Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab

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Background: The Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) assessed the long-term safety of omalizumab in a clinical practice setting as part of a phase IV US Food and Drug Administration postmarketing commitment.
Objective: We sought to evaluate long-term safety in omalizumab-treated and nonomalizumab-treated patients. Primary outcome measures focused on assessment of malignancies.
Methods: EXCELS was a prospective observational cohort study in patients (≥12 years of age) with moderate-to-severe allergic asthma. There were 2 cohorts: omalizumab (taking omalizumab at baseline) and nonomalizumab (no history of omalizumab treatment). Primary outcomes included all confirmed, incident, study-emergent primary malignancies (malignancies), including and excluding nonmelanoma skin cancer (NMSC); all malignancies were externally adjudicated.
Results: The omalizumab cohort had a higher proportion of patients with severe asthma compared with the nonomalizumab cohort (50.0% vs 23.0%). Median follow-up was approximately 5 years for both cohorts. Crude malignancy rates were similar in the omalizumab and nonomalizumab cohorts, with a rate ratio of 0.84 (95% CI, 0.62-1.13) for all malignancies and 0.98 (95% CI, 0.71-1.36) for all malignancies excluding NMSC. Kaplan-Meier plots of time to first confirmed study-emergent primary malignancy were similar for the 2 treatment cohorts. Cox proportional hazards modeling, adjusting for confounders and risk factors, resulted in a hazard ratio (omalizumab vs nonomalizumab) of 1.09 (95% CI, 0.87-1.38) for all malignancies and 1.15 (95% CI, 0.83-1.59) for all malignancies excluding NMSC.
Conclusion: Results from EXCELS suggest that omalizumab therapy is not associated with an increased risk of malignancy. (J Allergy Clin Immunol 2014;134:560-7.)

Key words: *Cancer, safety, anti-IgE, EXCELS, allergic asthma*

Omalizumab (Xolair; Novartis Pharmaceuticals, Basel, Switzerland), a humanized anti-IgE mAb, is indicated in the United States for treatment of adults and adolescents (≥12 years of age) with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids.[1] In controlled clinical studies conducted in patients receiving maintenance therapy with inhaled corticosteroids, long-acting β_2-agonists, or both, addition of omalizumab reduced asthma exacerbations, decreased inhaled corticosteroid and rescue medication use, and improved symptom control and quality of life.[2-7] However, a 2003 analysis of pooled clinical trial data in 2003 showed malignancies in 0.5% of omalizumab-treated patients compared with 0.2% of control subjects.[8] Consequently, the package insert for omalizumab includes malignancy as a potential risk.

The Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) was initiated as a postmarketing commitment to the US Food and Drug Administration to assess the long-term safety of omalizumab and provided the opportunity to evaluate malignancy rates in clinical practice. Interim data from EXCELS have been published previously.[9-12] EXCELS was completed in April 2012, and we report the final analysis of the incidence of malignancy.

METHODS

Patients

EXCELS enrolled patients between June 2004 and November 2006. Patients were recruited from a variety of practice settings, including managed care organizations, community physicians' practices, and academic centers. Patients were eligible for inclusion if they were 12 years of age or older with moderate-to-severe allergic physician-diagnosed asthma and had a positive skin test result or *in vitro* reactivity to a perennial aeroallergen (eg, RAST).

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Abbreviations used
AE: Adverse event
EXCELS: Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma
NMSC: Nonmelanoma skin cancer
PH: Proportional hazards
SAE: Serious adverse event
SEER: Surveillance Epidemiology and End Results

Patients had to be willing to participate for the 5-year study duration. Key exclusion criteria included the following: acute asthma exacerbation within 2 weeks before screening; acute flare of significant systemic disease (eg, infection, hematologic, renal, hepatic, cardiovascular, or gastrointestinal diseases) or recent hospitalization because of their disease within the previous 2 months; diagnosis of cystic fibrosis; and contraindication for omalizumab therapy. According to the original protocol (dated December 22, 2003), prior malignant neoplasm, a premalignant condition, or current investigation for possible cancer diagnosis were exclusion criteria. However, the study protocol was amended on September 23, 2005, to allow enrollment of patients with these characteristics.

Study design

EXCELS was a phase IV, prospective, observational cohort study of omalizumab-treated and nonomalizumab-treated patients enrolled from multiple US centers and followed for up to 5 years. The primary objective of the study was to compare the long-term clinical safety profile of patients treated with omalizumab with that of similar patients who had not been treated with omalizumab. Study primary outcome measures included all confirmed study-emergent primary malignancies (hereafter referred to as malignancies), all malignancies excluding nonmelanoma skin cancer (NMSC), and incidence of serious adverse events (SAEs; data outside the scope of the present publication).

Patients were screened consecutively as they presented at the clinic and were prescribed treatment as clinically indicated at the treating physician's discretion (without randomization). Eligible patients who consented entered study cohorts according to their use of omalizumab at enrollment. Patients already receiving omalizumab at enrollment or initiating omalizumab within 30 days after study entry were assigned to the omalizumab cohort. Patients were designated as "new starts" if they had initiated omalizumab within 7 days before or 30 days after enrollment into the omalizumab cohort to identify subjects who had recently started treatment. The nonomalizumab cohort enrolled patients who had not previously been treated with omalizumab and did not initiate omalizumab within 30 days after study entry. Cohort enrollment was in a 2:1 ratio (omalizumab/nonomalizumab), which was maintained at the site level by the enrolling investigators; maintenance of this ratio was approximate, depending on the types of patients presenting at the individual sites. During the study, a patient's ongoing treatment was determined by the treating physician. Consequently, some patients in the nonomalizumab cohort switched to omalizumab during the study, and some patients in the omalizumab cohort discontinued omalizumab during the study (see the "Patient disposition" section below).

