Safety and efficacy of inactivated varicella zoster virus vaccine in immunocompromised patients with malignancies: a two-arm, randomised, double-blind, phase 3 trial

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Summary

Background Patients who are immunocompromised because of malignancy have an increased risk of herpes zoster and herpes zoster-related complications. We aimed to investigate the efficacy and safety of an inactivated varicella zoster virus (VZV) vaccine for herpes zoster prevention in patients with solid tumour or haematological malignancies.

Methods This phase 3, two-arm, randomised, double-blind, placebo-controlled, multicentre trial with an adaptive design was done in 329 centres across 40 countries. The trial included adult patients with solid tumour malignancies receiving chemotherapy and those with haematological malignancies, either receiving or not receiving chemotherapy. Patients were randomly assigned (1:1) to receive four doses of VZV vaccine inactivated by γ irradiation or placebo approximately 30 days apart. The patients, investigators, trial site staff, clinical adjudication committee, and sponsor's clinical and laboratory personnel were masked to the group assignment. The primary efficacy endpoint was herpes zoster incidence in patients with solid tumour malignancies receiving chemotherapy, which was assessed in the modified intention-to-treat population (defined as all randomly assigned patients who received at least one dose of inactivated VZV vaccine or placebo). The primary safety endpoint was serious adverse events up to 28 days after the fourth dose in patients with solid tumour malignancies receiving chemotherapy. Safety endpoints were assessed in all patients who received at least one dose of inactivated VZV vaccine or placebo and had follow-up data. This trial is registered (NCT01254630 and EudraCT 2010-023156-89).

Findings Between June 27, 2011, and April 11, 2017, 5286 patients were randomly assigned to receive VZV vaccine inactivated by γ irradiation (n=2637) or placebo (n=2649). The haematological malignancy arm was terminated early because of evidence of futility at a planned interim analysis; therefore, all prespecified haematological malignancy endpoints were deemed exploratory. In patients with solid tumour malignancies in the modified intention-to-treat population, confirmed herpes zoster occurred in 22 of 1328 (6·7 per 1000 person-years) VZV vaccine recipients and in 61 of 1350 (18·5 per 1000 person-years) placebo recipients. Estimated vaccine efficacy against herpes zoster in patients with solid tumour malignancies was 63·6% (97·5% CI 36·4 to 79·1), meeting the prespecified success criterion. In patients with solid tumour malignancies, serious adverse events were similar in frequency across treatment groups, occurring in 298 (22·5%) of 1322 patients who received the vaccine and in 283 (21·0%) of 1346 patients who received placebo (risk difference 1·5%, 95% CI –1·7 to 4·6). Vaccine-related serious adverse events were less than 1% in each treatment group. Vaccine-related injection-site reactions were more common in the vaccine group than in the placebo group. In the haematological malignancy group, VZV vaccine was well tolerated and estimated vaccine efficacy against herpes zoster was 16·8% (95% CI –17·8 to 41·3).

Interpretation The inactivated VZV vaccine was well tolerated and efficacious for herpes zoster prevention in patients with solid tumour malignancies receiving chemotherapy, but was not efficacious for herpes zoster prevention in patients with haematological malignancies.

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Introduction

Advanced malignancy and associated immunosuppressive therapies are risk factors for herpes zoster.[1–4] The incidence of herpes zoster is approximately 15 cases per 1000 person-years in patients with solid tumour malignancies receiving chemotherapy[3] and 31 cases per 1000 person-years in patients with haematological malignancies,[1,4] compared with nine cases per 1000 person-years in the general adult population aged 50 years and older (five cases per 1000 person-years across all ages).[2] Patients who are immunocompromised are at increased risk of developing severe and life-threatening complications of herpes zoster, including disabling post-herpetic neuralgia, visceral organ involvement, and bacterial superinfection.[5,6] The clinical presentation of herpes zoster can be atypical in these patients, including disseminated varicella-like skin lesions

Research in Context

Evidence before this study

We searched PubMed for published articles in English with no date restrictions with the terms "varicella zoster virus vaccine", "herpes zoster", in conjunction with the terms "cancer", "tumour", or "malignancy", and found that patients immunocompromised either because of malignancy or receipt of immunosuppressive cancer therapy have a higher incidence of herpes zoster than the general immunocompetent adult population. A live, attenuated varicella zoster virus (VZV) vaccine, licensed for use in healthy adults aged 50 years and older for herpes zoster prevention, is contraindicated in patients who are immunocompromised, including patients with solid tumour malignancies receiving chemotherapy and those with haematological malignancies. A phase 1 trial showed immunogenicity and safety of a heat-inactivated VZV vaccine in patients with solid tumour malignancies receiving chemotherapy and with haematological malignancies. Another phase 1 trial showed safety and immunogenicity of VZV vaccine inactivated by γ irradiation in patients with haematological malignancies receiving anti-CD20 monoclonal antibodies. A phase 3 trial was done to assess the efficacy and safety of this vaccine for prevention of herpes zoster and herpes zoster-related complications in patients with solid tumour malignancies receiving chemotherapy or haematological malignancies. Phase 2 immunogenicity and safety trials of an adjuvant recombinant subunit VZV vaccine in patients who are immunocompromised were ongoing when the phase 3 study was planned.

Added value of this study

To our knowledge, this is the first randomised, double-blind, placebo-controlled, international, phase 3 trial evaluating the efficacy and safety of the investigational VZV vaccine inactivated by γ irradiation for the prevention of herpes zoster and herpes zoster-related complications in patients with solid tumour malignancies receiving chemotherapy and those with haematological malignancies.

Implications of all the available evidence

The results of this trial show that the vaccine is well tolerated in both patient populations and that inactivated VZV vaccine is effective for herpes zoster prevention in patients with solid tumour malignancies receiving chemotherapy but not in patients with haematological malignancies.

and no obvious primary dermatome involvement or severe abdominal pain preceding the appearance of rash.

Treatment of herpes zoster in patients who are immuno-compromised typically includes intravenous aciclovir,[7,8] and in cases of aciclovir-resistant herpes zoster, foscarnet or cidofovir.[6,9] Two licensed vaccines for herpes zoster prevention in healthy adults aged 50 years and older are available: a live attenuated varicella zoster virus (VZV) vaccine (Zostavax; Merck & Co, Inc, Kenilworth, NJ, USA),[10–12] which is contraindicated in patients who are immunocompromised, and an adjuvanted recombinant subunit VZV vaccine (Shingrix; GlaxoSmithKline, King of Prussia, PA, USA), for which efficacy in patients with malignancies has not yet been established.[13–17] Thus, prevention of herpes zoster disease in patients with solid tumour or haematological malignancies represents an area of substantial unmet medical need.

