an uncontrolled bleeding disorder. Amendments to the protocol, exclusion criteria, efficacy and safety follow-up procedures, and patient withdrawal information are provided in the appendix (pp 14–16). A summary of the protocol can be found online.

All patients gave written informed consent for analysis of MAGE-A3 expression, gene expression profiling, and study participation. The study was done in accordance with the principles of good clinical practice, the principles of the Declaration of Helsinki, and all applicable regulatory requirements. The protocol was approved by national, regional, or investigational centre institutional review boards or ethics committees. An independent data monitoring committee (IDMC) monitored the study and reviewed study endpoints and safety data.

Randomisation and masking

We used a centralised randomisation system to randomly assign patients (2:1) to receive either the MAGE-A3 immunotherapeutic or placebo at the investigator site. Randomisation and assignment to treatment was handled centrally at GSK Belgium. The central randomisation system was accessed by staff at the investigator sites via the internet. We used a 2:1 ratio for allocation to make a potentially active treatment available to a larger proportion of trial participants. A minimisation algorithm (with a 10% random element) accounted for disease stage (IIIB or IIIC or IIIx [undefined stage III Tx]), nodal status (N1, N2, or N3), stage of the primary tumour (Tx-0, T1-2, T3, or T4), extracapsular extension of the lymph nodes (yes or no), study centre, and previous treatment with interferon or anti-CTLA-4 (yes or no), or both.

Individual treatment assignment was masked at all levels except to the IDMC and the independent statistician who did safety assessments and efficacy analyses every 6 months. Treatment allocation was masked until the primary analysis of disease-free survival in patients with a gene signature potentially predictive of treatment benefit (the GS-positive population) was available on Aug 18, 2015. This analysis was done 2 years after the primary analysis of disease-free survival in the overall population (cutoff date May 23, 2013) because of the development and analytical validation of the gene expression assay.

Procedures

Full details of the composition and treatment schedule of the MAGE-A3 immunotherapeutic and placebo are given in the appendix (p 17).

Patients received up to 13 intramuscular injections of recombinant MAGE-A3 with AS15 immunostimulant (MAGE-A3 immunotherapeutic; 300 µg MAGE-A3 antigen plus 420 µg CpG 7909 reconstituted in AS01B to a total volume of 0·5 mL), or placebo, over a 27-month period: five doses at 3-weekly intervals, followed by eight doses at 12-weekly intervals.

Although no dose reductions were permitted, doses could be interrupted or delayed if the patient was acutely ill at the scheduled time of administration, if influenza vaccine or blood products needed to be given (with at least 7 days between vaccination or blood products and treatment), or for any other medical reason that would expose the patient to an unacceptable risk, as judged by the investigators. If the administration of study treatment was postponed for any reason, a visit to give the missed treatment was planned as soon as possible to catch up to the original schedule. The next study visit was planned at a time that allowed a minimum of 14 days between two administrations of treatment and to keep up with the schedule based on the date that the study treatment was first given.

Patients were required to permanently discontinue treatment if they met any of the following criteria: evidence of disease recurrence; receipt of other anticancer treatments or investigational products; any allergic reaction of grade 3 or worse after study treatment was given; any intolerable adverse event or persistent moderate

adverse event that could be worsened by further administration of study treatment; signs or symptoms of an immune disorder (except vitiligo); any immune deficient or suppressive condition; inability of the patient to complete the study evaluations; development of other conditions for which, according to the investigator, it was in the patient's best interest to withdraw; patient request to withdraw; and, for female patients, pregnancy or the decision to try to become pregnant.

Procedures for the assessment of efficacy are shown in the appendix (p 16). Efficacy assessments during treatment were done every 3 months, alternating between chest and upper abdomen CT scans or chest x-rays. At every visit, the investigator did a physical examination and clinical assessment. Brain CT or MRI were done if clinically indicated. We planned to continue active follow-up to assess survival and disease recurrence for at least 5 years from the first study treatment.

Because of various differences in assays, sample type, and clinical setting between the phase 2 and phase 3 studies, optimisation and clinical validation of the gene signature were done with a split-sample approach, based on an adaptive signature design.[16,17] The first set of patients (training set; a third of study patients) was used to define a predictive gene signature that could identify patients who were most likely to benefit from treatment. Different classification models for the gene signature were used in the training set, starting with 55 target genes measured by quantitative real-time RT-PCR. The remaining two-thirds of patients were the test set and were used for clinical validation of the selected gene signature (39 genes) after the final analysis of the primary outcome in the overall population and validation of the gene signature assay. Details of the real-time RT-PCR assay and methods for gene classifiers development and clinical validation of a multigene predictive signature are given in the appendix (pp 39–44). The schedule for laboratory evaluations of safety and the reporting period for adverse events is shown in the appendix (p 18).

Adverse events were recorded for 31 days (days 0–30) after each dose. Serious adverse events were recorded from the start of the study until the end of the treatment phase. Serious adverse events related to the investigational drug or any concurrent GSK drug were recorded from consent until the end of the study. New onset of autoimmune disease and pregnancies were recorded for 5 years from the first treatment. The severity of adverse events was graded by the investigators according to Common Terminology Criteria for Adverse Events (version 3.0).[18] Individual adverse events were coded to the preferred term level with the Medical Dictionary for Regulatory Activities (MedDRA). The investigator assessed potential causal associations between the intervention and each adverse event.

Safety laboratory assays assessing haematological parameters and renal and hepatic functions were done during screening, at week 12, and at months 12, 24, and 30. We used an enzyme-linked immunosorbent assay (GSK laboratories, Rixensart, Belgium)[19] to measure anti-MAGE-A3-specific IgG antibodies at baseline, after two, four, six, seven, nine, and 13 administrations of treatment, and at 1 year post-treatment. Seropositivity was defined as an antibody titre of at least 27 ELISA units per mL.

We used the European Quality of Life-5 dimensions (EQ-5D) questionnaire utility score and visual analogue score to assess health-related quality of life (QOL).[20] Patients self-completed the questionnaire before injection at treatment doses one, three, five, six, seven, eight, and 12, at the first follow-up visit, and after the patient had been informed of a recurrence before starting a new anticancer treatment. QOL was reassessed by staff via telephone on the day after injection on visits one, three, and five.

Outcomes

The co-primary outcomes were efficacy of the MAGE-A3 immunotherapeutic compared with placebo in terms of disease-free survival (defined as the interval from randomisation to either the date of first disease recurrence or death from any cause) in the overall population and in the GS-positive population.

Secondary outcomes were disease-free survival in the population of patients who do not present the predictive gene signature (GS-negative), and in the overall population and in GS-negative or GS-positive patients: overall survival (interval from randomisation to the date of death from any cause), disease-free specific survival (interval from randomisation to the date of first recurrence or death due to melanoma) at 1, 2, 3, and 4 years, distant metastasis-free survival (the interval from randomisation to the date of first distant metastasis or date of death from any cause), immunogenicity (MAGE-A3 seropositivity), validate the predictive value of the gene signature by the association between disease-free survival and gene signature status, occurrence of adverse events and autoimmunity, and evaluation of QOL.