After a baseline visit, study visits were scheduled every 6 months. Nonstudy medical care visits were dictated by the patient's requirements for medical reasons and routine asthma care. Routine clinic visits for patients treated with omalizumab were every 2 or 4 weeks for omalizumab injections. The protocol was approved by a local or central institutional review board at each study site.

Assessments

Study evaluations at baseline and during the study have been described previously.[9] Briefly, baseline evaluation included detailed assessment of asthma history, allergy and asthma medication use, and overall health. The treating physician determined asthma severity. All patients' data were collected with an electronic data-capture system.

Enrolled patients were classified into 1 of 3 baseline cancer status categories: *category A* patients were cancer free, with no personal cancer history and no premalignant conditions at baseline; *category B* patients had no active cancer at baseline but had a personal cancer history or precancerous condition; and *category C* patients had active cancer at baseline. A detailed cancer history was collected at the baseline visit for patients enrolled after the protocol amendment and gathered retrospectively for patients enrolled previously; patients who could not be accurately assigned were not categorized.

Identification, authentication, and attribution of primary malignancy events

Specific questions relating to safety, such as SAEs and malignancy events, were queried at all study visits; malignant neoplasms were reported as they were detected. Search methods to identify all reported malignancy adverse events (AEs) included review of all events indicated by the study centers as serious or nonserious malignancies, all events identified by using the standardized Medical Dictionary for Regulatory Activities query search for malignancy preferred terms, and any additional events that could potentially be malignant conditions. All potential malignancies were reviewed and adjudicated by external independent oncologists to confirm them as true malignancies and distinguish primary malignant conditions from metastases, progression, or recurrence of a previously reported malignancy. All malignancy AEs reported for patients of the omalizumab cohort were attributed to the omalizumab cohort, regardless of whether omalizumab had been discontinued. Thus, person-time at risk for the omalizumab cohort continued to accrue after discontinuation of omalizumab. For patients in the nonomalizumab cohort who initiated omalizumab during the study, only study-emergent malignancy AEs with onset dates before the patient began omalizumab were counted as nonomalizumab malignancies, and consistent with this accounting, person-time at risk for these malignancies ceased to accrue at the time of switching to omalizumab. Study-emergent malignancy events reported for patients initially assigned to the nonomalizumab cohort with onset dates after the start of omalizumab treatment were summarized separately.

Statistical analysis

Analyses in this observational study focused on descriptive statistics and estimates of treatment effects with corresponding CIs, rather than hypothesis testing. No adjustments were made to estimates or confidence levels to account for multiple comparisons. Statistical analyses were performed with SAS statistical software (version 9.2; SAS Institute, Cary, NC). The primary analysis of malignancy risk modeled the time to first confirmed study-emergent primary malignancy by using the Cox proportional hazards (PH) model and was based on all patients enrolled into the omalizumab and nonomalizumab cohorts. The time to first primary malignancy was defined as the number of months from day 0 (defined as the date of the study visit at which a patient's final baseline evaluations were completed) to the date of onset of symptoms for the first confirmed primary malignancy (or next primary malignancy in patients who entered the study with a pre-existing malignancy). If a patient died, was lost to follow-up, discontinued from the study, initiated omalizumab after being enrolled in the nonomalizumab cohort, or completed the study before experiencing a malignancy, then that patient's follow-up time was censored at the earliest of these dates. Per the prespecified analysis, the Cox PH model was stratified by baseline cancer status (category A, B, or C) and adjusted for baseline risk covariates: treatment cohort (omalizumab or nonomalizumab), age, race (white or nonwhite), sex, smoking history (current, former, or never), family history of cancer (yes, no, or unknown), investigator-assessed asthma severity (moderate or severe), and body mass index at baseline (<30 kg/m^2 or ≥ 30 kg/m^2). The time to first confirmed study-emergent primary malignancy was also summarized by treatment cohort by using Kaplan-Meier estimates.

Overall incidence rates for malignancies (and malignancies excluding NMSC) per 1000 person-years of observation time were computed (from

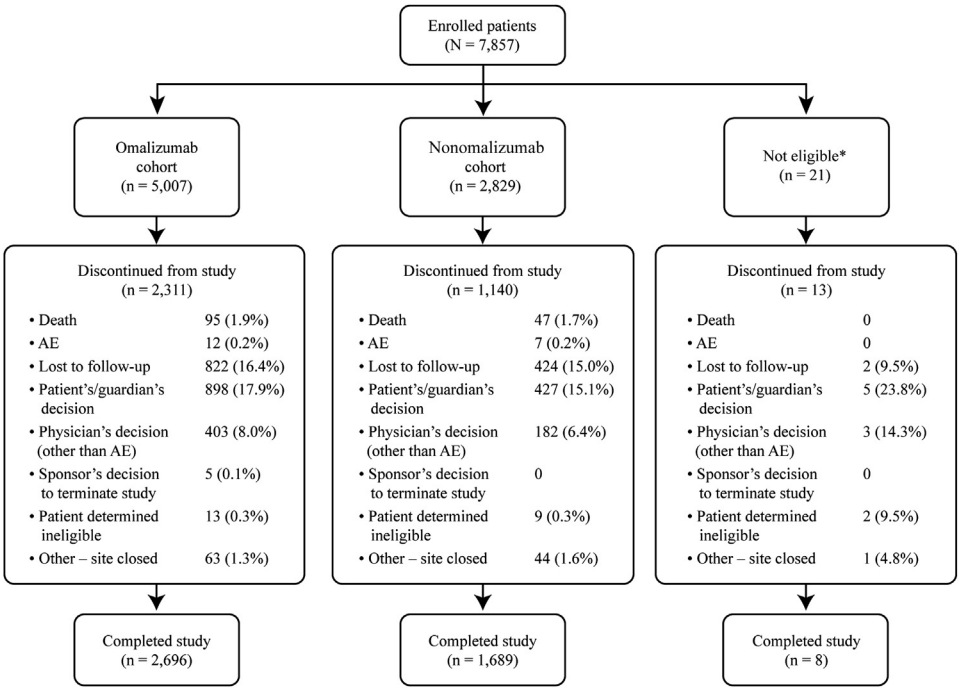

FIG 1. Patient disposition. *Patients with missing omalizumab treatment information at baseline or who were previously treated with omalizumab but were not receiving omalizumab at the time of enrollment.