In proof-of-concept studies and a small phase 1 trial, heat-inactivated VZV vaccine reduced herpes zoster morbidity and decreased herpes zoster incidence in haematopoietic stem-cell transplant recipients,[18,19] and showed immunogenicity and safety in patients with solid tumour malignancies receiving chemotherapy and in patients with haematological malignancies.[20] Phase 1 and 2 trials showed safety and immunogenicity of a VZV vaccine inactivated by γ irradiation (Merck & Co, Inc) in patients with haematological malignancies receiving anti-CD20 monoclonal antibodies and in patients with autoimmune disease receiving immunosuppressive therapy.[21,22] Subsequently, the efficacy, immunogenicity, and safety of this vaccine was established in a large phase 3 trial in recipients of autologous haematopoietic stem-cell transplants.[23] In this study, we aimed to assess the efficacy and safety of the VZV vaccine inactivated by γ irradiation for prevention of herpes zoster and herpes zoster-related complications in patients with solid tumours receiving chemotherapy or patients with haematological malignancies.

See Online for appendix

Methods

Study design and participants

This adaptively designed, two-arm, phase 3, randomised, double-blind, placebo-controlled, multicentre trial was done in 329 centres across 40 countries. Eligible patients were aged 18 years or older, had been diagnosed with a solid tumour malignancy (for which they were receiving a cytotoxic or immunosuppressive chemotherapy regimen) or haematological malignancy, and were not likely to undergo haematopoietic stem-cell transplantation. Patients had to have a history of varicella infection (chickenpox) or be seropositive for antibodies to VZV. Patients with haematological malignancies who were aged 50 years or older and not in remission were eligible regardless of whether they were receiving chemotherapy. Exclusion criteria included a history of herpes zoster within 1 year of enrolment, history or expected receipt of any VZV-containing vaccine, or current or expected receipt of long-term (>4 weeks) antiviral prophylaxis against herpes simplex virus, VZV, or cytomegalovirus. Detailed eligibility criteria are provided in the appendix pp 3–4.

Written informed consent was obtained from each participant before trial entry. The institutional review board of each participating site reviewed and approved

the final clinical protocol. The study protocol is in the appendix.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive VZV vaccine inactivated by γ irradiation or placebo. An integrated voice response system was used to register patients at the time of randomisation and subsequent visits, and to assign patients to the vaccine or placebo groups according to central randomisation schedules generated by the trial statistician. Randomisation was stratified by disease type (solid tumour malignancy *vs* haematological malignancy). Patients with haematological malignancies were further stratified into slightly immunocompromised versus moderately to highly immunocompromised. The patients, investigators, trial site staff, members of the clinical adjudication committee, and sponsor's clinical and laboratory personnel were masked to the group assignment. An unmasked statistician (not otherwise involved with the trial) provided summary data to an independent, external, unmasked data monitoring committee.

Procedures

The investigational VZV vaccine inactivated by γ irradiation (Merck & Co, Inc) contained attenuated VZV vaccine virus (Oka strain used in Zostavax). Placebo was the vaccine stabiliser with no viral antigen. VZV vaccine and placebo were reconstituted with 0·7 mL of sterile water immediately before administration and were visually indistinguishable from each other. At each vaccination, 0·5 mL of the reconstituted vaccine was administered via subcutaneous injection.

Participants were given treatment as a four-dose regimen administered approximately 30 days apart. Dose one of VZV vaccine or placebo was administered at enrolment (day 1). Doses two to four were administered approximately 30 days after each previous dose. In patients receiving cyclic chemotherapy, dose one of VZV vaccine or placebo was administered approximately 5 days before any chemotherapy dose in the cycle. Doses two to four were administered approximately 20–40 days after the previous dose of vaccine or placebo, with the condition that VZV vaccine or placebo had to be administered approximately 5 days before the upcoming chemotherapy dose.

Patients were monitored throughout the trial for clinical signs and symptoms of herpes zoster. Patients were also asked to promptly notify trial site personnel if they had a rash or other symptoms suggestive of herpes zoster. Patient contact was made monthly, by telephone, internet, or during a follow-up clinic visit, to remind the patient to report any suspected VZV infection. During each contact, patients provided answers to prespecified questions related to herpes zoster symptoms. Patients with suspected herpes zoster were seen every 3–5 days until no new lesions developed, or if no rash was present, until acute herpes zoster symptoms improved. Thereafter, they were followed up for 6 months after the initial report of suspected herpes zoster for assessment of herpes zoster-associated pain and complications.

Patients were monitored for any adverse event from the time of the first vaccination dose up until 28 days following the fourth vaccination dose via a vaccination report card, in which patients recorded safety information after each vaccine dose. Patients were monitored for serious adverse events regardless of causality and instructed to call the trial site immediately if a serious adverse event occurred. Beginning 4 months after the fourth vaccination dose, patients were contacted by trial staff every 3 months through the duration of the trial either at a scheduled visit or by telephone, using a prespecified script, to determine whether all serious adverse events had been reported since the last contact. Each patient had planned follow-up for at least 1 year after their last vaccination dose, including individuals with early discontinuation from the vaccination schedule who were alive and remained in the trial for follow-up.

Skin lesion specimens obtained from patients suspected of having VZV infection were primarily evaluated by PCR assay done at a central laboratory for the presence of wildtype VZV, Oka strain VZV, or herpes simplex virus. Detection of VZV DNA defined a confirmed case of herpes zoster. For suspected cases that did not have a skin lesion PCR assay result, either because of inadequate collection or a missing sample, case confirmation was based on the results of masked adjudication by the clinical adjudication committee. The clinical adjudication committee included clinicians with expertise in herpes zoster in patients who are immunocompromised and provided available clinical and laboratory data for each case of suspected herpes zoster. All herpes zoster cases confirmed by the clinical adjudication committee were also adjudicated by the committee for herpes zoster-related complications in a masked manner. In general, assessments by the clinical adjudication committee were based on clinical findings, laboratory and radiographic data, and results from the investigational blood VZV PCR testing.

The ELISPOT substudy comprised the first 500 patients with haematological malignancies and the first 500 patients with solid tumours enrolled at study sites that were identified as substudy sites on the basis of proximity to qualified peripheral blood mononuclear cell processing labs. Subgroups of patients in both the VZV vaccine and placebo groups were tested for VZV-specific cell-mediated immune responses by an interferon-γ enzyme-linked immunospot assay (IFNγ ELISPOT; ViraCor-IBT Laboratories, Inc, Lenexa, KS, USA),[24] and all patients with solid tumour malignancies were tested for VZV-specific antibody responses with a glycoprotein ELISA (PPD Vaccines and Biologics, LLC, Wayne, PA, USA).[25] These assays had previously been used in studies of live attenuated and inactivated VZV vaccines.[11,20–23] Blood samples for the assays were collected on day 1 (before dose one) and 28–60 days after.

Outcomes

The primary efficacy endpoint was confirmed herpes zoster after the fourth dose through to the end of the trial in patients with solid tumour malignancies receiving chemotherapy. A confirmed case of herpes zoster was defined as a suspected case of herpes zoster that was confirmed as VZV-positive by PCR or adjudicated as a herpes zoster case by the clinical adjudication committee if no laboratory results were available or laboratory results were inconclusive.

