Neoplasms Reported With Liraglutide or Placebo in People With Type 2 Diabetes: Results From the LEADER Randomized Trial

*Michael A. Nauck,[1] Thomas Jon Jensen,[2] Carina Rosenkilde,[2] Salvatore Calanna,[2] John B. Buse,[3] and the LEADER Publication Committee on behalf of the LEADER Trial Investigators**

Diabetes Care 2018;41:1663–1671 | https://doi.org/10.2337/dc17-1825

OBJECTIVE

This study explored neoplasm risk with liraglutide versus placebo in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) cohort.

RESEARCH DESIGN AND METHODS

LEADER (NCT01179048) was an international, phase 3b, randomized, double-blind, controlled trial. Participants aged ≥50 years with type 2 diabetes and high cardiovascular risk were assigned 1:1 to receive liraglutide (≤1.8 mg daily; *n* = 4,668) or placebo (*n* = 4,672) in addition to standard care and monitored for 3.5–5 years (median follow-up 3.8 years). The occurrence of neoplasms was a prespecified, exploratory secondary end point. Post hoc analyses of the time to the first confirmed neoplasms were conducted using a Cox regression model.

RESULTS

Neoplasm was confirmed in 10.1% of patients with liraglutide versus 9.0% with placebo (hazard ratio [HR] 1.12 [95% CI 0.99; 1.28]). The HR (95% CI) for liraglutide versus placebo was 1.06 (0.90; 1.25) for malignant neoplasms and 1.16 (0.93; 1.44) for benign neoplasms. Sensitivity analyses excluding neoplasms occurring <1 year or <2 years after randomization and analyses by sex provided similar results. In our main analyses, the 95% CI for the HR included one for all malignant neoplasms evaluated (including pancreatic and thyroid neoplasms) except for prostate neoplasms, which occurred in fewer liraglutide-treated patients.

CONCLUSIONS

LEADER was not primarily designed to assess neoplasm risk. Firm conclusions cannot be made regarding numeric imbalances observed for individual neoplasm types (e.g., pancreatic cancer) that occurred infrequently. LEADER data do, however, exclude a major increase in the risk of total malignant neoplasms with liraglutide versus placebo. Additional studies are needed to assess longer-term exposure.

Diabetes and obesity have been identified as risk factors for cancer and cancer-related mortality (1–5). Glucose-lowering medications may also affect the risk of these events (1,3). Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) improve glycemic control with a low risk of hypoglycemia in people with type 2 diabetes (6). GLP-1

[1]Diabetes Center Bochum-Hattingen, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany
[2]Novo Nordisk A/S, Bagsværd, Denmark
[3]University of North Carolina School of Medicine, Chapel Hill, NC

Corresponding author: Michael A. Nauck, michael.nauck@rub.de.

Received 31 August 2017 and accepted 29 April 2018.

Clinical trial reg. no. NCT01179048, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1825/-/DC1.

**A complete list of the LEADER Committee Members and Trial Investigators can be found in the Supplementary Data online.*

receptor expression has been reported in a wide range of rodent and human tissues, including the pancreatic islets, lung, heart, kidney, gastrointestinal tract, pituitary, skin, and several regions of the nervous system (7,8). This widespread expression of the GLP-1 receptor may help to explain the range of effects of GLP-1RAs (9–15).

Data from some preclinical (16–19), clinical (15), and/or epidemiological database studies (20,21) have suggested an increase in the risk of thyroid cancer (16,20,21), pancreatic cancer (17,18,20, 21), intestinal neoplasms (15,19), and breast neoplasms (15) with the use of incretin-based therapy (GLP-1RAs and/or dipeptidyl peptidase 4 [DPP-4] inhibitors). In contrast, other clinical and epidemiological database studies have indicated that incretin-based therapy does not increase the risk of these events (22–25). Results from large, prospective clinical trials may help clarify a potential risk for neoplasms with GLP-1RAs or other glucose-lowering medications (26).