Statistical analysis

We used Bonferroni correction to control the two-sided type I error (<5%), with a two-sided 4% α assigned to disease-free survival in the overall population and a two-sided 1% α assigned to this primary outcome in the GS-positive population. To detect a relevant increase in median disease-free survival in the overall population with a two-sided nominal α of 4% and a power of 80%, we needed to randomly assign 1300 patients to have 850 events for final analysis. This number of events was calculated on the basis of simulations that took into account a potential delayed treatment effect, assuming a hazard ratio (HR) of 0·90 during the first 2 months after randomisation and an HR of 0·77 after that. The co-primary outcome in the GS-positive population was assessed on the test set of two-thirds of patients with a

sample available. Based on the assumption that 50% of patients were GS-positive, we expected at least 184 events in patients allocated to the test set in the final analysis, which would provide 80% power to detect a statistically significant treatment difference in disease-free survival at the two-sided 1% significance level, assuming an HR of 0·59.

The primary outcome analysis for the total cohort of participants treated included all patients who received at least one dose of treatment. We estimated HRs using Cox proportional hazards regression, with minimisation factors (except study centre) and ulceration status as covariates in the model.[21] Efficacy analyses in test-set patients presenting with the potentially predictive gene signature were also adjusted for the prognostic gene signature score (a gene signature associated with a worse clinical prognosis in the placebo group, appendix p 14), prospectively defined in the training set as the T-helper-type 1 and interferon γ gene expression signature (eight genes). Additional details are given in the appendix (p 14).

The final co-primary endpoint analysis in the overall population was done on May 23, 2013, when 850 disease-free survival events were reached, as specified by the protocol. The IDMC reviewed the analyses and granted permission to continue the study as planned to collect up to 5 years of efficacy and safety data after first study treatment for the analyses of the co-primary endpoint in the GS-positive population. The follow-up analysis (cutoff date Aug 18, 2015) was planned to be used for the analysis of disease-free survival in the GS-positive population; however, based on a request from the US Food and Drug Administration, the plan was modified to analyse the second co-primary endpoint on the same database as the first co-primary endpoint (cutoff date May 23, 2013).

After review of the follow-up analysis data (Aug 18, 2015), the IDMC concluded that the trial did not meet either of the prespecified co-primary endpoints and the study was permanently closed. The list of adverse events reported here and the final immunogenicity report used the follow-up data (cutoff Aug 18, 2015). Safety analyses were done on all patients who received at least one treatment dose, according to the actual treatment received and not the randomisation group. We analysed immunogenicity in all eligible patients who received at least first four consecutive treatment doses, complied with the protocol, and for whom immunogenicity data were available.

For the primary analysis of efficacy, we used the likelihood ratio test to compare the two groups. We used the Kaplan-Meier method to calculate non-parametric estimates of median time-to-event endpoints, with 95% CIs calculated using the Brookmeyer and Crowley method. All CIs were 95% two-sided nominal, and all reported p values were two-sided. The covariates for efficacy analyses were based on values recorded in the patient case report form, except when missing, in which event we used the value reported at randomisation. We also did prespecified exploratory analyses to identify predictive factors using a likelihood ratio test for interaction between the baseline covariate and treatment after including both as main effects in a Cox model. Only patients with all baseline values available were included in the predictive analysis, and a few patients with an ineligible stage were pooled with the closest category.

Sensitivity analyses in the overall population and the GS-positive population included the analysis of disease-free survival using a log-rank test without stratification and with stratification by the minimisation factors (except centre) and ulceration status. For these analyses, we used an unadjusted Cox model to estimate HR and 95% CI. Disease-free survival was also assessed via a Cox model adjusted for all baseline covariates. We repeated the log-rank tests and Cox models using variations of the disease-free survival endpoint definition, including using the date of a previous assessment as the date of event for patients with a recurrence, considering the start of a new therapy for a melanoma recurrence before a documented recurrence as an event, and using the recurrence date as assessed via electronic case report form data by a physician employed by GSK before study unblinding.

EQ-5D health dimensions, utility values, and visual analogue scores and their changes from baseline were reported descriptively. We compared differences between the two treatment groups per timepoint using the non-parametric Wilcoxon test. We did not correct for multiple testing. We did an exploratory analysis to assess changes in mean scores over time and overall, with a repeated measures analysis using a mixed effects model. Full details of how we translated responses into scores and calculated mean (SD) are given in the appendix (p 28).

We used SAS (version 9.2) for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT00796445.

The results summary for this study (GSK study number 111482) is available on the GSK Clinical Study Register. For interventional studies that evaluate GSK medicines, anonymised patient-level data will be made available to independent researchers, subject to review by an independent panel at within 6 months of publication. To protect the privacy of patients and individuals involved in our studies, GSK does not publicly disclose patient-level data.

For the **GSK Clinical Study Register** see www.gsk-clinicalstudyregister.com/

To request **anonymised patient-level data** see www.clinicalstudydatarequest.com/

Role of the funding source

The study was designed, and results were interpreted, by GlaxoSmithKline Biologicals SA in cooperation with an international steering committee. Data collection, statistical analysis, and writing were done by GSK Biologicals SA. BD, CD, and MD had access to all the raw data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

Patients were enrolled between Dec 1, 2008, and Sept 19, 2011. 3914 patients were screened; 3182 (81%) of 3914 patients had a tumour sample available for screening, of which 2092 (66%) had MAGE-A3-positive tumours. Of 1391 patients who were randomly assigned, 1345 (97%) received at least one dose of study treatment and formed the total treated population (as randomised) for the final efficacy analysis (893 patients the MAGE-A3 group and 452 the placebo group). The