The primary safety endpoint was the incidence of serious adverse events observed from time of first vaccination dose until 28 days after the fourth vaccination dose in patients with solid tumour malignancies receiving chemotherapy. Serious adverse events were defined as any adverse event that resulted in death; was life-threatening; resulted in a persistent or substantial disability; resulted in hospitalisation or prolonged hospitalisation; was a congenital anomaly or birth defect in the offspring of a participant or a cancer; or was associated with an overdose or any other important medical event that might jeopardise the patient or require medical or surgical intervention. The causality of each adverse event was assessed by the investigator. Patients with serious adverse events with suspected VZV infection were evaluated for the presence of wildtype or vaccine-type VZV strain by PCR. Safety and efficacy data were periodically monitored by a data monitoring committee.

Secondary efficacy endpoints (assessed in patients with solid tumour malignancies receiving chemo-therapy) were the incidence of moderate to severe herpes zoster-associated pain, herpes zoster compli-cations, and post-herpetic neuralgia. Moderate to severe herpes zoster-associated pain was defined as two or more occurrences of score 3 or greater (0–10 scale) on the Zoster Brief Pain Inventory,[26] at any time from herpes zoster onset through to the end of the 6-month follow-up period. Only collected data contributed to the endpoint of moderate to severe herpes zoster-associated pain. Herpes zoster compli cations were defined as admission to hospital or prolongation of hospital stay due to herpes zoster, disseminated herpes zoster (including disseminated herpes zoster rash or VZV viraemia), visceral herpes zoster, ophthalmic herpes zoster, neurological impair ment due to herpes zoster, or administration of intravenous aciclovir therapy for herpes zoster. Cases of herpes zoster confirmed by the clinical adjudication committee were assessed by the committee for each herpes zoster complication. Post-herpetic neuralgia was defined as pain in the area of herpes zoster rash with a "worst pain in the last 24 hours" score of 3 or greater (on a 0–10 scale) on the Zoster Brief Pain Inventory that persisted or appeared 90 days or more after onset of herpes zoster rash. Only collected data contributed to the endpoint of post-herpetic neuralgia.

Immunogenicity of the VZV vaccine was assessed as an exploratory endpoint.

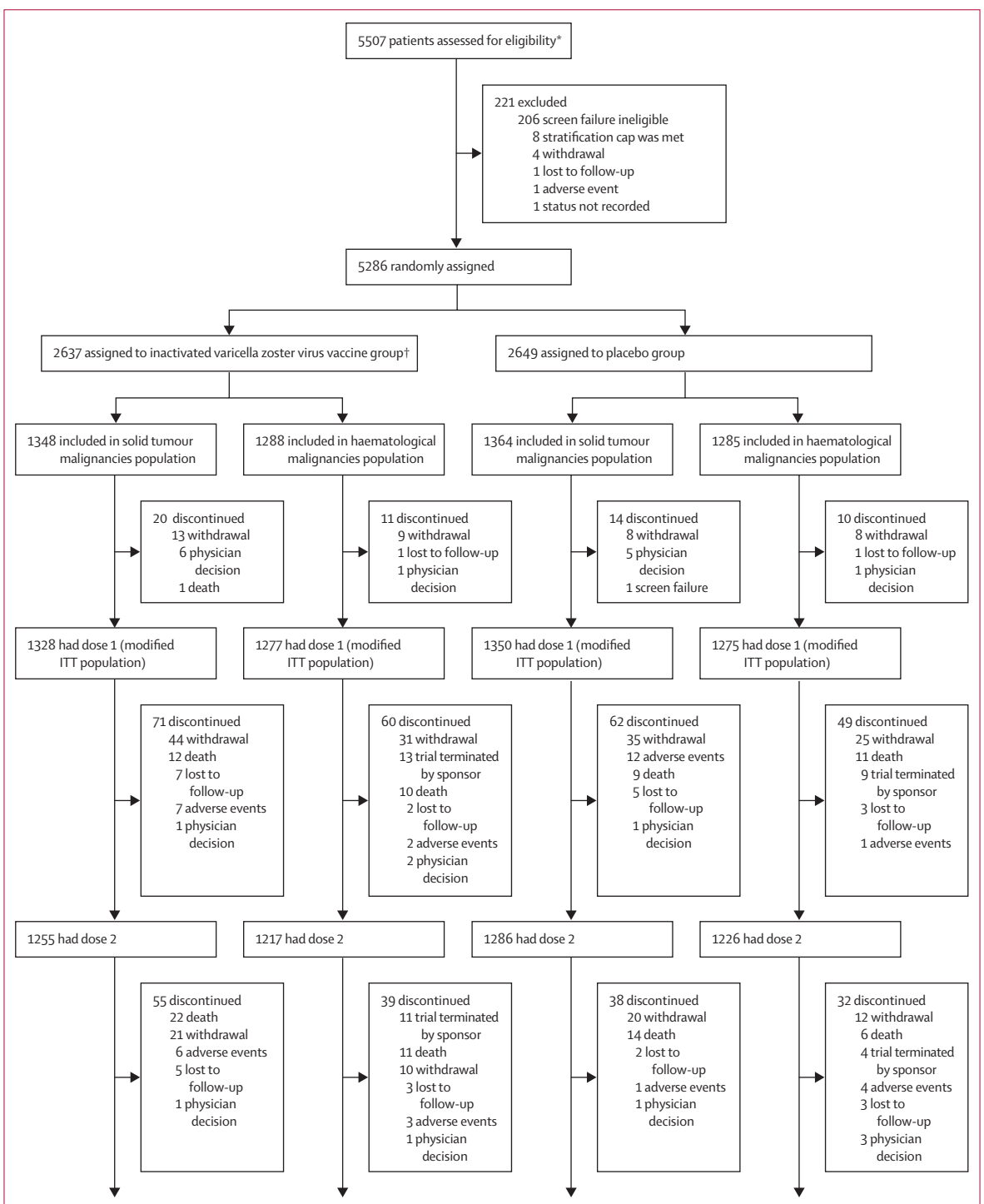
Statistical analysis

An adaptive design was planned to allow an interim analysis of futility for each of the patient populations (haematological malignancies and solid tumour malig-nancies) when about 50% of the target number of herpes zoster cases had accrued in each population. Specifically, for the haematological malignancy group, a futility analysis was done when at least 68 cases of herpes zoster had accrued, whereas in the solid tumour malignancy group, it was done when at least 48 cases had accrued. At the time of the interim analysis in the haematological malignancy group, we found that the incidence of herpes zoster was less than 30%. As a result, enrolment and vaccination in the group were terminated early, and all endpoints related to this patient population were deemed exploratory by protocol amendment. The study continued in patients with solid tumour malignancies. Additional participants were not enrolled into the solid tumour population as per initial protocol. Instead, a final case count of 90 (reduced from the originally planned 210) was targeted in the solid tumour population; this provided adequate power for the primary endpoint without the need for enrolment of additional participants. With 90 herpes zoster cases in the solid tumour population of 2696 patients, the study had an overall power of 84·2% to detect a 65% vaccine efficacy at the overall two-sided 0·025 significance level, based on the success criterion of the lower bound 97·5% CI for vaccine efficacy being greater than 25%.