The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial was designed to assess the cardiovascular (CV) safety of liraglutide but provided the opportunity to evaluate other important safety end points in a population of 9,340 participants monitored for 3.5–5 years (median follow-up, 3.8) (11). The primary analysis showed liraglutide treatment was associated with a lower rate of major adverse CV events and total mortality (11). The present report explores intermediate-term neoplasm risk with liraglutide versus placebo, based on detailed analyses of data from LEADER.

RESEARCH DESIGN AND METHODS

Trial Design

The design of the LEADER trial (clinicaltrials .gov, NCT01179048) has been published previously (11,27). LEADER was a phase 3b, randomized, double-blind, controlled trial, conducted between 2010 and 2015 in 32 countries (11,27). During the trial, 9,340 participants aged ≥50 years with type 2 diabetes and high CV risk were assigned, in a 1:1 ratio, to receive liraglutide (up to 1.8 mg daily) or matched placebo as a subcutaneous injection, in addition to their standard-of-care treatment (11,27). The presence of malignant neoplasms requiring chemotherapy, surgery, radiotherapy, or palliative therapy in the previous 5 years was an exclusion criterion. Also excluded were patients with a familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer (MTC) (11). Patients with intraepithelial squamous cell carcinoma of the skin (Bowen's disease) treated with topical 5-fluorouracil and patients with basal cell skin cancer were allowed to enter the trial (11). Participants were monitored for 3.5–5 years (median follow-up, 3.8) (11). The primary end point was time to first occurrence of CV death, nonfatal (including silent) myocardial infarction, or nonfatal stroke (11).

Evaluation of Neoplasms

The occurrence of neoplasms was a prespecified, exploratory secondary end point. The investigators were asked to report all types of suspected neoplasms, including malignant neoplasm, in situ neoplasm, and neoplasm of uncertain or unknown behavior.

Potential neoplasms identified via investigator reports, Medical Dictionary for Regulatory Activities (MedDRA) search, the event adjudication committee (EAC), or the contract research organization were sent for adjudication (Supplementary Fig. 1). All potential neoplasms were adjudicated in a blinded manner by the neoplasms subcommittee of the external, independent EAC. The clinical evaluation of neoplasms by the EAC could be based on diagnostic tests, pathology reports, specialist consultations, related imaging reports, and/or biomarkers. For thyroid neoplasms, operative reports and relevant laboratory findings (e.g., tumor markers) were also used as diagnostic criteria. The EAC used a prespecified definition for adjudication of potential neoplasms, and a pathologic diagnosis by histology or cytology was considered of foremost importance for confirmation. After database lock, EAC-confirmed neoplasm events categorized as tissue of origin "other" were classified according to the organ system affected by medically qualified personnel at Novo Nordisk.

The EAC was not required to specify its reason for not confirming a neoplasm event. Possible reasons for nonconfirmation could include sufficient evidence that an event was not a neoplasm or insufficient evidence (e.g., lack of a pathology report) to confirm an event as a neoplasm.

To confirm the robustness of the analyses based on adjudicated data, a review of investigator-reported adverse events of malignant neoplasms was also undertaken by the sponsor, who performed MedDRA term searches after the unblinding of data after database lock. In addition, case reviews of all investigator-reported adverse events of malignant neoplasms not confirmed by the EAC were performed by the sponsor at this time. Because the EAC was blinded, external, and independent, its assessments were prioritized over the sponsor's assessments; however, the latter are reported for transparency and completeness.

Evaluation of Cause of Death

All deaths were adjudicated by a CV subcommittee to identify potential CV deaths. The subcommittee classified the cause of deaths as "known" or "unknown" and further, for a known cause, as CV or non-CV deaths. This required formal agreement/adjudication. Based on comments that were not subject to reconciliation between adjudicators, the sponsor further categorized the non-CV deaths according to plausible cause, which could include neoplastic disease.

Statistical Methods

Post hoc analyses of the time to the first EAC-confirmed neoplasm events were conducted using a Cox regression model to compare liraglutide treatment with placebo. Exploratory statistical testing without correction for multiplicity was performed if one or more events occurred in both treatment groups. The main analyses used an intention-to-treat approach, including all first events collected from randomization until the end-of-trial follow-up visit.