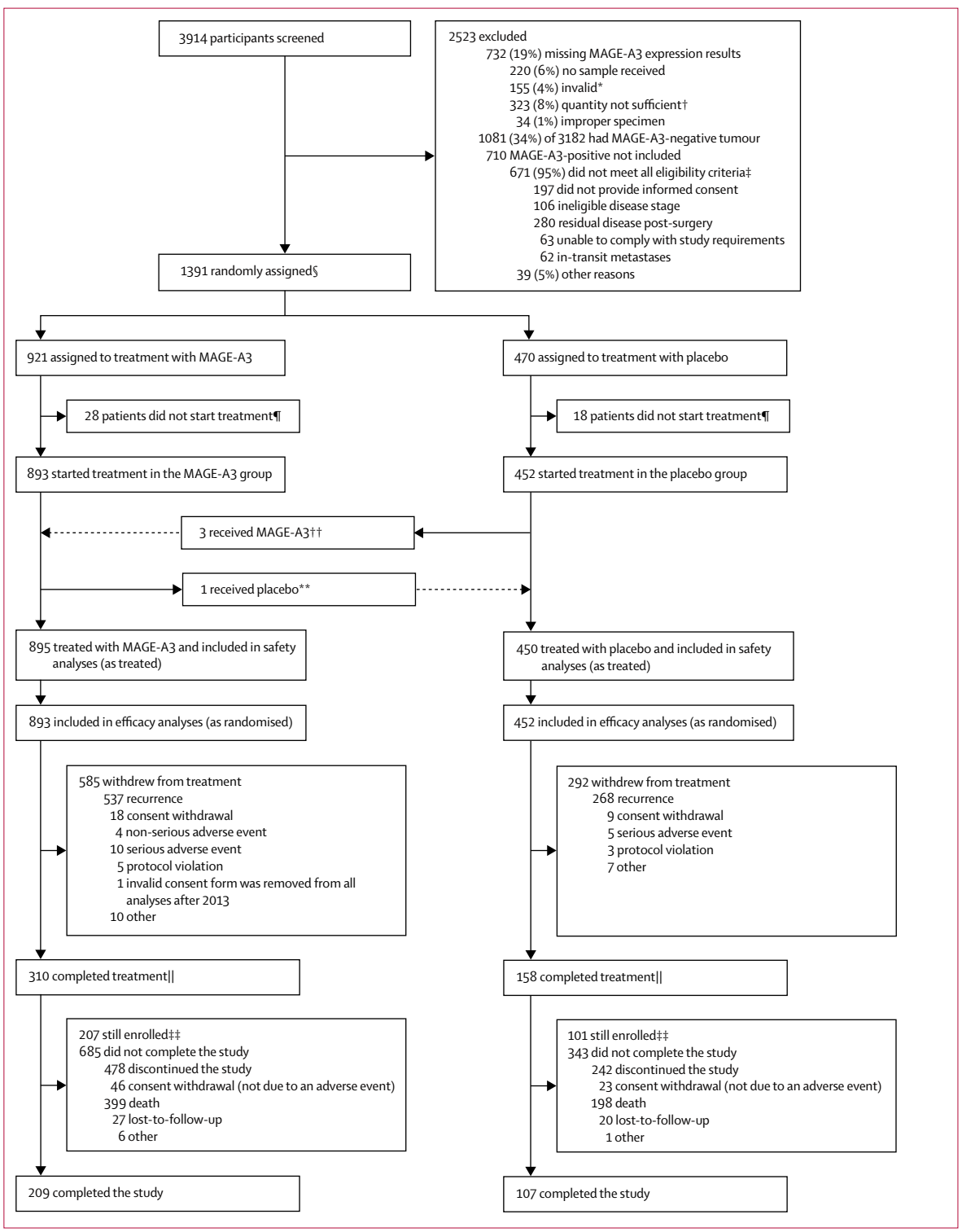

Figure 1: **Trial profile**
The final analysis was done on the population as randomised. One patient who was randomised to the treatment group received placebo and three patients who were randomised to placebo received MAGE-A3 immunotherapeutic; this mistake led to differences in the denominator in populations evaluated for efficacy (as randomised) and safety (as treated). *Contamination with genomic DNA or result out of range. †Not enough tumour tissue or insufficient RNA. ‡Patients could be ineligible for more than one reason. §Nine patients (MAGE-A3-negative, unknown, or inconclusive results) were randomly assigned by error but did not start treatment. ¶The main reason for not starting treatment was ineligibility. ||13 doses given and attended concluding visit. **Included in as-treated analysis for placebo group. ††Included in as-treated analysis for MAGE-A3 group. ‡‡At final analysis (Aug 18, 2015).

	MAGE-A3 group (n=893)	Placebo group (n=452)
Age at screening, years		
Range	18–87	20–88
Median (IQR)	57 (44–66)	57 (44–66)
Sex		
Female	344 (39%)	189 (42%)
Male	549 (61%)	263 (58%)
Primary tumour ulceration		
Yes	322 (36%)	157 (35%)
No	397 (44%)	210 (46%)
Unknown or missing	174 (19%)	85 (19%)
Tumour stage		
T1	122 (14%)	65 (14%)
T2	197 (22%)	100 (22%)
T3	202 (23%)	110 (24%)
T4	210 (24%)	101 (22%)
TX	162 (18%)	76 (17%)
Nodal stage		
N1a	1 (<1%)	0
N1b	356 (40%)	181 (40%)
N2a	1 (<1%)	2 (<1%)
N2b	272 (30%)	137 (30%)
N3	263 (29%)	132 (29%)
Performance status		
0	740 (83%)	378 (84%)
1	153 (17%)	73 (16%)
3	0	1 (<1%)
Stage		
Stage IIIA	1 (<1%)	0
Stage IIIB	292 (33%)	155 (34%)
Stage IIIC	483 (54%)	241 (53%)
Undefined stage III (TX)	109 (12%)	53 (12%)
Stage IV	8 (1%)	3 (1%)
(Table 1 continues in next column)		
(Continued from previous column)		
Previous therapy		
Interferon	130 (15%)	67 (15%)
Anti-CTLA-4	3 (<1%)	2 (<1%)
Interferon, anti-CTLA-4, or both	133 (15%)	69 (15%)
Radiotherapy	8 (1%)	5 (1%)
Number of lymph nodes invaded		
1	360 (40%)	187 (41%)
2	198 (22%)	89 (20%)
3	81 (9%)	51 (11%)
>3	223 (25%)	110 (24%)
Matted	31 (3%)	15 (3%)
Extracapsular extension		
No	591 (66%)	304 (67%)
Yes	300 (34%)	148 (33%)
Missing	2 (<1%)	0
Region		
Europe	658 (74%)	327 (72%)
Other countries	98 (11%)	50 (11%)
North America	137 (15%)	75 (17%)

Data are n (%) unless otherwise stated. The final analysis was done on the total treated population as randomised (May 23, 2013 analysis). CTLA-4=cytotoxic T-lymphocyte-associated antigen 4.

Table 1: **Baseline characteristics**

safety population included all patients who received at least one dose of the actual study treatment, MAGE-A3 or placebo, independently of the initial assignment group (as treated; 894 patients in the MAGE-A3 group and 450 in the placebo group; figure 1). 786 (88%) of 895 patients in the MAGE-A3 group and 403 (90%) of 450 in the placebo group received at least four doses of study treatment. After the final efficacy analysis and building of the gene signature classifier (May 23, 2013), one patient in the MAGE-A3 group was found to have an invalid consent form and was not included in the follow-up safety and efficacy analysis (Aug 18, 2015; 894 patients in the MAGE-A3 group and 450 patients in the placebo group).

The study groups were similar in terms of baseline characteristics (table 1). Median time from lymphadenectomy to randomisation was 7·1 weeks (IQR 5·9–7·9) in both groups.

For the final disease-free survival analysis (cutoff May 23, 2013), there were 856 events of recurrence or death, including 572 events (64%) in 893 patients in the MAGE-A3 group and 284 (63%) of 452 in the placebo group, and the median follow-up was 28·0 months (IQR 23·3–35·5) for the MAGE-A3 group and 28·1 months (IQR 23·7–36·9) for the placebo group. Median disease-free survival was 11·0 months (95% CI 10·0–11·9) in the MAGE-A3 group and 11·2 months (8·6–14·1) in the placebo group (HR 1·01, 95% CI 0·88–1·17, p=0·86).

For the co-primary analysis (data from May, 2013, analysis done in August, 2015) of disease-free survival in patients with a positive predictive gene classifier status, 366 (27%) of 1345 patients were allocated to the training set and 729 (54%) to the test set to validate the gene signature found in the phase 2 studies. However, this gene signature had a strong prognostic effect with no predictive effect in the training set and was used to adjust the final statistical analysis. When we adjusted for the prognostic effect of this signature in the training set, a novel gene signature of 39 genes (appendix p 51) was identified and the MAGE-A3 immunotherapeutic had a clinical benefit over placebo for disease-free survival for patients in the training set who were GS-positive for this novel gene signature (appendix p 46). As per protocol, the study team remained unaware of the result in the overall population until after gene signatures were evaluated (August, 2015). When the 39-gene predictive gene signature was applied to the remaining two-thirds of the samples (test set; n=316 [200 in the MAGE-A3 group, 116

in the placebo group]) in August, 2015, the median disease-free survival in the GS-positive population was 9·9 months (95% CI 5·7–17·6) in the MAGE-A3 group and 11·6 months (5·6–22·3) in the placebo group (HR 1·11, 95% CI 0·83–1·49, p=0·48).