enrollment through study completion or discontinuation) by treatment cohort and reported with exact 95% CIs. The ratios and differences in malignancy incidence rates between the omalizumab and nonomalizumab cohorts were computed and reported with 95% CIs calculated by using a bias-corrected bootstrap procedure.

Observed rates for individual cancer types (except NMSC, which is not captured in the Surveillance Epidemiology and End Results [SEER] database) were compared with the number of cases that would be expected if the age- and sex-specific incidence rates recorded in the SEER database were applied to the age and sex distribution in EXCELS. Standardized morbidity ratios were calculated.[13] Because of small stratum sizes, separate analyses of specific age subgroups were not performed (eg, pediatric subjects).

Sensitivity analyses. Potential sources of bias in the malignancy analysis included recall bias, malignancy detection bias arising from the open-label nature of the study and the more frequent medical office visits in the omalizumab group, selection/survivor bias arising from inclusion of patients receiving omalizumab before enrollment, and the confounding of treatment comparisons caused by cohort differences in baseline characteristics. These potential biases were evaluated by using various sensitivity and exploratory analyses. Propensity score estimates were calculated for patients by using logistic regression to model the probability of receiving omalizumab as a function of potentially confounding baseline variables in an exploratory analysis of malignancy risk to reduce potential confounding. Time to first study-emergent confirmed primary malignancy was modeled by using the Cox PH model, including treatment cohort (omalizumab treated or nonomalizumab treated) and the propensity score as covariates in the model. Omalizumab-treated patients were seen every 2 or 4 weeks (for drug administration) rather than every 6 months for the nonomalizumab-treated patients. Thus, patients receiving omalizumab might have more consistently reported malignancy events because they had more frequent medical office visits. Furthermore, patients and investigators might have been more vigilant in screening for and identifying cancer events in patients receiving omalizumab because they had more frequent visits. The potential for recall bias was evaluated for skin cancers, asthma exacerbations, and selected other events by examining the distribution of onset dates relative to reporting dates. The frequencies of various cancer-screening procedures were summarized by treatment cohort over time to evaluate the potential for malignancy detection bias. Furthermore, in anticipation of the potential for detection bias in skin cancers, the incidence and risk of all malignancies excluding NMSC were analyzed in a parallel fashion to the incidence and risk of all malignancies (including NMSC; primary outcome). The incidence of malignancy in patients in the omalizumab cohort who were considered omalizumab naive (ie, "new starts") was compared with that of patients in the nonomalizumab cohort to address the potential for selection/survivor bias. Censoring patterns within the 2 treatment cohorts were examined to evaluate the possibility of informative censoring (ie, biased censoring related to the risk of malignancy or SAEs). Given the long duration of the study, it was anticipated that time to malignancy outcomes would be censored in a sizeable number of patients because of premature discontinuation from the study or change in asthma treatment before completing the 5-year follow-up. The potential for informative censoring was therefore evaluated by monitoring the frequency and reasons for study discontinuation and censoring.

Subgroup and exploratory analyses. A subgroup analysis of malignancies (all malignancies and excluding NMSC) according to cancer status at baseline was prespecified in the study protocol, as was an exploratory analysis conducted for the omalizumab-treated cohort based on total time on omalizumab, including exposure before and during the study.

RESULTS

Patient enrollment

A total of 7857 patients were enrolled in the study from 445 sites (omalizumab cohort, n = 5007; nonomalizumab cohort, n = 2829; initially enrolled but ineligible, n = 21; Fig 1). The small group of initially enrolled patients (n = 21) did not meet the eligibility criteria for enrollment into EXCELS because they had missing omalizumab treatment information at baseline or were previously treated with omalizumab but were not receiving omalizumab at the time of enrollment. The baseline data for these patients were summarized separately as the not eligible group (data not shown), and these patients were not included in the analyses of safety outcomes. A total of 4398 (56.0%) patients were enrolled before and 3459 (44.0%) were enrolled after the protocol amendment, allowing inclusion of patients at risk of/with a history of malignancy.

Patient disposition

More than half of the enrolled population (55.9%) completed the study (Fig 1). In the omalizumab cohort 1622 (32.4%) patients stopped omalizumab treatment for at least 6 months during the study: primary reasons included therapy expense/out-of-pocket costs (10.5%), lack of response (5.5%), and other reasons (10.2%), including issues relating to insurance coverage, physician's recommendation, and/or patient's decision to discontinue. In the nonomalizumab cohort 275 (9.7%) patients started omalizumab treatment during the study. Among all patients in the nonomalizumab cohort, the most frequent reasons for starting omalizumab therapy were as follows: unresponsive to current therapy (6.2%) and interest in reducing other asthma medications (0.8%).