Plots were prepared showing the cumulative incidence probability of confirmed neoplasm index events with liraglutide or placebo over time. The cumulative incidence was estimated using the Aalen-Johansen method with death as a competing risk. Definitions of neoplasm index events, first events, and recurrent events are provided in the Supplementary Data.

Sensitivity analyses were conducted that excluded neoplasm events occurring

<1 year and <2 years after randomization to treatment, in case of an induction or latency time of these durations. In addition to Cox regression, a Fine and Gray method that adjusted for death as a competing risk was also used to analyze the time to the first neoplasm events.

Separate summaries were prepared to investigate the occurrence of neoplasms in sex (male and female) and age (<65 and ≥65 years) subgroups. A Cox regression model was used to conduct post hoc analyses to assess the interaction between treatment group and these subgroups. A *P* value of <0.05 was taken to indicate a statistically significant difference. However, because the interaction analyses were exploratory, the results of these analyses should be interpreted with caution.

In this report, increased attention is paid to specific types of neoplasms, including pancreatic, thyroid, colorectal, breast, prostate, nonmelanoma skin, melanoma, and lung and bronchus neoplasms. This selection of neoplasms of interest was based on several considerations, including GLP-1 receptor tissue expression (7,8), published findings from LEADER (11), and other previously reported data. The sponsor also conducted a post hoc review of clinical narratives to categorize confirmed malignant neoplasms of the liver and gallbladder or bile duct. The investigator-reported terms for these malignancies were reviewed.

RESULTS

Baseline Characteristics

The baseline characteristics for the LEADER trial population (*n* = 9,340) have been published previously (11). The mean duration of diabetes (mean glycated hemoglobin [HbA_{1c}] 8.7% [72 mmol/mol]) was 12.8 years, and 81.3% of the participants had established CV disease (11). Participants were a mean age of 64.3 years, and 64.3% were men. At baseline, 12.1% of participants were smokers, 46.5% were previous smokers, and 41.4% had never smoked.

Exposure to Randomized Treatment and Follow-up

As reported previously, the median duration of exposure to liraglutide or placebo was 3.5 years (11). The median dose of liraglutide was 1.78 mg daily (interquartile range 1.54–1.79), including periods during which the participants did not receive liraglutide (11). Overall, 96.8% of all randomized participants completed a final visit, died, or experienced a component of the primary composite outcome, and 99.7% of the participants had known vital status at the end of the trial (11).

Adjudication Flow for Neoplasms

According to the broad study definition, 3,802 potential neoplasms were identified and sent for adjudication. The EAC confirmed 1,477 (38.8%) of the potential neoplasms sent for adjudication as neoplasms (Supplementary Fig. 1).

Frequency of Confirmed Neoplasms

Excluding duplicate events and events occurring before randomization or after the end-of-trial follow-up, 1,123 confirmed neoplasms occurred. A total of 595 neoplasms (in 470 of 4,668 patients) in the liraglutide group and 528 neoplasms (in 419 of 4,672 patients) in the placebo group were confirmed. Overall, the proportion of patients who had confirmed neoplasms was 10.1% (3.34 events per 100 patient-years of observation [PYO]) in the liraglutide group and 9.0% in the placebo group (2.98 events per 100 PYO; estimated hazard ratio [HR] 1.12 [95% CI 0.99; 1.28]) (Fig. 1*A*). The proportion of patients with confirmed malignant neoplasms was 6.2% (1.92 events per 100 PYO), and a benign neoplasm was confirmed in 3.4% of patients (1.03 events per 100 PYO). The HR (95% CI) for liraglutide versus placebo was 1.06 (0.90; 1.25) for "all malignant neoplasms" and 1.16 (0.93; 1.44) for "all benign neoplasms" (Fig. 1*A*).