Prevalence of disease-free survival in the MAGE-A3 group was 47% (95% CI 43–50) at year 1, 37% (34–40) at year 2, 33% (30–37) at year 3, and 31% (27–35) at year 4. In the placebo group, disease-free survival was 47% (42–51) at year 1, 39% (34–43) at year 2, 35% (30–40) at year 3, and 33% (27–38) at year 4.

The results of the follow-up analysis (Aug 18, 2015), with a median follow-up of 54·3 months (IQR 47·8–58·6) in the MAGE-A3 group and 54·3 months (47·0–58·1) in the placebo group, were consistent with the final analysis: median disease-free survival was 11·0 months (95% CI 10·0–11·9) in the MAGE-A3 group and 11·2 months (8·6–13·3) in the placebo group (HR 1·02, 95% CI 0·89–1·18, p=0·75; figure 2).

All sensitivity analyses of the primary outcomes were consistent with the main conclusion of no treatment effect (data not shown). Upon completion of the follow-up analyses (August, 2015), the complete trial results were reviewed by the IDMC, and based on their feedback and the absence of treatment effect for both co-primary endpoints, the study was terminated early on Sept 8, 2015, to ensure that participants would not be unnecessarily exposed to study-related procedures.

At the final analysis (cutoff May 23, 2013), 467 patients died, including 314 (35%) of 893 in the MAGE-A3 group and 153 (34%) of 452 in the placebo group. Median overall survival was 46·6 months (95% CI 39·6–not reached) in the placebo group and was not reached in the MAGE-A3 group (41·7–not reached; overall survival curves were compared by adjusted Cox regression model HR 1·07, 0·88–1·29, p=0·52; appendix p 17). At the final analysis (August, 2015), there was no change in outcomes (figure 3). Overall survival did not differ either in the GS-positive population analysis (appendix p 17). Overall survival results for the follow-up analysis are shown in figure 3.

There were 850 disease-free-specific survival events (566 [63%] of 893 in MAGE-A3 and 284 [63%] of 452 in placebo) and 743 events of distant metastasis-free survival (502 [56%] of 893 in MAGE-A3 and 241 [53%] of 452 in placebo) at the time of the final analysis (May, 2013). The median disease-free-specific survival was 11·1 months (95% CI 10·4–12·3) in the MAGE-A3 group and 11·2 (8·6–14·1) in the placebo group (HR 1·00, 0·87–1·16; p=0·98). The median distant metastasis-free survival was 18·7 months (16·3–22·1) in the MAGE-A3 group and 23·9 months (18·9–30·7) in the placebo group (HR 1·09, 0·94–1·27; p=0·27).

The GS-positive and GS-negative populations did not differ between the MAGE-A3 and placebo groups in terms of disease-free survival, overall survival, disease-free-specific survival, or distant metastasis-free survival in any of the analyses or in the assessment of disease-free survival for each year of follow-up (final analysis appendix p 18 and follow up analysis appendix pp 18–19). Exploratory subgroup analyses of GS-positive and GS-negative populations showed that groups did not differ for all parameters (appendix pp 34–35).

In our follow-up analysis of August, 2015, the prespecified secondary endpoint of anti-MAGE-A3 and

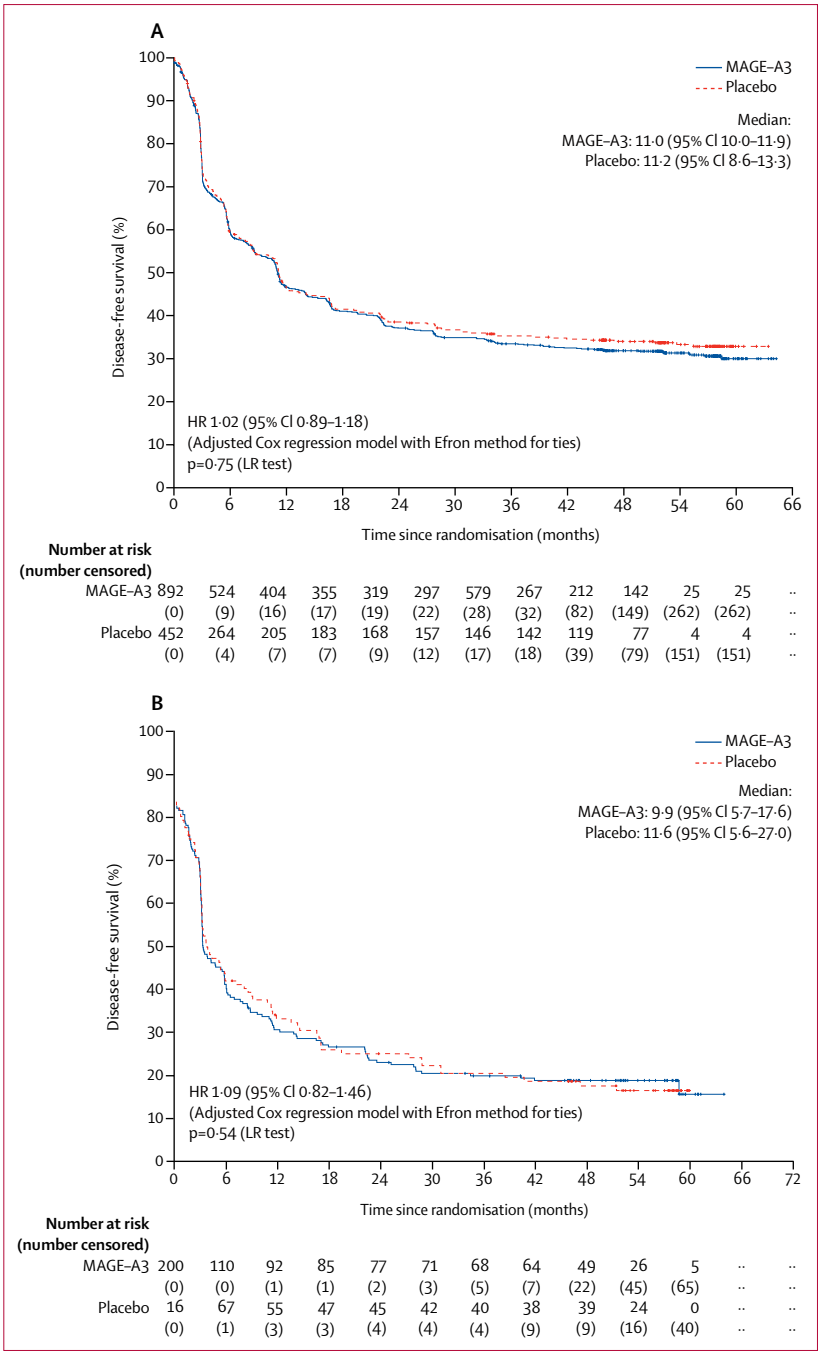

***Figure 2*: Disease-free survival**
The data reported here are from the follow-up analysis (Aug 18, 2015). (A) Overall population (as randomised) and (B) GS-positive population (as randomised). LR=likelihood ratio.