To accrue around 90 confirmed herpes zoster cases in the population of patients with solid tumour malignancies receiving chemotherapy, we needed to enrol approximately 2696 patients, assuming a herpes zoster incidence of 17 cases per 1000 person-years in the placebo group,[1,4] 30% loss to follow-up, a vaccine efficacy against herpes zoster of 65%, and 36 months of trial enrolment. Per protocol, the trial could be terminated after 5 years of herpes zoster case surveillance even if the target number of herpes zoster cases in the solid tumour malignancies population had not been achieved. The trial ended after 5 years because of infeasibility, with 83 confirmed herpes zoster cases in patients with solid tumour malignancies. The overall power re-assessed post-hoc for 83 confirmed herpes zoster cases in a modified intention-to-treat population (defined as all randomly assigned patients who received at least one dose of inactivated VZV vaccine or placebo) was approximately 77% to detect a 63% vaccine efficacy at the overall one-sided significance level of 0·0125, on the basis of a prespecified success criterion of greater than 25% for the lower boundary of the 97·5% CI for the primary endpoint.[27]

Per protocol, vaccine efficacy against herpes zoster was defined as the relative reduction of the incidence rate of confirmed herpes zoster in the VZV vaccine group versus the placebo group in patients with solid

tumour malignancies and calculated as one minus the hazard ratio between inactivated VZV vaccine and placebo recipients. To address the primary hypothesis of herpes zoster prevention, a Cox proportional hazards regression model, stratified by age (<50 years *vs* ≥50 years), based on the modified intention-to-treat population, was used to compare the herpes zoster incidence between the inactivated VZV vaccine and placebo groups. Herpes zoster incidence rate varies by age and increases substantially from around 50 years



(Figure 1 continues on next page)

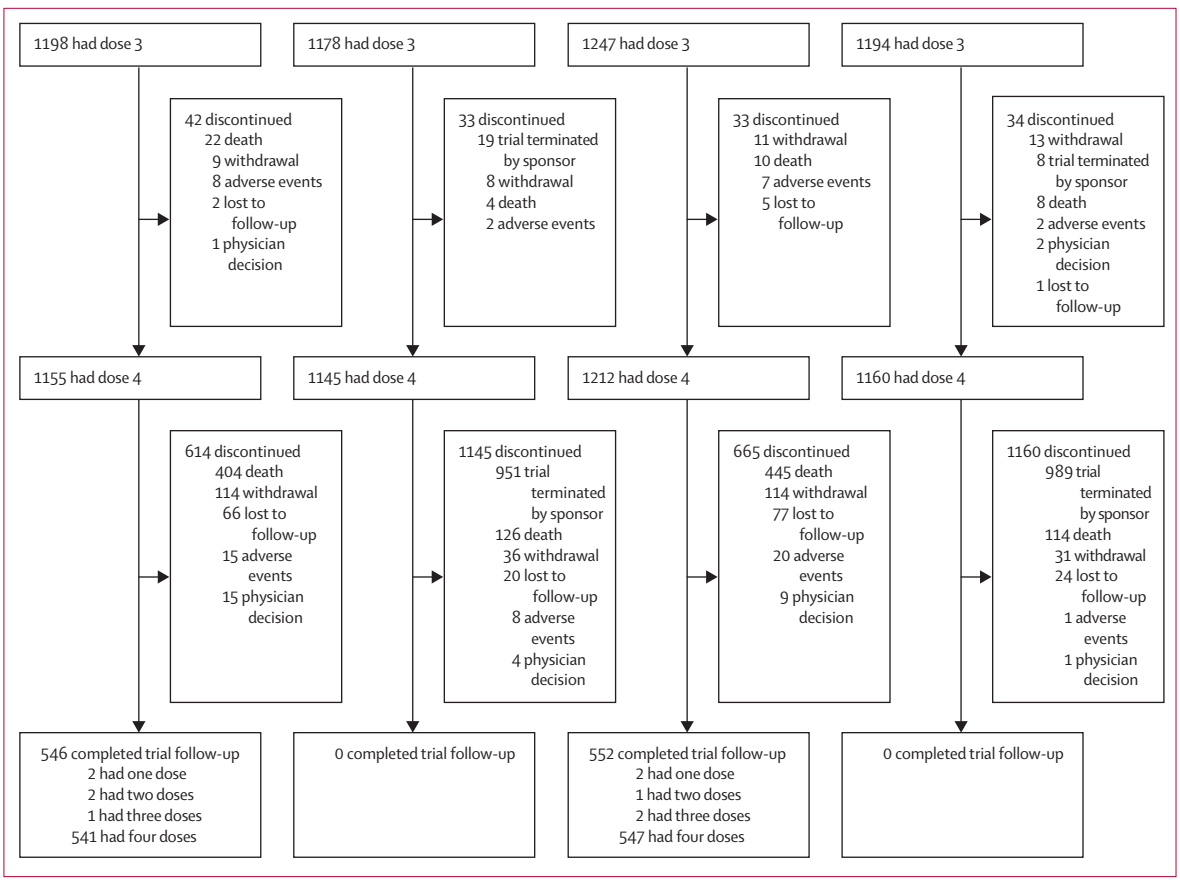


Figure 1: **Trial profile**
The safety population included 1322 patients with solid tumour malignancies and 1274 patients with haematological malignancies who received the vaccine, and 1346 patients with solid tumour malignancies and 1274 patients with haematological malignancies who received placebo. ITT=intention-to-treat. *19 patients from a single trial site were excluded because of Good Clinical Practice Compliance issues. †One patient was randomly assigned to inactivated zoster vaccine but not vaccinated; this patient did not have population recorded, and the patient is not included in any of the analyses.

old. To avoid the age effect from confounding the efficacy estimates, the population was stratified by age at 50 years.

The trial period in the primary analysis was the time interval from initial patient enrolment to the end of herpes zoster surveillance. Patients who did not develop herpes zoster were censored on the final day of herpes zoster surveillance. A Kaplan-Meier plot assessed the cumulative herpes zoster incidence over time. The incidence rate of herpes zoster in the VZV vaccine and placebo groups were compared by the non-parametric log-rank statistic without covariate adjustment.

All patients who received one or more doses of VZV vaccine or placebo and had follow-up data were included in the per-protocol population, used for the safety analyses. See the appendix (pp 5–6) for additional statistical procedures used for efficacy, safety, and immunogenicity analyses. We used SAS 9.4 software in all analyses. An unmasked data monitoring committee was used. This trial is registered with ClinicalTrials.gov, number NCT01254630, and the European Clinical Trials Database, number 2010-023156-89.