The cumulative incidence of confirmed overall neoplasms, malignant neoplasms, and benign neoplasms was similar with liraglutide treatment and placebo during the randomized treatment period (Fig. 2). A small separation in the cumulative incidence of confirmed benign neoplasms appeared after ~14 months (Fig. 2*G*) and was also observed for the cumulative incidence of confirmed overall neoplasms (Fig. 2*A*), but thereafter and for the remainder of the trial these events occurred at constant and similar rates in both treatment groups.

Sensitivity Analyses

Sensitivity analyses excluding neoplasms occurring <1 year (Figs. 1*B* and 2*B*, *E*, and *H*) or <2 years after randomization to treatment (Figs. 1*C* and 2*C*, *F*, and *I*) provided similar results to the main analysis for the overall neoplasm categories evaluated ("all neoplasms," "all malignant neoplasms," and/or "all benign neoplasms"). The subdistribution HRs estimated using the Fine and Gray method were consistent with the Cox regression analyses.

Results from the sensitivity analyses of events captured by the sponsor's MedDRA searches for malignant tumors were generally consistent with the adjudicated outcome (Supplementary Table 1). Additional data regarding pancreatic cancer are provided in Supplementary Table 2.

Frequency of Confirmed Neoplasms by Sex and Age Subgroups

The proportions of patients experiencing confirmed overall neoplasms, malignant neoplasms, or benign neoplasms with liraglutide versus placebo were similar within male and female subgroups (Table 1). The frequencies of overall neoplasms (HR 1.24 [95% CI 1.04; 1.47]; *P* = 0.10 for interaction) as well as combined malignant neoplasms (HR 1.15 [95% CI 0.94; 1.41]; *P* = 0.24 for interaction) and combined benign neoplasms (HR 1.21 [95% CI 0.89; 1.64]; *P* = 0.72 for interaction) were numerically higher with liraglutide versus placebo in the subgroup aged ≥65 years (Table 1).

Deaths Among Individuals With Malignant Neoplasm

Among patients who had a confirmed malignant neoplasm, the proportions that died of any cause (including deaths not related to cancer) were similar in the liraglutide and placebo groups (25.3% vs. 25.1%, respectively) (Table 2). In both treatment groups, most of these deaths were classified as non-CV and attributed to malignancy (19.6% vs. 19.7% of patients with an EAC-confirmed malignant neoplasm treated with liraglutide vs. placebo, respectively) (Table 2).

Neoplasms of Interest

Results for pancreatic, thyroid, colorectal, breast, prostate, nonmelanoma skin, melanoma, and lung and bronchus neoplasms are presented in Fig. 1, Table 2, and the Supplementary Data. Findings from the analyses of malignant hepatic and biliary neoplasms are presented in the Supplementary Data. Demographics and baseline characteristics of patients