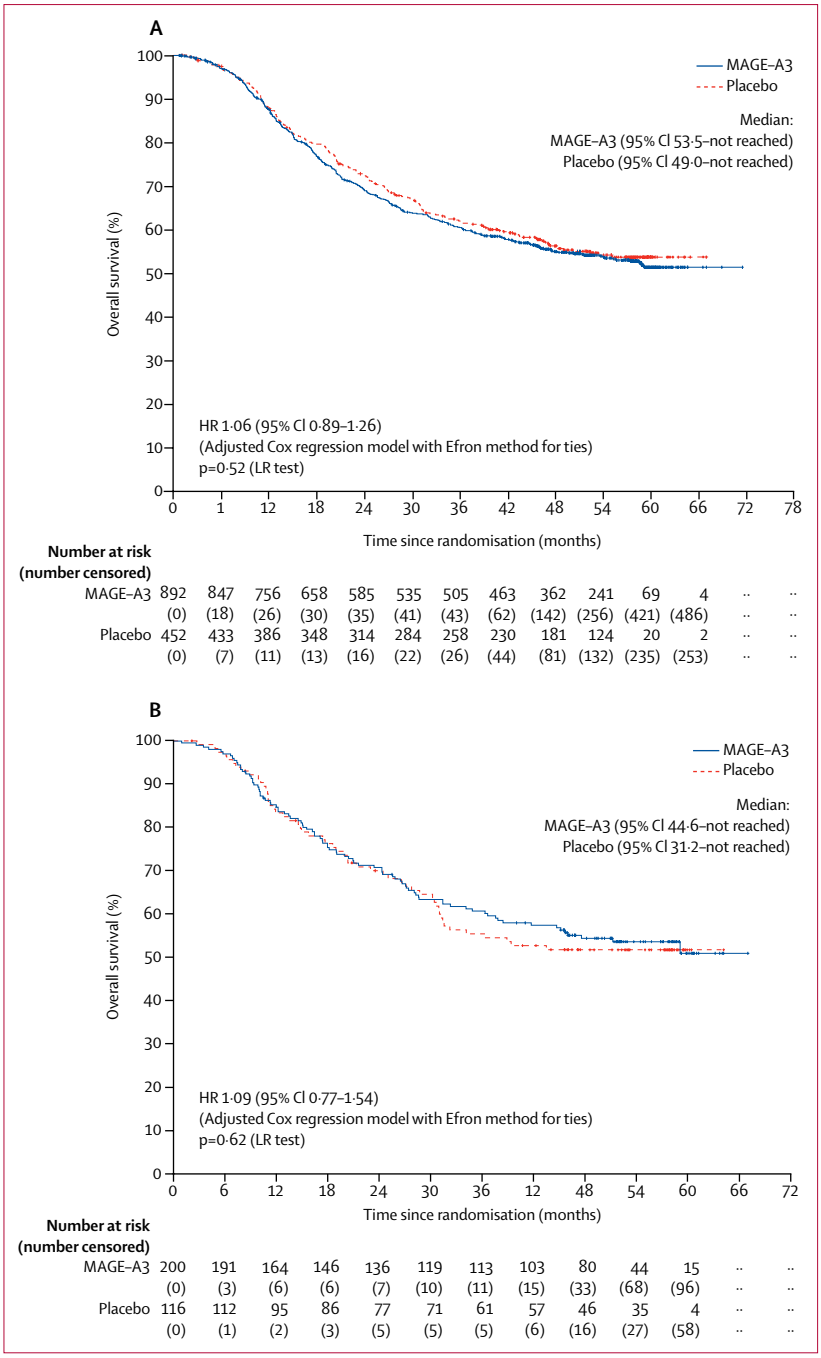

Figure 3: **Overall survival**
The data reported here are from the follow-up analysis (Aug 18, 2015). (A) Overall population (as randomised) and (B) GS-positive population (as randomised). LR=likelihood ratio.

anti-Protein D seropositivity status showed that antibody geometric mean concentrations increased rapidly with MAGE-A3 immunotherapeutic treatment and remained elevated throughout the treatment period (appendix p 36). Results for the GS-positive and GS-negative populations were consistent with those of the overall population (appendix p 37).

Exploratory subgroup analyses (data cutoff May 23, 2013) of disease-free survival for the final analysis according to baseline demographics, and disease and treatment parameters, showed that none of the subgroups benefited from treatment to a larger extent, except for nodal stage (figure 4).

822 (92%) of 894 patients in the MAGE-A3 group and 334 (74%) of 450 patients in the placebo group had an adverse event within 31 days of treatment (August, 2015; table 2). The most common adverse events were pyrexia, injection site pain, and influenza-like illness, all of which were more common in the MAGE-A3 group than in the placebo group. In the MAGE-A3 group, 126 (14%) patients had adverse events of grade 3 or worse, compared with 56 (12%) in the placebo group. The most common adverse events of grade 3 or worse were neoplasms (33 [4%] patients in the MAGE-A3 group *vs* 17 [4%] patients in the placebo group), general disorders and administration site conditions (25 [3%] for MAGE-A3 *vs* four [<1%] for placebo), and infections and infestations (17 [2%] for MAGE-A3 *vs* seven [2%] for placebo). Treatment-related adverse events of grade 3 or worse within 31 days of treatment occurred in 36 (4%) of 894 patients in the MAGE-A3 group and six (1%) of 450 patients in the placebo group. No treatment-related grade 4 or grade 5 adverse events were reported in either group. At least one serious adverse event was reported by 14% of patients in both groups (129 of 894 in the MAGE-A3 group and 64 of 450 in the placebo group; appendix p 24). The most frequently reported serious adverse events according to MedDRA system organ classes were neoplasms (benign, malignant, and unspecified) and infection and infestations. All other MedDRA system organ classes were uncommon (≤1% of patients) in each group (appendix pp 20–23). Serious adverse events considered by the investigator to be related to treatment were reported in eight (<1%) of 894 patients in the MAGE-A3 group (pyrexia, autoimmune thyroiditis, polyneuropathy, erysipelas, wound infection, blurred vision, lymphadenitis, and subarachnoid haemorrhage) and in four (<1%) of 450 patients in the placebo group (retinopathy, thrombocytopenic purpura, invasive lobular breast carcinoma, and pain in extremity; appendix p 24).

Deaths that occurred at any time from randomisation until the end of study were reported in five (<1%) patients in the MAGE-A3 group and one (<1%) in the placebo group (appendix p 25). None of the fatal serious adverse events were considered by the investigator to be related to treatment.

New onset of potential immune-mediated diseases occurred in 33 (4%) of 894 patients in the MAGE-A3 group and in 23 (5%) of 450 patients in the placebo group (table 3). Potential immune-mediated diseases considered by the investigator to be related to treatment were reported by 3% of patients in both groups (26 of 894 in the MAGE-A3 group, 12 of 450 in the placebo group), of