Role of the funding source
In collaboration with a scientific advisory committee (KMM, VAM, LHC, and AA), the trial was designed, executed, and analysed by some members (JD, BC, S-CS, ISFC, JP, SSK, ZP, and PWA) of the trial funder. All authors and the funder were responsible for data collection and data analysis. All authors had full access to the data and, in collaboration with the funder, were involved in data interpretation, writing, and approval of the manuscript, and were responsible for the decision to submit the manuscript for publication.

Results
Between June 27, 2011, and April 11, 2017, 5507 patients were assessed for eligibility, of whom 5286 were enrolled and randomly assigned to receive VZV vaccine inactivated by γ irradiation (n=2637) or placebo (n=2649; figure 1). Baseline characteristics of both groups were similar across treatment groups and patient populations, with a median age of 60 years (IQR 52–69) and a slight predominance of female participants (2810 [53·2%] of 5285; table 1). 1619 (62·9%) of 2573 patients with

	Patients with solid tumour malignancies		Patients with haematological malignancies	
	Inactivated VZV vaccine (n=1348)	Placebo (n=1364)	Inactivated VZV vaccine (n=1288)	Placebo (n=1285)
Age, years	57·6 (11·5)	57·7 (11·5)	61·0 (14·9)	61·4 (14·5)
<50 years	299 (22·2%)	320 (23·5%)	235 (18·2%)	223 (17·4%)
≥50 years	1049 (77·8%)	1044 (76·5%)	1053 (81·8%)	1062 (82·6%)
Sex				
Men	481 (35·7%)	472 (34·6%)	760 (59·0%)	762 (59·3%)
Women	867 (64·3%)	892 (65·4%)	528 (41·0%)	523 (40·7%)
Race				
White	1044 (77·4%)	1031 (75·6%)	976 (75·8%)	986 (76·7%)
Multiracial	144 (10·7%)	159 (11·7%)	157 (12·2%)	141 (11·0%)
Black or African American	86 (6·4%)	92 (6·7%)	41 (3·2%)	57 (4·4%)
Asian	55 (4·1%)	64 (4·7%)	110 (8·5%)	94 (7·3%)
Other or not reported	19 (1·4%)	18 (1·3%)	4 (0·3%)	7 (0·5%)
Ethnicity				
Not Hispanic or Latino	971 (72·0%)	979 (71·8%)	985 (76·5%)	979 (76·2%)
Hispanic or Latino	356 (26·4%)	366 (26·8%)	286 (22·2%)	290 (22·6%)
Unknown, not reported, or missing	21 (1·6%)	19 (1·4%)	17 (1·3%)	16 (1·2%)
Primary diagnosis*				
Breast cancers	499/1328 (37·6%)	496/1350 (36·7%)	0	0
Colon, colorectal, and rectal cancers	289/1328 (21·8%)	279/1350 (20·7%)	0	0
Lung cancers	152/1328 (11·4%)	146/1350 (10·8%)	0	0
Ovarian cancers	64/1328 (4·8%)	69/1350 (5·1%)	0	0
Chronic lymphocytic leukaemia	0	0	324/1277 (25·4%)	343/1275 (26·9%)
Plasma cell myelomas	0	0	199/1277 (15·6%)	197/1275 (15·5%)
Chronic myeloid leukaemias	0	0	154/1277 (12·1%)	152/1275 (11·9%)
Non-Hodgkin lymphomas	0	0	116/1277 (9·1%)	93/1275 (7·3%)
Other	324/1328 (24·4%)	360/1350 (26·7%)	484/1277 (37·9%)	490/1275 (38·4%)
Most frequent concomitant medications*†				
Anti-neoplastic agents	1292/1328 (97·3%)	1315/1350 (97·4%)	702/1277 (55·0%)	682/1275 (53·5%)
Anti-emetics and anti-nauseants	996/1328 (75·0%)	1021/1350 (75·6%)	316/1277 (24·7%)	329/1275 (25·8%)
Systemic corticosteroids	972/1328 (73·2%)	981/1350 (72·7%)	479/1277 (37·5%)	497/1275 (39·0%)
Drugs for acid-related disorders‡	803/1328 (60·5%)	815/1350 (60·4%)	567/1277 (44·4%)	530/1275 (41·6%)
Analgesics	737/1328 (55·5%)	754/1350 (55·9%)	785/1277 (61·5%)	755/1275 (59·2%)

Data are mean (SD), n (%), or n/N (%). VZV=varicella zoster virus. *Data are shown for the modified intention-to-treat population. †Medications taken by ≥50% of patients are shown; concomitant means drugs taken after any vaccination through to 28 days after the fourth dose. ‡Including histamine 2 receptor blockers and proton pump inhibitors.

Table 1: **Baseline characteristics**

haematological malignancies were in the the moderately to highly immunocompromised group.

2712 patients with solid tumour malignancies were randomly assigned to receive VZV vaccine inactivated by γ irradiation (n=1348) or placebo (n=1364). Among them, 2678 (98·7%) received at least one dose and were included in the modified intention-to-treat population (1328 in the VZV vaccine group and 1350 in the placebo group), 2668 (98·4%) received at least one dose and had follow-up data and were included in the per-protocol safety population (1322 in the VZV vaccine group and 1346 in the placebo group), and 2367 (87·3%) received all four doses (figure 1). The proportion of patients discontinuing treatment was the same in both groups (59·5%). The reasons for study discontinuation were similar among groups, with death being the most common reason, followed by elective patient withdrawal, loss to follow-up, adverse events, and physician decision (most frequently due to site closure; figure 1).

Patients with solid tumour malignancies who were included in the modified intention-to-treat population were followed up for a mean of 2·45 years (SD 1·52) after the final dose for the development of suspected herpes zoster. In these patients, there were 22 confirmed herpes zoster cases (6·7 per 1000 person-years) in the VZV vaccine group versus 61 (18·5 per 1000 person-years) in the placebo group, with an estimated vaccine efficacy of 63·6% (97·5% CI 36·4–79·1), which exceeded the prespecified statistical criterion for success. 11 (50%) of 22 herpes zoster cases in the VZV vaccine group and