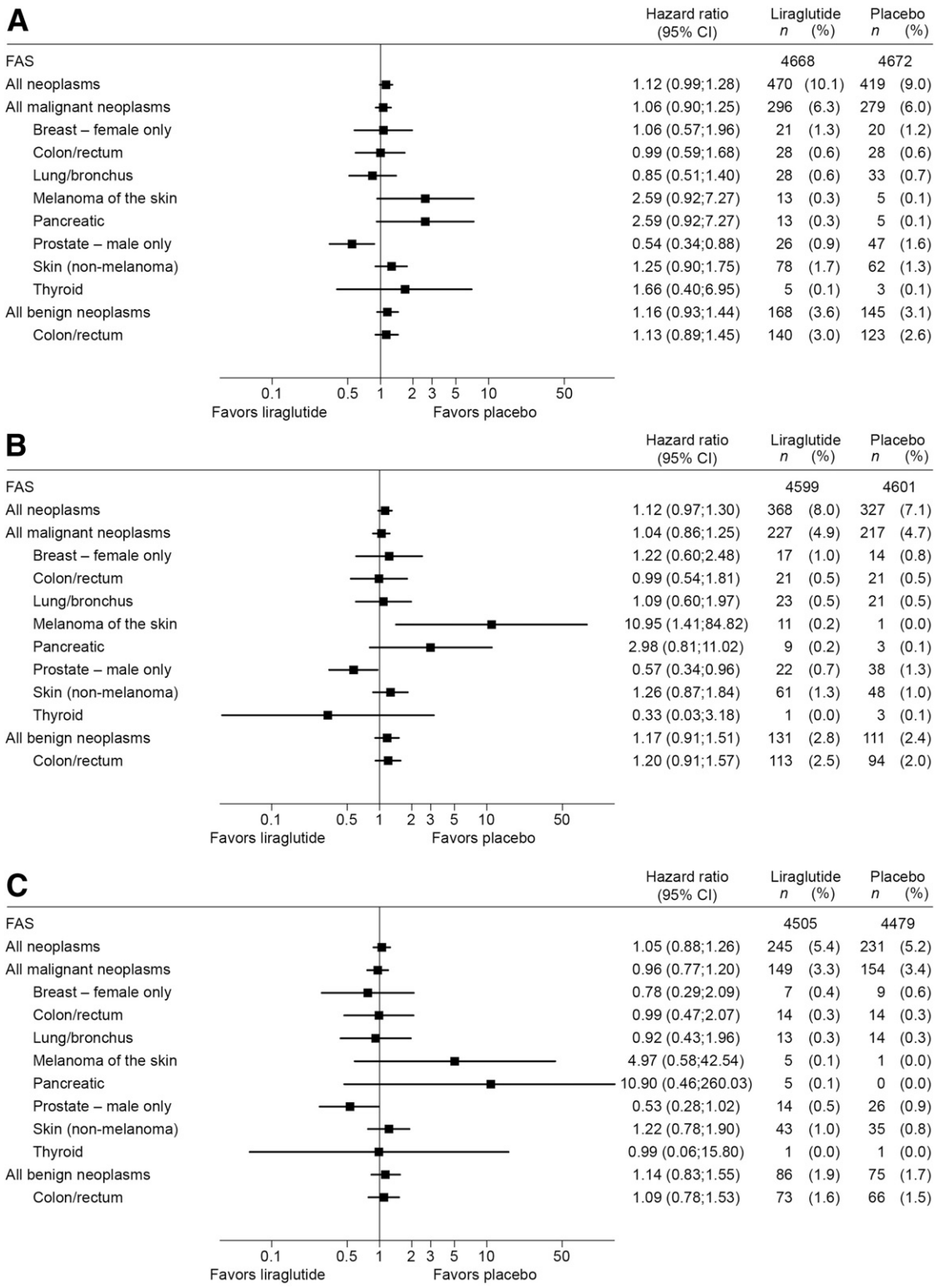

Figure 1—Frequency of all confirmed neoplasms, malignant neoplasms, benign neoplasms, and neoplasms of interest. *A*: Main analysis. *B* and *C*: Events occurring later than 1 year (*B*) and later than 2 years (*C*) after randomization (sensitivity analysis) (11). Data presented in this table refer to the full analysis set (FAS). HRs are derived from a Cox proportional hazard regression model adjusted for treatment. Firth correction was used for malignant pancreatic neoplasms occurring later than 2 years after randomization (*C*). Proportions for breast neoplasms are calculated based on the number of female participants. Proportions for prostate neoplasms are calculated based on the number of male participants. Reprinted from Marso et al. (11) with permission from the Massachusetts Medical Society.