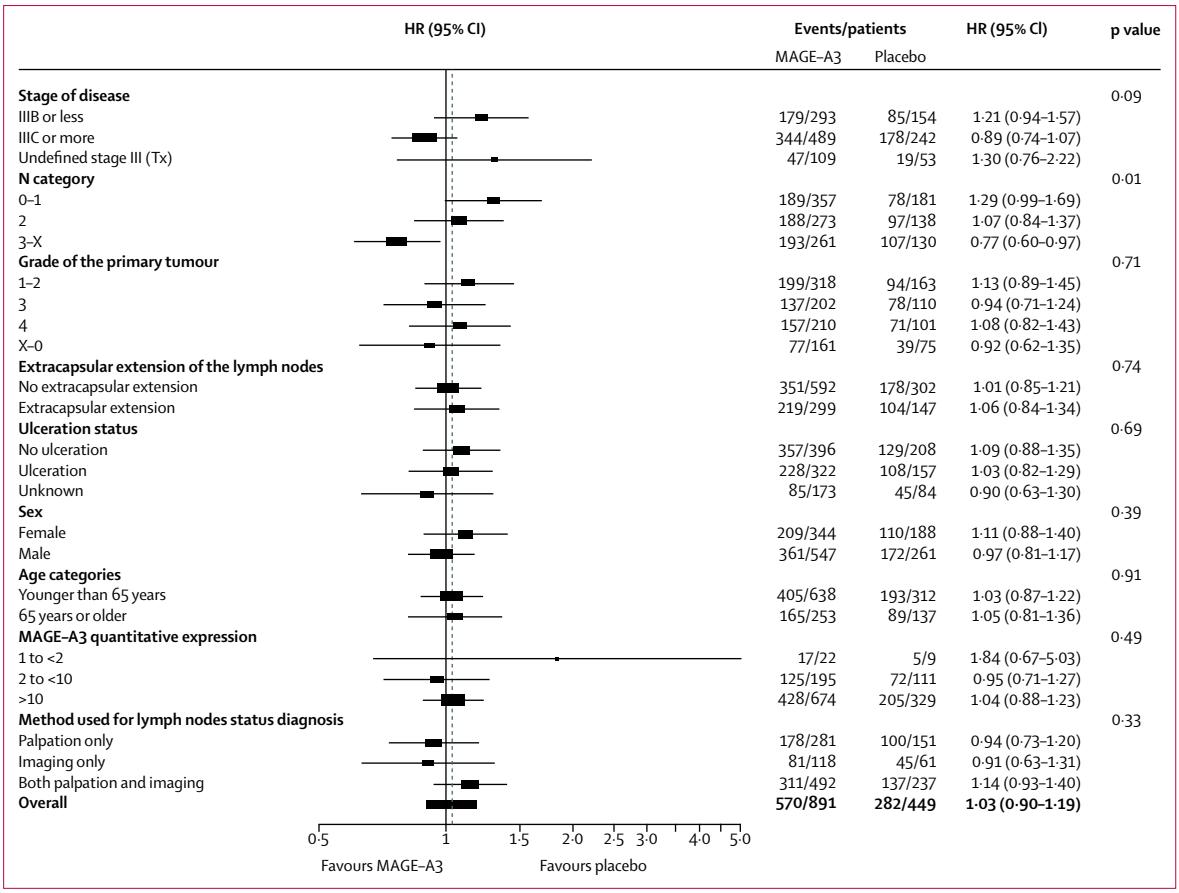

Figure 4: **Forest plots for disease-free survival in subgroups defined by baseline, disease, and treatment variables**
The data reported here are from the final analysis (cutoff date May 23, 2013). Patients with missing values for at least one baseline variable were not included.

which 19 in the MAGE-A3 group and 11 in the placebo group had vitiligo.

14 (2%) of 894 patients in the MAGE-A3 group and five (1%) of 450 patients in the placebo group discontinued study treatment prematurely because of adverse events (figure 1). Of these, seven patients in the MAGE-A3 and no patients in the placebo group discontinued because of a treatment-related adverse event. Safety results for the GS-positive and GS-negative populations were consistent with those of the overall population (appendix pp 26–27). Four patients (all in the MAGE-A3 group) discontinued treatment because of an adverse event considered by the investigator to be related to vaccination (rash, autoimmune hepatitis, fatigue, and influenza-like illness). Three patients (all in the MAGE-A3 group) discontinued treatment because of a serious adverse event considered by the investigator to be related to vaccination (polyneuropathy, pyrexia, and blurred vision). One dose was skipped by eight patients (1%) in the MAGE-A3 group and five patients (1%) in the placebo group; two doses were skipped by one patient (<1%) in the MAGE-A3 group. In the MAGE-A3 group, five patients had reached the maximum delay for postponing the treatment, one patient had an adverse event, one had a serious adverse event, and three doses were skipped for other reasons. In the placebo group, three patients had reached the maximum delay for postponing the treatment and two doses were skipped for other reasons (data not shown). At least one dose was delayed in 181 (20%) patients in the MAGE-A3 group and in 93 (21%) patients in the placebo group. Reasons for delaying doses were adverse events (25 [7%] of 370 delayed doses in the MAGE-A3 group and ten [6%] of 185 delayed doses in the placebo group), serious adverse events (13 [4%] for MAGE-A3 and one [1%] for placebo), other reasons (323 [87%] for MAGE-A3 and 169 [91%] for placebo), and reason not known (nine [2%] for MAGE-A3 and five [3%] for placebo).

QOL scores as measured by the EQ-5D mean utility scores between 0·80 and 0·90 were observed during the treatment period. Analysis of change from baseline in EQ-5D utility scores over time showed that MAGE-A3 treatment had a detrimental effect on the day after the first, third, and fifth treatment administrations, and at recurrence (day after visit 1 mean –0·067 standard deviation [SD] 0·011 on MAGE-A3 and 0·020 [0·016] on