Omalizumab treatment and follow-up

In the final data set, follow-up was 18,426 person-years in the omalizumab cohort and 10,844 person-years in the nonomalizumab cohort (approximately 9,963 person-years before omalizumab exposure and approximately 882 person-years after omalizumab initiation). Median follow-up was approximately 5 years for both cohorts. The mean prestudy duration of omalizumab treatment for the 5,007 patients in the omalizumab cohort was 7.9 months (SD, 7.6 months). The majority of these patients (4,418 [88.3%]) were considered established users of omalizumab at the time of study enrollment; 587 (11.7%) of the omalizumab cohort patients were classified as "new starts" and represent an omalizumab-naive population. The median duration of on-study omalizumab treatment for the omalizumab cohort was 36.6 months (range, 0-73). The mean total treatment duration, including treatment before study enrollment and on study, was 43.1 months (SD, 24.8 months). Approximately 70% of patients in this cohort received omalizumab for 2 or more years. The median duration of omalizumab treatment for the 275 patients in the nonomalizumab cohort who started omalizumab during the study was 24.4 months (range, 0-60 months).

TABLE I. Patients' baseline characteristics

	Omalizumab cohort (n = 5007)	Nonomalizumab cohort (n = 2829)
Mean (SD) age (y)	44 (17)	46 (17)
Female sex, no. (%)	3199 (63.9)	1880 (66.5)
Mean (SD) BMI (kg/m^2)	31 (11.9)	31 (12.9)
Race: white, no. (%)	3949 (78.9)	2322 (82.2)
Smoking history, no. (%)		
Current	245 (4.9)	159 (5.6)
Former	1477 (29.5)	826 (29.2)
Baseline cancer status, no. (%)		
Cancer-free and no previous cancer history (category A)	4511 (90.1)	2521 (89.1)
No active cancer but cancer history (category B)	432 (8.6)	276 (9.8)
Active cancer (category C)	35 (0.7)	19 (0.7)
Unclassified*	29 (0.6)	13 (0.5)
Physician-assessed asthma severity,† no. (%)		
Moderate	2519 (50.4)	2185 (77.4)
Severe	2482 (49.6)	637 (22.6)
Baseline IgE level (IU/mL),‡ median	202.0	108.0
Intubation caused by asthma,§ no. (%)	419 (8.4)	128 (4.5)
Daily use of asthma controller medications,‖ no. (%)	4172 (83.5)	2066 (73.3)
Daily use of asthma quick-relief medications,‖ no. (%)	1120 (22.4)	420 (14.9)

Note: The first protocol amendment removed exclusion of patients with active cancer or cancer history.
BMI, Body mass index.
*Missing data for 1 or more variables.
†Omalizumab, n = 5001; nonomalizumab, n = 2822.
‡For omalizumab-treated patients: level reported at the time of initial omalizumab dosing, n = 4998; for nonomalizumab-treated patients: level reported at the time of the baseline visit, n = 2782.
§Omalizumab, n = 4993; nonomalizumab, n = 2825.
‖Omalizumab, n = 4999; nonomalizumab, n = 2818.

Patients' characteristics at baseline

Patients were predominantly white, female, nonsmoking, and cancer free with no previous cancer history (Table I). However, the omalizumab cohort had higher baseline IgE levels, and a higher proportion of patients were classified as having severe asthma, higher use of daily asthma controller and quick-relief medications, and a higher likelihood of having been intubated compared with the nonomalizumab cohort.

Confirmed primary study-emergent malignancy AEs

A total of 625 potential malignancy events were identified. Of these, 38 events were not submitted for external adjudication based on an internal clinical review, which determined that 28 represented procedures that are often performed to diagnose or treat a malignant condition (eg, hysterectomy) but were not malignancies and 10 represented an obvious benign condition (eg, uterine fibroid) or worsening/recurrence of a previously reported malignancy. Of the 587 events submitted for external adjudication, 80 events were not assessed to be primary malignancies, and 10 events were excluded because they were not study emergent (7 events) or were reported for patients in the not eligible group (3 events). The remaining 497 malignancy AEs in 354 patients were adjudicated as confirmed primary study-emergent malignancies (Fig 2). These events occurred in 220 patients (295 malignancies) in the omalizumab cohort and 126 patients (190 malignancies) in the nonomalizumab cohort. A further 12 malignancies occurred in 8 patients in the nonomalizumab cohort after omalizumab treatment was initiated. The most common malignancy AEs reported in each cohort were skin cancer (nonmelanoma), followed by breast cancer, prostate cancer, colorectal cancer, melanoma, and lung cancer. Few meaningful differences were noted between observed frequencies of individual cancer types and expected frequencies based on SEER data,[13] especially when the precision of each rate was taken into account (see Table E1 in this article's Online Repository at www.jacionline.org).

Crude rates of confirmed study-emergent primary malignancies

Crude rates of malignancies (per 1000 person-years) were computed for each cohort for all malignancies and all malignancies excluding NMSC (Table II). Crude rates of malignancies were 16.0 and 19.1 per 1000 patient-years in the omalizumab and