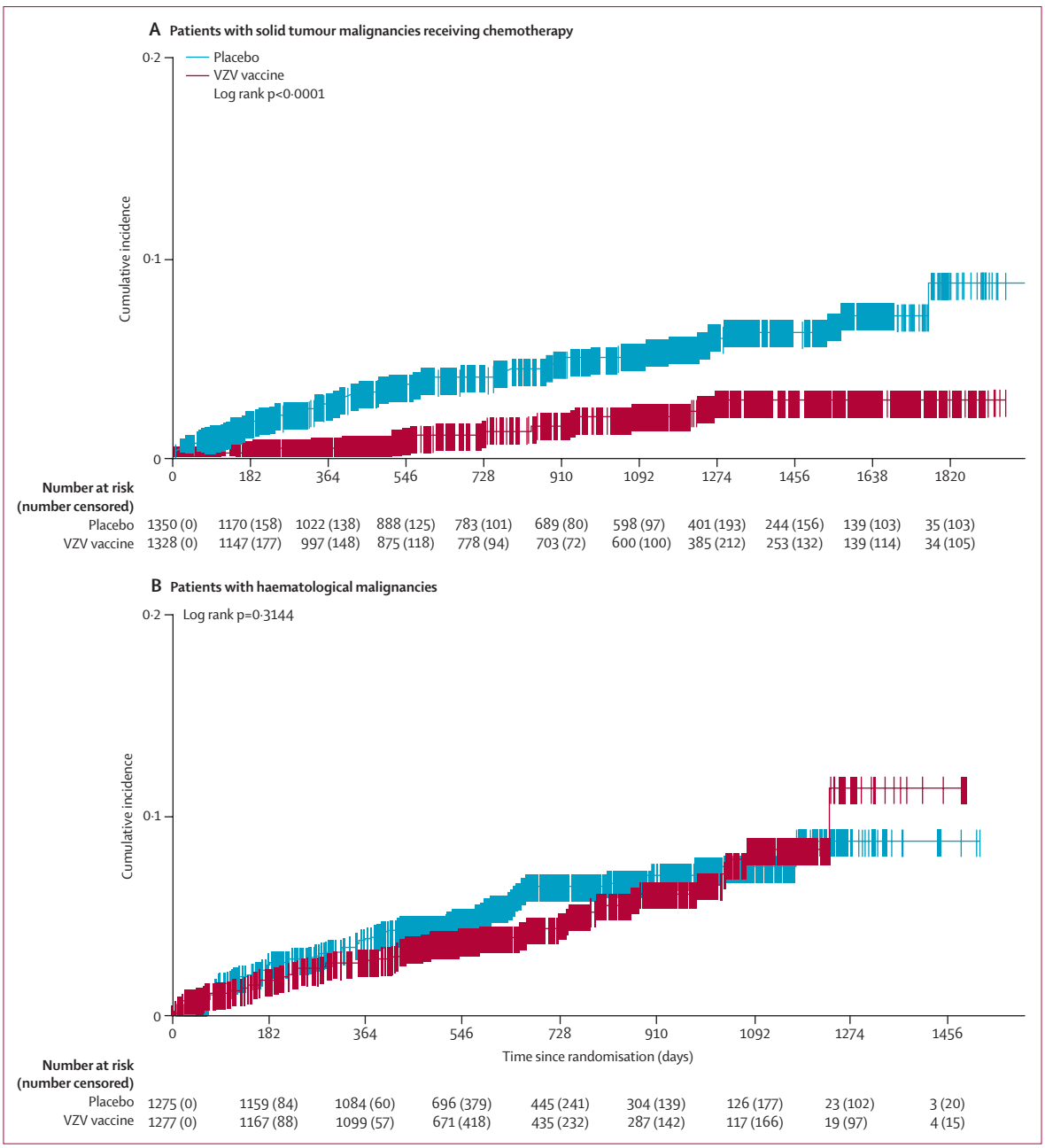


***Figure 2*: Kaplan-Meier plot showing cumulative incidence of herpes zoster cases**
VZV=varicella zoster virus.

52 (85%) of 61 herpes zoster cases in the placebo group were confirmed by PCR. In most cases for which PCR test results were missing, the patient had presented late after disease onset, when herpes zoster lesions had mostly healed, or samples had not been collected because skin vesicles were not present at the time of visit.

A Kaplan-Meier curve of vaccine efficacy confirmed the lower cumulative herpes zoster incidence over time in the inactivated VZV vaccine group versus the placebo group (figure 2A). The estimated vaccine efficacy against herpes zoster was 80·7% (95% CI 43·7 to 93·4) between 0 and 6 months after randomisation, 79·7% (7·3 to 95·6) between 6 and 12 months, and 43·8% (–4·0 to 69·5) beyond 12 months (appendix p 8). The VZV vaccine reduced the incidence of moderate to severe herpes zoster-associated pain compared with placebo (table 2). Vaccine efficacy for complications was 87·4% (95% CI –0·5 to 98·4) and vaccine efficacy for post-herpetic neuralgia was 74·6% (–127·5 to 97·2). Herpes zoster complications are described in detail in the appendix (p 9).

	Inactivated VZV vaccine (n=1328)			Placebo (n=1350)			Estimated vaccine efficacy
	n	Total follow-up time (person-years)	Observed incidence per 1000 person-years (CI)	n	Total follow-up time (person-years)	Observed incidence per 1000 person-years (CI)	
Primary efficacy endpoint*							
Confirmed herpes zoster	22	3266	6·7 (97·5% CI 4·2 to 10·2)	61	3305	18·5 (97·5% CI 14·1 to 23·7)	63·6% (97·5% CI 36·4 to 79·1)
Secondary efficacy endpoints*							
Moderate to severe herpes zoster-associated pain	7	3266	2·1 (95% CI 0·9 to 4·4)	31	3305	9·4 (95% CI 6·4 to 13·3)	77·1% (95% CI 48·0 to 89·9)
Herpes zoster complications	1	3266	0·3 (95% CI 0·01 to 1·7)	8	3305	2·4 (95% CI 1·1 to 4·8)	87·4% (95% CI −0·5 to 98·4)
Post-herpetic neuralgia	1	3266	0·3 (95% CI 0·01 to 1·7)	4	3305	1·2 (95% CI 0·3 to 3·1)	74·6% (95% CI −127·5 to 97·2)

Data are as specified. VZV=varicella zoster virus. *Per original protocol.

Table 2: **Efficacy endpoints in patients with solid tumour malignancies in the modified intention-to-treat population**

	Patients with solid tumour malignancies receiving chemotherapy			Patients with haematological malignancies		
	Inactivated zoster vaccine (n=1322)	Placebo (n=1346)	Risk difference versus placebo	Inactivated zoster vaccine (n=1274)	Placebo (n=1274)	Risk difference versus placebo
Patients with one or more adverse events	1086 (82·1%)	1077 (80·0%)	2·2% (−0·8 to 5·1)	1030 (80·8%)	911 (71·5%)	9·3% (6·0 to 12·5)
Systemic adverse events	1006 (76·1%)	1057 (78·5%)	−2·4% (−5·6 to 0·7)	902 (70·8%)	866 (68·0%)	2·7% (−0·9 to 6·3)
Vaccine-related adverse event	479 (36·2%)	190 (14·1%)	22·2% (19·1 to 25·4)	570 (44·7%)	216 (17·0%)	28·0% (24·5 to 31·4)
Vaccine-related injection site adverse event	448 (33·9%)	116 (8·6%)	25·4% (22·4 to 28·3)	512 (40·2%)	167 (13·1%)	27·2% (24·0 to 30·5)
Vaccine-related non-injection site adverse event	77 (5·8%)	88 (6·5%)	−0·7% (−2·5 to 1·2)	131 (10·3%)	72 (5·7%)	4·7% (2·6 to 6·8)
Serious adverse event	298 (22·5%)	283 (21·0%)	1·5% (−1·7 to 4·6)	203 (15·9%)	190 (14·9%)	1·0% (−1·8 to 3·8)
Serious vaccine-related adverse event	2 (0·2%)	0	0·2% (−0·1 to 0·5)	8 (0·6%)	3 (0·2%)	0·4% (−0·1 to 1·0)
Discontinued due to adverse event	29 (2·2%)	23 (1·7%)	0·5% (−0·6 to 1·6)	25 (2·0%)	12 (0·9%)	1·0% (0·1 to 2·0)
Death	123 (9·3%)	107 (7·9%)	1·3% (−0·8 to 3·5)	35 (2·7%)	34 (2·7%)	0·1% (−1·2 to 1·4)