	MAGE-A3 group (n=894)					Placebo group (n=450)				
	Grade 1 or 2	3	4	5	Unknown	Grade 1 or 2	3	4	5	Unknown
Preferred term (≥10% of patients)										
Any event	696 (78%)	97 (11%)	28 (3%)	1 (<1%)	0	278 (62%)	46 (10%)	9 (2%)	1 (<1%)	0
Pyrexia	376 (42%)	5 (1%)	0	0	0	35 (8%)	0	0	0	0
Injection site pain	324 (36%)	1 (<1%)	0	0	0	22 (5%)	0	0	0	0
Influenza-like illness	261 (29%)	0	0	0	0	30 (7%)	0	0	0	0
Fatigue	202 (23%)	8 (<1%)	0	0	0	62 (14%)	1 (<1%)	0	0	0
Headache	200 (22%)	5 (1%)	0	0	0	53 (12%)	2 (<1%)	0	0	0
Myalgia	185 (21%)	3 (<1%)	0	0	0	23 (5%)	0	0	0	0
Pain	186 (21%)	5 (1%)	0	0	0	19 (4%)	0	0	0	0
Asthenia	140 (16%)	9 (1%)	0	0	0	43 (10%)	3 (1%)	0	0	0
Chills	177 (20%)	2 (<1%)	0	0	0	15 (3%)	0	0	0	0
Injection site reaction	160 (18%)	0	0	0	0	6 (1%)	0	0	0	0
Nausea	123 (14%)	0	0	0	0	32 (7%)	0	0	0	0
Erythema	137 (15%)	0	0	0	1 (<1%)	10 (2%)	0	0	0	0
Pain in extremity	113 (13%)	2 (<1%)	0	0	0	25 (6%)	1 (<1%)	0	0	0
Injection site erythema	90 (10%)	0	0	0	0	3 (1%)	0	0	0	0
Primary system organ class										
Any event	696 (78%)	97 (11%)	28 (3%)	1 (<1%)	0	278 (62%)	46 (10%)	9 (2%)	1 (<1%)	0
General disorders and administration site conditions	735 (82%)	25 (3%)	0	0	1 (<1%)	189 (42%)	4 (1%)	0	0	0
Musculoskeletal and connective tissue disorders	365 (41%)	17 (2%)	1 (<1%)	0	0	103 (23%)	8 (2%)	0	0	0
Nervous system disorders	287 (32%)	11 (1%)	1 (<1%)	0	0	83 (18%)	6 (1%)	0	0	0
Skin and subcutaneous tissue disorders	280 (31%)	1 (<1%)	0	0	0	84 (19%)	0	0	0	0
Gastrointestinal disorders	235 (26%)	4 (<1%)	1 (<1%)	0	0	79 (18%)	2 (<1%)	0	0	0
Infections and infestations	180 (20%)	14 (2%)	3 (<1%)	0	0	91 (20%)	6 (1%)	1 (<1%)	0	0
Respiratory, thoracic, and mediastinal disorders	84 (9%)	2 (<1%)	2 (<1%)	0	0	40 (9%)	0	0	0	0
Vascular disorders	69 (8%)	11 (1%)	1 (<1%)	0	0	35 (8%)	9 (2%)	0	0	0
Psychiatric disorders	77 (9%)	0	1 (<1%)	0	1 (<1%)	31 (7%)	0	1 (<1%)	0	0
Neoplasms (benign, malignant and unspecified, including cysts and polyps)	32 (4%)	16 (2%)	17 (2%)	0	0	23 (5%)	10 (2%)	7 (2%)	0	0
Investigations	62 (7%)	5 (1%)	0	0	0	26 (6%)	1 (<1%)	0	0	0
Injury, poisoning, and procedural complications	56 (6%)	4 (<1%)	0	0	0	29 (6%)	1 (<1%)	0	0	0
Metabolism and nutrition disorders	57 (6%)	3 (<1%)	0	0	0	13 (3%)	0	0	0	0
Blood and lymphatic system disorders	24 (3%)	4 (<1%)	0	0	0	17 (4%)	0	0	1 (<1%)	0
Reproductive system and breast disorders	27 (3%)	0	0	0	0	12 (3%)	1 (<1%)	0	0	0
Eye disorders	21 (2%)	0	0	0	0	13 (3%)	3 (1%)	0	0	0
Ear and labyrinth disorders	19 (2%)	0	0	0	0	17 (4%)	0	0	0	0
Cardiac disorders	12 (1%)	5 (1%)	1 (<1%)	1 (<1%)	0	4 (1%)	0	0	0	0
Renal and urinary disorders	14 (2%)	4 (<1%)	0	0	0	4 (1%)	1 (<1%)	0	0	0
Hepatobiliary disorders	5 (1%)	1 (<1%)	0	0	0	4 (1%)	1 (<1%)	0	0	0
Immune system disorders	4 (<1%)	0	0	0	0	7 (2%)	0	0	0	0
Endocrine disorders	4 (<1%)	0	0	0	0	2 (<1%)	0	0	0	0

Data are n (%). Adverse events reported are from the follow-up analysis (Aug 18, 2015) in the safety population (overall population as treated). Only events that occurred in at least 10% of patients in any group are reported here; the full adverse events list is the appendix pp 20–23.

Table 2: **Adverse events**

placebo; p<0·0001; day after visit 3 –0·129 [0·011] on MAGE-A3 and 0·019 [0·016] on placebo; p<0·0001; day after visit 5 –0·060 [0·012] on MAGE-A3 and 0·022 [0·018] on placebo; p=0·0001; at recurrence –0·100 [0·017] on MAGE-A3 and –0·029 [0·027] on placebo; p=0·026). At year 1, the difference was in favour of the

	MAGE-A3 group (n=894)	Placebo group (n=450)
Any event		
Any event	33 (4%)	23 (5%)
Blood and lymphatic system disorders		
Thrombocytopenic purpura	0	1 (<1%)
Endocrine disorders		
Autoimmune thyroiditis	3 (<1%)	0
Basedow's disease	1 (<1%)	1 (<1%)
Hypothyroidism	1 (<1%)	0
Lymphocytic hypophysitis	0	1 (<1%)
Polyglandular autoimmune syndrome type II	0	1 (<1%)
Eye disorders		
Blurred vision	1 (<1%)	0
Gastrointestinal disorders		
Colitis ulcerative	0	1 (<1%)
Hepatobiliary disorders		
Autoimmune hepatitis	1 (<1%)	1 (<1%)
Immune system disorders		
Sarcoidosis	0	2 (<1%)
Musculoskeletal and connective tissue disorders		
Polymyalgia rheumatica	0	1 (<1%)
Neoplasms benign, malignant and unspecified (including cysts and polyps		
Langerhans cell histiocytosis	0	1 (<1%)
Nervous system disorders		
Multiple sclerosis	1 (<1%)	0
7th nerve paralysis	1 (<1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders		
Pulmonary fibrosis	1 (<1%)	1 (<1%)
Skin and subcutaneous tissue disorders		
Alopecia areata	1 (<1%)	0
Psoriasis	1 (<1%)	1 (<1%)
Skin hypopigmentation	1 (<1%)	0
Vitiligo	20 (2%)	13 (3%)

Data are n (%). Adverse events reported are from the follow-up analysis (Aug 18, 2015) in the safety population (overall population as treated). Diseases were determined from a predefined list of preferred terms or by the investigator, or both. MedDRa=Medical Dictionary for Regulatory Activities.

Table 3: **Potential immune-mediated diseases, as defined by MedDRA**

MAGE-A3 group (mean at year 1 of follow-up –0·067 [SD 0·0277] on MAGE-A3 and –0·208 [0·044] on placebo; p=0·0057; appendix pp 29–30). A similar observation was made for visual analogue scores on the day after the first and third administrations (appendix pp 31–32). Changes in the QOL from baseline in the overall model as measured by utility score differed between groups (adjusted mean –0·037 [SD 0·010] for MAGE-A3 and 0·002 [0·011] for placebo; p=0·0006), but change from baseline in the visual analogue scores in the overall model did not (adjusted mean –4·025 [SD 1·283] for MAGE-A3 and –1·268 [1·532] for placebo; p=0·0683; appendix p 28). The decreased scores on MAGE-A3 treatment after the first and third treatment administrations are most likely to be related to the dimension pain or discomfort at the injection site. This observation from the descriptive EQ-5D analysis is consistent with the clinical safety results.

Discussion

To our knowledge, the DERMA randomised, phase 3 trial is the largest adjuvant trial ever done in patients with melanoma. Treatment with the MAGE-A3 immunotherapeutic was well tolerated and immunogenic, inducing large increases in anti-MAGE-3 antibody concentrations, but these factors did not translate into clinical efficacy. The MAGRIT study,[22] a similarly designed phase 3 trial of adjuvant MAGE-A3 immunotherapeutic in patients with resected NSCLC that became available before our study ended, drew similar conclusions. Despite initially encouraging, but ultimately discordant, results from phase 2 studies, treatment with the MAGE-A3 immunotherapeutic did not improve disease-free survival, overall survival, or any other clinical outcome in the overall population of patients with advanced melanoma, nor in subgroups according to tumour characteristics or treatment procedures. Although a gene signature potentially predictive of clinical benefit from MAGE-A3 immunotherapeutic over placebo in the GS-positive population was found in the training set, it could not be clinically validated in the test set. Notably, a T-helper-type 1 and interferon γ prognostic gene signature (eight genes) associated with outcome in the placebo group of the training set was validated in the test set of this study. Although we did not succeed in validating the predictive gene signature using the adaptive signature design, we have shown that this approach is feasible for optimisation and validation of biomarkers for which not all parameters have been set at the start of the clinical trial.