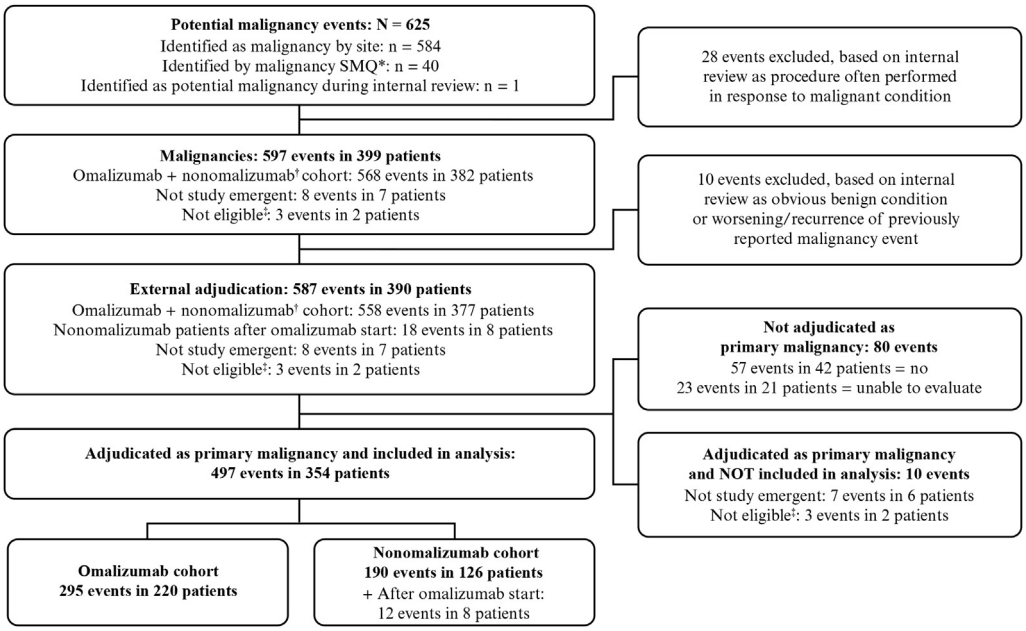

FIG 2. Assessment of potential malignancy events. *Events identified by using the standardized Medical Dictionary for Regulatory Activities query *(SMQ)*. †Data are for patients in the nonomalizumab cohort before initiation of omalizumab treatment. ‡Patients with missing omalizumab treatment information at baseline or who were previously treated with omalizumab but were not receiving omalizumab at the time of enrollment.

TABLE II. Study-emergent primary malignancy AE crude rates in enrolled patients

	Omalizumab cohort (n = 5007)	Nonomalizumab* cohort (n = 2829)	Crude differences in rates (95% CI)	Crude ratio of rates
Person-years at risk for any malignancy	18,425.5	9,962.6		
No. of malignancy events† (any type)	295	190		
Malignancy rate‡ (any type [95% CI])	16.0 (14.2 to 17.9)	19.1 (16.5 to 22.0)	−3.06 (−9.19 to 2.03)	0.84 (0.62 to 1.13)
No. of malignancies† (excluding NMSC events)	114	63		
Malignancy rate‡ (excluding NMSC [95% CI])	6.2 (5.1 to 7.4)	6.3 (4.9 to 8.1)	−0.14 (−2.23 to 1.80)	0.98 (0.71 to 1.36)

*All nonomalizumab-treated patients before any treatment with omalizumab.
†Allows for multiple events per patient.
‡All rates and their differences are expressed as per 1000 patient-years.

nonomalizumab cohorts, respectively. Crude rates of malignancies excluding NMSC were 6.2 and 6.3 per 1000 person-years in the omalizumab and nonomalizumab cohorts, respectively.

Time to first study-emergent confirmed primary malignancy

Kaplan-Meier plots of time to first confirmed study-emergent primary malignancy (Fig 3) and primary malignancy excluding NMSC (Fig 4) appeared similar for the omalizumab and nonomalizumab cohorts. Results of the analyses of time to first study-emergent confirmed primary malignancy based on the Cox PH model stratified by baseline cancer status and including treatment cohort and other cancer risk factors as covariates in the model are summarized in Table III. The hazard ratio comparing the risks of malignancy for the omalizumab cohort versus the nonomalizumab cohort was 1.09 (95% CI, 0.87-1.38). Similar results were obtained when time to first study-emergent confirmed primary malignancy (excluding NMSC) was modeled (1.15; 95% CI, 0.83-1.59).

Nonmalignant SAEs

Overall, 1263 (25.2%) patients in the omalizumab cohort and 571 (20.2%) patients in the nonomalizumab cohort reported having 1 or more study-emergent SAE(s) (excluding malignancy AEs). The system organ classes most commonly affected were as follows: respiratory, thoracic, and mediastinal disorders; infections and infestations; and cardiac disorders. The frequency of study-emergent SAEs by system organ class occurring in patients at a frequency of 1% or greater in either cohort is provided in Fig E1 in this article's Online Repository at www.jacionline.org.

Exploratory and subgroup analyses

Propensity scores were used to reduce potential confounding by adjusting for the probability of receiving omalizumab. The hazard ratios corresponding to the treatment cohort covariate (omalizumab vs nonomalizumab) from Cox PH models with propensity score quintiles as covariates were consistent with the results from the primary analyses (see Table E2 in this article's Online Repository at www.jacionline.org). A Cox PH model