Data are n (%) or % (95% CI).

Table 3: **Overall safety summary up until 28 days after the fourth vaccination dose**

A supportive analysis done in the per-protocol population to evaluate the confirmed incidence of herpes zoster and the vaccine efficacy against herpes zoster was consistent with the results from the primary efficacy analysis in the modified intention-to-treat population. In the per-protocol population, the observed incidence of herpes zoster was 6·6 per 1000 person-years for the VZV vaccine group and 16·0 per 1000 person-years for the placebo group, with an estimated vaccine efficacy of 59·1% (97·5% CI 24·7–77·8).

1923 (72·1%) of 2668 patients with solid tumour malignancies were followed up for 1 year or longer after the last vaccine dose for safety assessments (935 in the VZV vaccine group and 988 in the placebo group). For the primary safety endpoint of serious adverse events occurring up to 28 days after the fourth dose, there was no significant difference between the VZV vaccine and placebo groups (table 3). The incidence of systemic adverse events, vaccine-related (possibly or definitely related to the intervention with vaccine or placebo), non-injection site adverse events, serious vaccine-related adverse events, and discontinuation because of an adverse event was also similar between groups. Of the two patients in the VZV vaccine group who had a vaccine-related serious adverse event, one had thrombocytopenia and the other had palpitations. A higher proportion of patients had vaccine-related adverse events in the VZV vaccine group than in the placebo group due to the occurrence of more injection-site reactions with VZV vaccine than with placebo (table 3). Vaccine-related injection-site adverse events were generally mild in intensity.

There was no difference between groups in the incidence of death or serious adverse events resulting in death (table 3, appendix p 12). No patient with a solid tumour malignancy died because of a vaccine-related adverse event, and no patient with an adverse event suspected to be due to VZV had a PCR sample positive for the vaccine strain. The estimated mortality rate per 1000 person-years up until the end of the trial was similar

	Inactivated VZV vaccine (n=1277)			Placebo (n=1275)			Estimated vaccine efficacy (95% CI)
	n	Total follow-up time (person-years)	Observed incidence per 1000 person-years (95% CI)	n	Total follow-up time (person-years)	Observed incidence per 1000 person-years (95% CI)	
Confirmed herpes zoster	58	2212	26·2 (19·9 to 33·9)	70	2239	31·3 (24·4 to 40·0)	16·8% (–17·8 to 41·3)
Moderate-to-severe herpes zoster-associated pain	24	2212	10·9 (7·0 to 16·2)	43	2239	19·2 (13·9 to 25·9)	43·6% (7·1 to 65·8)
Herpes zoster complications	18	2212	8·1 (4·8 to 12·9)	21	2239	9·4 (5·8 to 14·3)	13·2% (–62·9 to 53·8)
Post-herpetic neuralgia	3	2212	1·4 (0·3 to 4·0)	14	2239	6·3 (3·4 to 10·5)	78·1% (23·7 to 93·7)

Data are as specified. VZV=varicella zoster virus.

Table 4: **Exploratory efficacy endpoints per protocol amendment in patients with haematological malignancies in the modified intention-to-treat population**

for the VZV vaccine (144·3) and placebo (144·4) groups (risk difference –0·05, 95% CI –18·32 to 18·22). Additional safety data for patients with solid tumour malignancies are provided in the appendix (pp 11–13).

In patients with solid tumour malignancies, the observed geometric mean fold rise values from baseline to 28–60 days after dose four in the VZV vaccine group was approximately two-fold higher than in the placebo group, by IFN-γ ELISPOT and glycoprotein ELISA (appendix p 17).

2573 patients with haematological malignancies were randomly assigned to VZV vaccine (n=1288) or placebo (n=1285). Among them, 2552 (99·2%) received at least one dose and were included in the modified intention-to-treat population (1277 in the VZV vaccine group and 1275 in the placebo group), 2548 (99·0%) received at least one dose and had follow-up data and were included in the per-protocol safety population (1274 each in the VZV vaccine group and placebo group), and 2305 patients (89·6%) received all four doses (figure 1).

All patients with haematological malignancies were discontinued from the study during follow-up, mostly because of the sponsor's decision to terminate treatment and enrolment into the population on the basis of the findings of an interim analysis (figure 1).

Patients with haematological malignancies included in the modified intention-to-treat population were followed up for a mean of 1·74 years (SD 0·86) post-vaccination for the development of suspected herpes zoster. The VZV vaccine did not reduce herpes zoster incidence compared with placebo in patients with haematological malignancies (table 4). A Kaplan-Meier curve confirmed a similar cumulative herpes zoster incidence over time for the VZV vaccine and placebo groups (figure 2B).

2161 (84·8%) of 2548 patients with haematological malignancies were followed up for 1 year or longer after the last vaccine dose for safety assessments (1075 in the VZV vaccine group and 1086 in the placebo group). There was no difference between groups in serious adverse events occurring up to 28 days after the fourth dose (table 3). Similar numbers of patients with haematological malignancies died in the placebo and VZV vaccine groups (table 3). One death due to a vaccine-related adverse event (varicella zoster pneumonia) occurred in the VZV vaccine group (appendix p 16). Blood samples from this patient were negative for the inactivated VZV vaccine strain and positive for the wildtype VZV strain by PCR. The estimated mortality rate per 1000 person-years up until the end of the trial was similar in the VZV vaccine group (69·9) and placebo group (62·8; risk difference 7·10, 95% CI –7·81 to 22·14). Vaccine-related serious adverse events occurred in eight patients in the VZV vaccine group (herpes zoster in two, chronic lymphocytic leukaemia in two, pneumonia in one, sepsis in one, varicella zoster pneumonia in one, and B-cell lymphoma in one) and in three patients in the placebo group (febrile neutropenia in one, rheumatoid arthritis in one, and herpes zoster in one; appendix p 16). No patient with an adverse event suspected to be due to VZV was found to be positive for the inactivated VZV vaccine strain. Additional safety data for patients with haematological malignancies are provided in the appendix (pp 14–16).