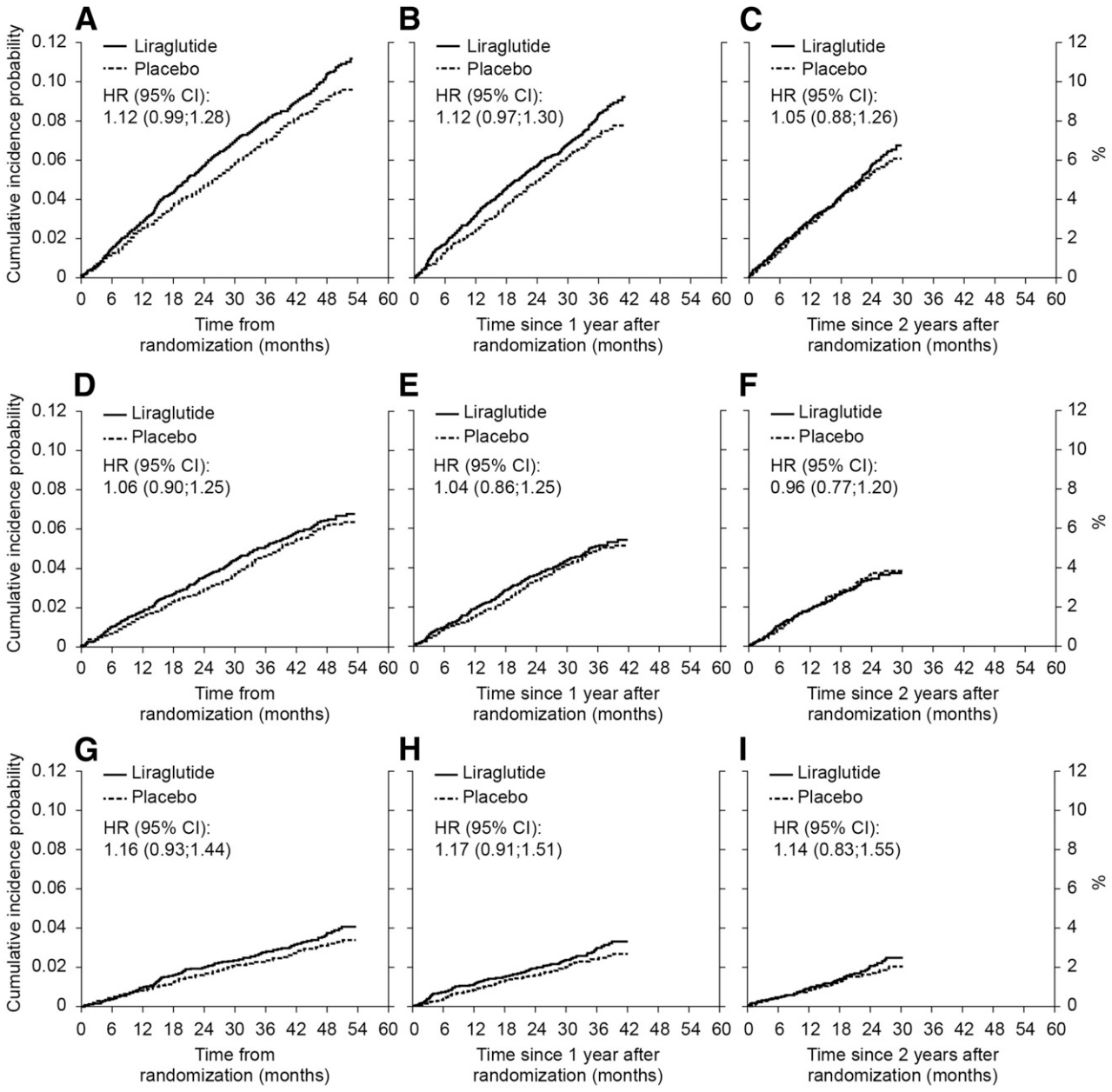

Figure 2—Cumulative incidence plots for confirmed neoplasms. *A*: Confirmed neoplasm index events. *B* and *C*: Confirmed neoplasm index events occurring later than 1 year (*B*) and later than 2 years (*C*) after randomization (sensitivity analysis). *D*: Confirmed malignant neoplasm index events. *E* and *F*: Confirmed malignant neoplasm index events occurring later than 1 year (*E*) and later than 2 years (*F*) after randomization (sensitivity analysis). *G*: Confirmed benign neoplasm index events. *H* and *I*: Confirmed benign neoplasm index events occurring later than 1 year (*H*) and later than 2 years (*I*) after randomization (sensitivity analysis). Cumulative incidence was estimated using the Aalen-Johansen method with death as a competing risk. A cumulative incidence probability of 0.1 is equivalent to 10%. HRs are derived from a Cox proportional hazard regression model adjusted for treatment and are for the proportion of patients with an event with liraglutide vs. placebo.

who experienced a malignant neoplasm of interest are presented in Supplementary Table 3.