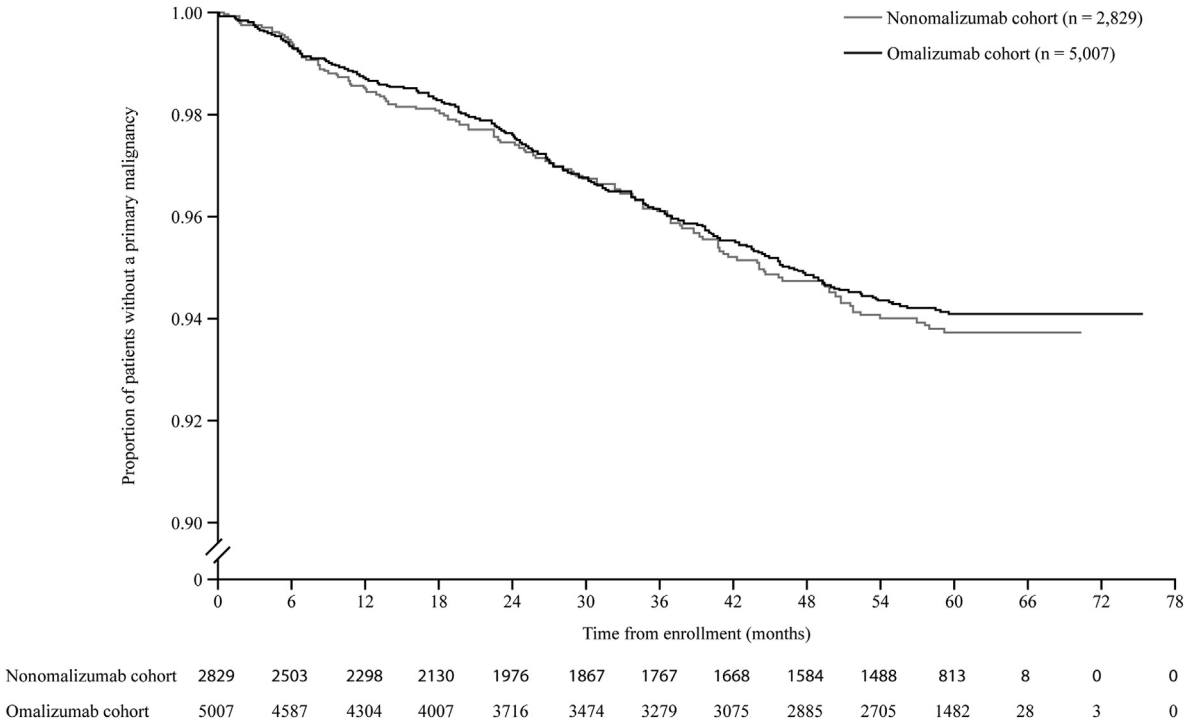

FIG 3. Kaplan-Meier plots of time to first confirmed study-emergent primary malignancy (all primary malignancies). The *vertical axis* is magnified to enhance visualization of curves.

adjusting for propensity scores as a continuous variable yielded very similar results (data not shown).

In general, the omalizumab and nonomalizumab cohorts reported similar cancer-screening rates across study visits. The crude rates of malignancies (per 1000 person-years) for the omalizumab "new starts" were 16.3 (95% CI, 11.1-23.0) for all malignancies and 6.6 (95% CI, 3.5-11.3) for all malignancies excluding NMSC and are consistent with the crude rates calculated for the overall omalizumab cohort. Proportions of patients with censored observations, distribution of reasons for censoring, and mean time to censoring were similar between cohorts.

Among patients with no active cancer at baseline but with a personal cancer history or premalignant condition (category B, n = 708), crude malignancy rates were 55.4 (95% CI, 44.92-67.58) and 63.2 (95% CI, 49.2-80.03) per 1000 patient-years in the omalizumab and nonomalizumab cohorts, respectively. Patients with active cancer at baseline (category C, n = 54) had crude malignancy rates of 89.7 (95% CI, 46.33-156.61) and 206.7 (95% CI, 115.67-340.88) per 1000 patient-years in the omalizumab and nonomalizumab cohorts, respectively. The majority of patients in both cohorts were cancer free at baseline (category A, n = 7032) and had crude malignancy rates of 11.23 (95% CI, 9.67-12.97) and 12.07 (95% CI, 9.88-14.60) in the omalizumab and nonomalizumab cohorts, respectively.

Kaplan-Meier estimates of time to first malignancy were similar for patients in the omalizumab cohort stratified by omalizumab exposure before enrollment: omalizumab "new starts" (n = 587); greater than 7 days to 1 year of omalizumab before enrollment (n = 3220); and greater than 1 year of omalizumab before enrollment (n = 1199; see Fig E2 in this article's Online Repository at www.jacionline.org).

DISCUSSION

The clinical benefit of omalizumab has been established in several large clinical trials.[2-6,14,15] However, concern regarding a potential association with malignancy risk has led to a need to evaluate further the long-term safety of omalizumab. EXCELS is the first study to evaluate the long-term safety of omalizumab in a large population of patients with moderate-to-severe allergic asthma in a real-world setting.

EXCELS had a median follow-up of approximately 5 years for both the omalizumab and nonomalizumab cohorts and included patients at high risk of cancers (smokers and family history of cancer) and patients with a history of malignancy. Analyses of time to first primary malignancy adjusted for potential confounders also demonstrated similar risk between the 2 cohorts. These results suggest that omalizumab is not associated with an increased risk of malignancy, a conclusion also supported by the results of the sensitivity analyses. In addition, although patient numbers in subgroup analyses of subjects with a personal history of cancer/premalignant condition and patients with active cancer at baseline were small, the results suggest that omalizumab is not associated with a risk of malignancy progression. An exploratory analysis of cumulative omalizumab exposure on malignancy risk showed no meaningfully increased risk of malignancy.

Reported malignancies were predominantly solid tumors, with no unexpected histologic patterns observed. The most common cancers in both cohorts were skin, breast, and prostate cancer. On the basis of SEER data, both the overall frequency and the frequency of individual cancer types observed in EXCELS are consistent with expectations for the general population. The results of EXCELS are also consistent with a recent analysis of pooled data from 67 phase I to phase IV clinical trials that reported no association between omalizumab and malignancy