In patients with haematological malignancies, the observed geometric mean fold rise values from baseline to 28–60 days after dose four in the VZV vaccine group was approximately two-fold higher than in the placebo group, by IFN-γ ELISPOT (appendix p 17).

Discussion

The results of our phase 3 trial of a VZV vaccine inactivated by γ irradiation add to those from earlier trials of inactivated VZV vaccines in patients who were immunocompromised,[18–22] and provide evidence of inactivated VZV vaccine efficacy for prevention of herpes zoster in patients with solid tumour malignancies receiving chemotherapy. Patients with solid tumour malignancies who received inactivated VZV vaccine had a significantly lower herpes zoster incidence than did patients who received placebo, meeting the study's primary efficacy endpoint. The incidence of herpes zoster in the placebo group (18·5 of 1000 person-years) was similar to the incidence reported in observational studies of patients with solid tumours.[1,4] Estimated vaccine efficacy against herpes zoster was 63·6%. Although the

study was not designed to support precise estimation of efficacy by 6-month time periods, this analysis was provided to understand trends in the durability of vaccine efficacy against herpes zoster and showed that it was around 80% during the first year after vaccination, declining thereafter to about 40% after 1 year. This pattern of waning is similar to what has been seen for other vaccines, such as Zostavax. Vaccine efficacy studies should include assessments of vaccine efficacy by time period to determine the durability of efficacy.

The inactivated VZV vaccine was also efficacious in reducing the incidence of moderate to severe herpes zoster-associated pain, as reported by patients in a validated questionnaire. The vaccine efficacy estimates for herpes zoster complications and post-herpetic neuralgia had wider confidence intervals owing to the small number of events; however, fewer events occurred in the inactivated VZV vaccine group than in the placebo group. Exploratory immunogenicity analyses suggested that the vaccine-elicited protection against herpes zoster was associated with both cell-mediated and humoral immunity, consistent with previous findings.[20,23] Except for more injection-site reactions reported in the inactivated VZV vaccine group than in the placebo group, the frequency and type of adverse events were similar across treatment groups. Thus, the overall safety profile of inactivated VZV vaccine administered as four doses to patients with solid tumour malignancies receiving chemotherapy was favourable, consistent with other studies in the inactivated VZV vaccine clinical development programme.[18–23]

This trial was discontinued early for the haematological malignancies population because of statistical evidence of futility shown at the prespecified interim analysis. Although inactivated VZV vaccine did not reduce herpes zoster incidence in these patients compared with placebo, patients receiving inactivated VZV vaccine did not have more frequent or more severe cases of herpes zoster than did placebo recipients (data not shown). Immunogenicity analysis indicated that the inactivated VZV vaccine elicited cell-mediated immunity in patients with haematological malignancies, consistent with previous phase 1 findings.[20] However, the observed cell-mediated immune response did not corroborate with the poor clinical efficacy observed in the haematological malignancies group. This discrepancy underlines the importance of assessing both vaccine immunogenicity and efficacy, and not only limiting investigations to vaccine immunogenicity. The safety findings for the haematological malignancies population were generally acceptable, with none of the differences between groups considered clinically meaningful.

The finding that inactivated VZV vaccine reduced herpes zoster incidence in patients with solid tumour malignancies receiving chemotherapy, but not in patients with haematological malignancies, highlights the importance of large phase 3 efficacy trials as vaccine efficacy differed depending on the underlying immunocompromising condition. Of note, heat-inactivated VZV vaccine was immunogenic in patients with solid tumour malignancies receiving chemotherapy or haematological malignancies in a phase 1 trial, although the responses were lower in the haematological malignancies group than in the solid tumour malignancies group.[20]

Some limitations of this trial might be related to the types of analyses done. The primary efficacy endpoint was analysed with the Cox proportional hazards regression model, in which deaths are censored, thereby not accounting for death as a competing risk. Similarly, the Kaplan-Meier survival analysis might have overestimated the cumulative herpes zoster incidence over time in the presence of the competing risk of death. Another potential limitation of our trial is that not all herpes zoster cases were confirmed by VZV PCR testing from a skin lesion. In the population with solid tumour malignancies, 50% of herpes zoster cases in the inactivated VZV vaccine group and 15% of herpes zoster cases in the placebo group were confirmed by the clinical adjudication committee. Among cases with no PCR testing, the proportion of suspected herpes zoster cases determined not to be herpes zoster was similar among the inactivated VZV vaccine and placebo groups (45% [nine of 20] *vs* 59% [13 of 22]), suggesting that the clinical adjudication was probably accurate. The high proportion of patients with solid tumour malignancies who discontinued the study (60% in each treatment group) is another limitation. The most common reason for discontinuation in both groups was death (34% in the inactivated VZV vaccine group and 35% in the placebo group, corresponding to >50% of the discontinued patients), reflecting the underlying health status of the population. Finally, the early termination of the haematological malignancies population represents another limitation of this study.

In summary, our study shows the efficacy, immunogenicity, and safety of a γ-irradiation-inactivated VZV vaccine for herpes zoster prevention in patients with solid tumour malignancies receiving chemotherapy. Our investigational VZV vaccine not only triggered immune responses and substantially decreased herpes zoster incidence in these patients but also reduced the incidence of moderate to severe herpes zoster-associated pain. The vaccine was not efficacious, but appeared to be safe, in patients with haematological malignancies.

Contributors

KMM, VAM, LHC, AA, BC, ISFC, and PWA contributed to the design of the trial. JD, S-CS, and ZP did data and statistical analyses. All authors participated in data collection and analysis, data interpretation, writing, and approval of the manuscript.

Declaration of interests

KMM reports grants and personal fees from Merck & Co, Inc, Astellas Pharma, Chimerix, Scynexis, and GlaxoSmithKline, and grants from Shire and SAGE Therapeutics. VAM reports speaker's fees from Celgene, Genentech, Gilead, Pharmacyclics, and GlaxoSmithKline, and personal fees from Genentech and Pharmacyclics for adviser activities and from Celgene for being a member of the CLL Data Monitoring Committee. VAM is a member of the Scientific Advisory Committee for this vaccine (V212) for Merck & Co, Inc. LHC reports speaker's fees from

Merck & Co, Inc. AA did this work as part of an outside consulting agreement with Merck & Co, Inc. The work is not associated in any way with Stanford University (Stanford, CA, USA). AA reports personal fees from Merck & Co, Inc. SAM reports grants and speaker's fees from GlaxoSmithKline, Merck & Co, Inc, Sanofi Pasteur, and Pfizer, and consultancy fees from Pfizer, Merck & Co, Inc, and GlaxoSmithKline. JD, BC, S-CS, ISFC, JP, SSK, ZP, and PWA were employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, during the conduct of this trial, and might hold stock or options in the company.

Data sharing

The data sharing policy of Merck & Co, Inc, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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