The study has some limitations. Although our study reflects real-world practice, there was a high percentage of participants with a cancer of unknown primary (TxN1b-N2b-N3 M0). Although some reports[23] suggest differences in outcome in patients with unknown primary melanoma, we saw no treatment effect in this subgroup in the exploratory subgroup analyses. The study did not have prespecified stopping criteria (futility analysis) because safety was overseen by an IDMC that reviewed study data every 6 months throughout the study period. The committee did not have any safety concerns. No recognised alternative treatment option was available in the absence of recurrence and the use of a futility rule was not compatible with the search for a subgroup of participants with a potentially more pronounced benefit from treatment (GS-positive), for which the assessment occurred later in the course of the study.

The reasons for the absence of clinical efficacy in our study are speculative, but could be related to the choice of antigen or immunostimulant or the absence of the induction of T-cell responses (particularly CD8 responses).

We might have selected a target population with disease too advanced for successful vaccine immunotherapy treatment; notably, the observed median disease-free survival of about 11 months (95% CI 10·0–11·9) is shorter than has been reported in previous trials.

MAGE-A3 was an attractive immunotherapeutic candidate because it is one of the most immunogenic cancer-testis antigens and is not HLA type specific.[8] The poor efficacy of MAGE-A3 in this trial could be due to an error in one or multiple steps of the cancer immunity cycle,[24] including failure to have an appropriate antitumour immune response and mechanisms of immune evasion and suppression. The success of adoptively transferred and genetically modified T cells in the treatment of haematological malignancies and solid tumours highlights the pivotal role of cytotoxic reactive T cells in antitumour responses.[25] CD8 responses were low or absent in the phase 2 study of the MAGE-A3 immunotherapeutic,[10] which might have contributed to the absence of clinical effect. Immunotherapeutics aim to induce antitumour T-cell responses but their effects can be inhibited by many immunosuppressive mechanisms, including the loss of MHC class I, expression of ligands for inhibitory receptors (programmed death-ligand 1, CD200, and HLA-E), infiltration with suppressive cells, secretion of indoleamine 2,3-dioxygenase, and secretion of immunosuppressive cytokines. Thus, immunotherapeutics might be more successful when used in the early stages of disease, when immune suppression is typically less pronounced and when combined with other treatments that can activate antitumour T-cell responses.[26] For future studies, the most promising combination might be an immunotherapeutic with a treatment that can activate cytotoxic T cells against melanoma antigens and benefit from the excellent tolerance of vaccines.

The treatment of metastatic melanoma has changed substantially in the past 5 years with the availability of BRAF and MEK inhibitors and multiple checkpoint inhibitors, which are immunopotentiators that are not specifically analogous to the MAGE-A3 immunotherapeutic. These drugs have changed the field of adjuvant therapy in melanoma. In the BRIM8 trial,[27] adjuvant vemurafenib was substantially beneficial for patients with completely resected stage IIC to IIIB $BRAF^{V600}$-positive melanoma and who were at high risk of recurrence, where fewer disease-free survival events and events of distant metastasis-free survival were observed with vemurafenib compared with placebo. However, the benefit of vemurafenib was not significant in patients with resected stage IIIC melanoma. The overall survival data are still immature for both cohorts. The benefit of interferon in metastatic disease is well documented to be about a 15% objective response, and the benefit of it in the adjuvant therapy of melanoma has been a reduction of about 25–33% in the frequency of relapse (HR 0·28–0·33) in E1684–E1694 intergroup trials.[28,29] Ipilimumab improves disease-free survival and overall survival in stage III melanoma but causes severe adverse events;[30] programmed cell death-1 inhibitors in the adjuvant setting have shown significant benefit in terms of disease-free survival over ipilimumab, although overall survival benefits are not yet mature.[5] Trials designed to increase the efficacy of checkpoint inhibitors in multiple combinations are ongoing (NCT02817633 and NCT02913313). To date, whether combinations of antigen-specific immunotherapies and checkpoint inhibitors might also improve outcomes is unknown; however, the combination of gp100 and the first-generation CTLA-4 checkpoint inhibitor ipilimumab provided no additional benefits in patients with advanced melanoma.[31]

Contributors

BD, TJ, EL, AT, JAT, AH, JJG, HCvH, FU-M, BD, BS, MD, JL, PT, CD, JMK, and VGB conceived and designed the study. BD, JFT, BMS, MS, TJ, RG, EL, PR, J-JG, SK, KD, FG, LM, PH, AT, RC, BG, WHJK, LD, JAT, IB, JJ, GC, SP, AH, FU-M, AC, BD, BS, JL, PT, CD, JMK, and VGB collected or generated the data. BD, JFT, BMS, MS, TJ, RG, EL, PR, J-JG, SK, KD, FG, LM, PH, IK, AT, RC, BG, WHJK, LD, JAT, IB, JJ, SP, AH, FU-M, BD, BS, JL, PT, CD, and JMK were study investigators. BD, EL, J-JG, KD, IK, AT, BG, JAT, IB, AH, HCvH, FU-M, BD, BS, JL, PT, CD, and VGB provided materials and analysis. BD, TJ, RG, EL, PR, J-JG, IK, AT, RC, BG, WHJK, JAT, IB, SP, AH, JJG, HCvH, FU-M, AC, BD, BS, MD, JL, PT, CD, and JMK did or supervised the data analysis. All authors critically reviewed the manuscript and approved the final version.

Declaration of interests

BD, BG, LD, SP, and WHJK received grants from the GSK group of companies during this study. BD received grants and personal fees from Roche and Bristol-Myers Squibb (BMS) outside the submitted work. WHJK also received personal fees from GSK during and outside this study. LD also received personal fees from Merck Sharp & Dohm (MSD), BMS, and Roche for expert testimony outside the submitted work. SP also received honorarium from GSK outside the submitted work. AH received grants and personal fees from GSK outside the submitted work and consultancy fees from Amgen, BMS, Celgene, Eisai, MedImmune, MelaSciences, Merck Serono, MSD, Novartis, Oncosec, and Roche outside the submitted work. RG received personal fees and non-financial support from GSK during and outside the conduct of this study, grants from Roche, Novartis, Pfizer, and Johnson & Johnson, personal fees from Roche, BMS, Novartis, Merck Serono, MSD, Almirall-Hermal, Mibe, Amgen, Galderma, Janssen, and Boehringer Ingelheim, and non-financial support from Roche, BMS, Novartis, and MSD outside the submitted work. J-JG received personal fees from GSK during and outside the conduct of this study and personal fees from Novartis, Roche, BMS, MSD, and AMGEN outside the submitted work. During this study, PR received personal fees from GSK, Novartis, BMS, Roche, Amgen, and MSD, and grants from BMS. PR also received personal fees from Pfizer and Bayer outside the submitted work. The institution of LM (Université François-Rabelais, Tours, France) received compensation from the GSK group of companies for extra costs linked to the study. The institution of RC (University of Alabama, AL, USA) received financial support from GSK during this study. GC received honoraria from GSK as the principal investigator of the DERMA trial and for participation in advisory boards. JMK received personal fees from BMS, Merck, Celgene, Ziopharm, and Vical, and grants from Prometheus outside the submitted work. FU-M, BS, JL, CD, BD, and PT received personal fees from GSK and hold employee shares in the company. AC and MD received personal fees from GSK (as employees) during the study. All other authors declare no competing interests.

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