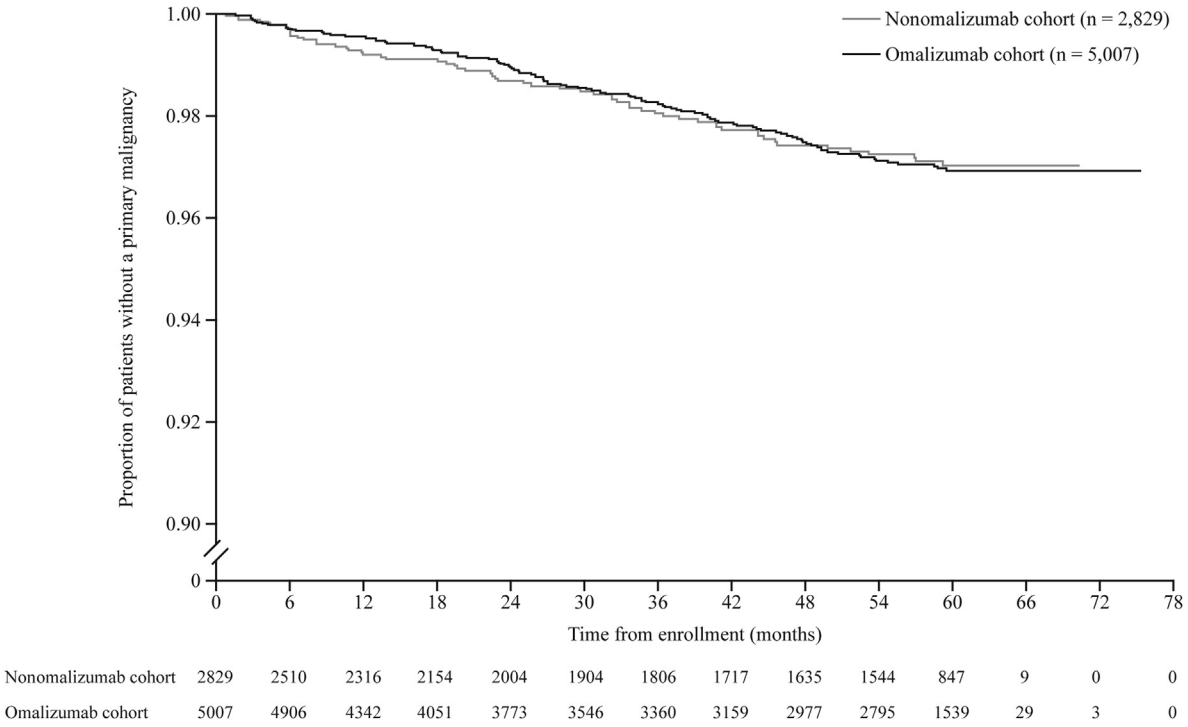

FIG 4. Kaplan-Meier plots of time to first confirmed study-emergent primary malignancy (all primary malignancies excluding NMSC). The *vertical axis* is magnified to enhance visualization of curves.

TABLE III. Cox PH model* of time to first confirmed study-emergent primary malignancy

	Parameter estimate	SE	HR (95% CI)
Any malignancy			
Treatment (omalizumab vs nonomalizumab)	0.088	0.118	1.09 (0.87-1.38)
Malignancies excluding NMSC			
Treatment (omalizumab vs nonomalizumab)	0.137	0.168	1.15 (0.83-1.59)

HR, Hazard ratio.
*Adjusted for age, race, sex, smoking history, family cancer history, asthma severity, and body mass index stratified by baseline cancer status.

risk and used a much larger data set (11,459 unique patients) than the earlier 2003 pooled analysis.[8,16] However, most of the studies included in this pooled analysis had a short duration of follow-up, and the effect of longer-term omalizumab therapy could not be fully assessed.[16] Although EXCELS was large and patients were followed for up to 5 years, the study size and follow-up time were insufficient to detect a meaningful increase in rates for individual cancer types (as opposed to the overall malignancy rates this study was designed to detect). In addition, follow-up was insufficient to assess slow-growing malignancies associated with a longer latency period.

Potential confounding in EXCELS was addressed by Cox PH analyses stratified by baseline cancer status and adjusted for patients' characteristics. These analyses provided similar results to the unadjusted analysis, implying a lack of any important confounding. Multiple exploratory and sensitivity analyses evaluated potential sources of bias in the analysis of malignancy. The consistency of malignancy rates between omalizumab "new starts" and the nonomalizumab cohort in the primary analysis (rate ratio, 0.85; 95% CI, 0.49-1.36) provides evidence against a selection bias caused by the inclusion of patients started on omalizumab before enrollment ("established users"). The comparability of the cohorts with respect to the on-study surveillance for malignancy, along with the similarity between cohorts with respect to malignancy rates (including and excluding NMSC), provides reassurance against meaningful detection bias. In addition, similarities between cohorts regarding proportions of patients with censored observations, distribution of reasons for censoring, and the mean time to censoring provided no clear indication of informative censoring.

In conclusion, the results from EXCELS suggest that omalizumab is not associated with an increased risk of malignancy. The results from multiple exploratory and sensitivity analyses, expected rates in the general population, and limited evidence of biologic plausibility[17-22] support this conclusion.

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Clinical implications: This study reports prospective clinical practice data indicating that omalizumab therapy is not associated with an increased risk of malignancy.

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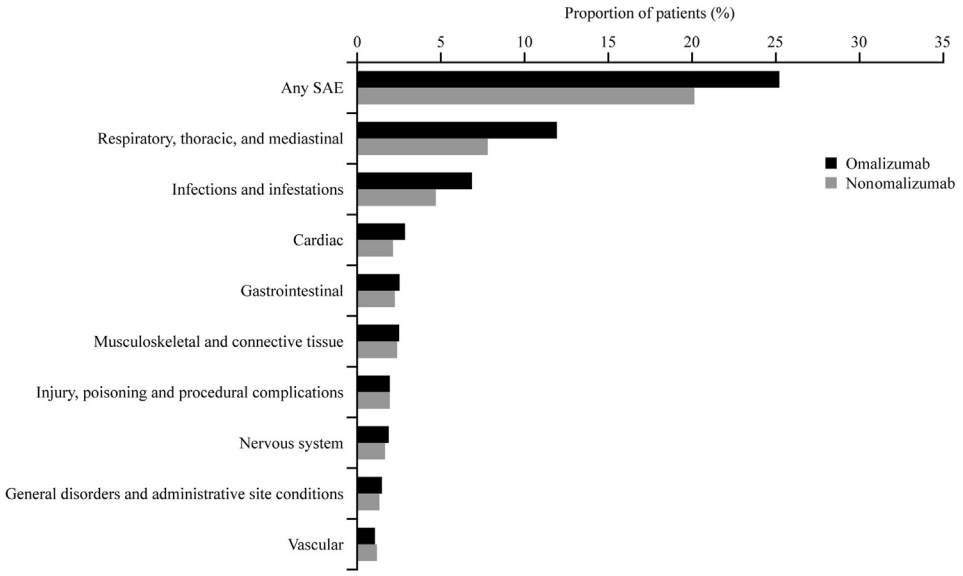
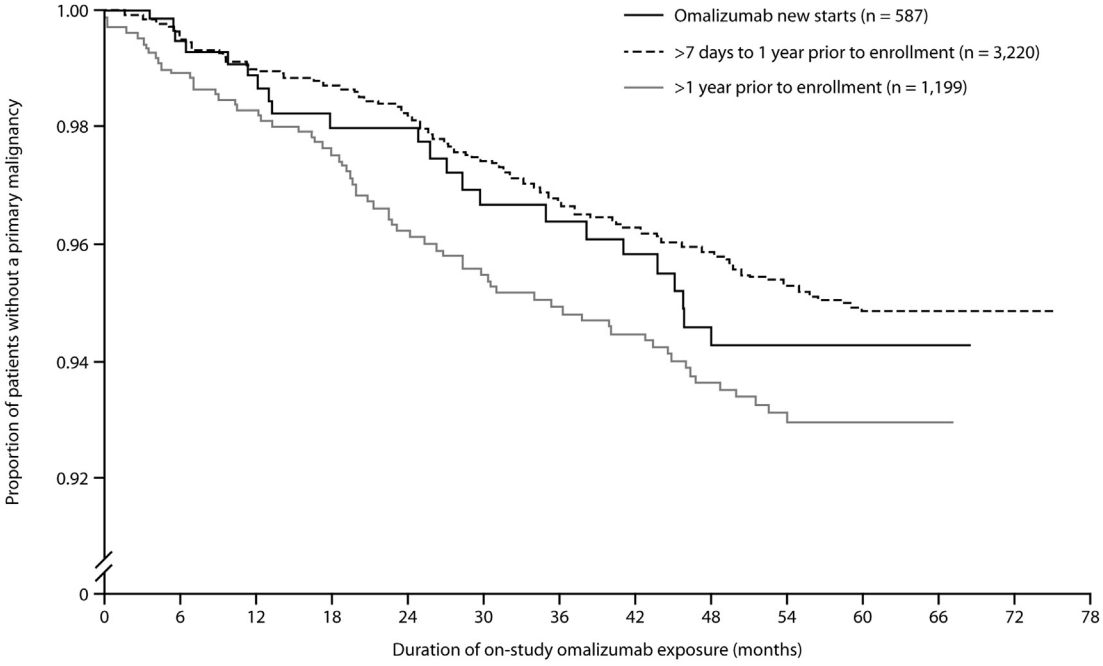


FIG E1. Frequency of study-emergent SAEs by system organ class occurring in patients at a frequency of 1% or greater in the omalizumab and nonomalizumab cohorts.



Number at risk														
New starts	587	517	466	432	396	358	338	321	302	281	149	4	0	0
>7 days to 1 year	3,220	2,943	2,758	2,563	2,373	2,219	2,094	1,954	1,825	1,710	951	21	3	0
>1 year	1,199	1,122	1,073	1,007	940	893	842	800	755	713	382	3	0	0

FIG E2. Kaplan-Meier estimates of time to first confirmed study-emergent primary malignancy AE by duration of omalizumab exposure before enrollment in all enrolled patients in the omalizumab cohort. The *vertical axis* is magnified to enhance visualization of the curves.

TABLE E1. Standardized morbidity ratios in reference to the SEER database* for selected malignancies with an overall frequency of greater than 7

	Omalizumab cohort (n = 5007)				Nonomalizumab cohort (n = 2829)			
	No. of malignancy events				No. of malignancy events			
Tumor type	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
All malignancies (excluding NMSC)	114	125.4	0.91	0.75-1.09	63	76.8	0.82	0.64-1.04
Breast cancer	29	25.4	1.14	0.78-1.62	13	15.5	0.84	0.47-1.39
Prostate cancer	17	16.0	1.06	0.64-1.66	5	9.2	0.54	0.21-1.19
Colorectal cancer	14	11.5	1.21	0.70-1.98	3	7.2	0.41	0.11-1.11
Melanoma	8	5.4	1.47	0.69-2.78	5	3.2	1.58	0.60-3.46
Lung cancer	6	16.1	0.37	0.15-0.77	7	10.5	0.66	0.30-1.31
Thyroid cancer	7	3.7	1.91	0.85-3.76	1	2.0	0.49	0.04-2.30

SMR, Standardized morbidity ratio.

*SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub, Vintage 2009 Pops (2000–2009) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission.

TABLE E2. Cox PH model of time to first confirmed study-emergent primary malignancy adjusted for propensity score quintile and stratified by baseline cancer status

	Parameter estimate	SE	HR (95% CI)
Any malignancy			
Treatment (omalizumab vs nonomalizumab)	0.132	0.128	1.14 (0.89-1.47)
Malignancies excluding NMSC			
Treatment (omalizumab vs nonomalizumab)	0.261	0.185	1.30 (0.90-1.87)

HR, Hazard ratio.