The most frequently occurring type of confirmed malignant neoplasm in the overall study population was malignant nonmelanoma skin neoplasm (1.5% of patients [*n* = 140]). In the main analyses comparing the occurrence of confirmed neoplasms with liraglutide treatment versus placebo, the 95% CI for the HR included one for all neoplasms of interest evaluated, except for malignant prostate neoplasms, which were experienced by a lower proportion of patients receiving liraglutide (HR 0.54 [95% CI 0.34; 0.88]) (Fig. 1*A*). Malignant pancreatic neoplasm or malignant melanoma events were confirmed infrequently in both groups and for more patients in the liraglutide group (*n* = 13 [0.28%] for each type of neoplasm) than in the placebo group (*n* = 5 [0.11%] for each type of neoplasm [HR 2.59 (95% CI 0.92; 7.27)] in the main analysis) (Fig. 1*A*). No patients in the placebo group had a confirmed malignant pancreatic neoplasm after 2 years of randomized treatment compared with five patients (0.11%) in the liraglutide group (HR 10.90 [95% CI 0.46; 260.03]), and only one patient (0.02%) had a confirmed malignant melanoma after 1 year of receiving placebo compared with

Table 1—Frequency of confirmed neoplasms by sex and age subgroups

	Liraglutide *n* (%)	Placebo *n* (%)	HR (95% CI)	*P* value for the interaction between treatment and subgroup
Full analysis set	4,668 (100.0)	4,672 (100.0)		
All neoplasms	470 (10.1)	419 (9.0)	1.12 (0.99; 1.28)	
Female	127 (7.7)	123 (7.3)	1.04 (0.81; 1.34)	Sex: 0.50
Male	343 (11.4)	296 (9.9)	1.16 (0.99; 1.35)	
Aged <65 years	178 (7.1)	177 (7.1)	0.99 (0.80; 1.22)	Age: 0.10
Aged ≥65 years	292 (13.5)	242 (11.1)	1.24 (1.04; 1.47)	
All malignant neoplasms	296 (6.3)	279 (6.0)	1.06 (0.90; 1.25)	
Female	86 (5.2)	77 (4.6)	1.13 (0.83; 1.54)	Sex: 0.60
Male	210 (7.0)	202 (6.8)	1.03 (0.85; 1.25)	
Aged <65 years	101 (4.0)	106 (4.2)	0.94 (0.71; 1.23)	Age: 0.24
Aged ≥65 years	195 (9.0)	173 (8.0)	1.15 (0.94; 1.41)	
All benign neoplasms	168 (3.6)	145 (3.1)	1.16 (0.93; 1.44)	
Female	41 (2.5)	42 (2.5)	0.98 (0.64; 1.51)	Sex: 0.40
Male	127 (4.2)	103 (3.4)	1.22 (0.94; 1.59)	
Aged <65 years	79 (3.1)	70 (2.8)	1.11 (0.80; 1.53)	Age: 0.72
Aged ≥65 years	89 (4.1)	75 (3.5)	1.21 (0.89; 1.64)	

Data presented in this table refer to the full analysis set. HRs are derived from a Cox proportional hazard regression model adjusted for treatment.

11 patients (0.24%) in the liraglutide group (HR 10.95 [95% CI 1.41; 84.82]) (Fig. 1). Details for individual cases of malignant or premalignant pancreatic neoplasm or melanoma are provided in Supplementary Tables 2 and 4. Several patients who developed malignant pancreatic neoplasm experienced weight loss before their diagnosis, and some experienced increases in HbA_{1c} before diagnosis, but there was no universal pattern.

CONCLUSIONS

LEADER has provided information about intermediate-term neoplasm risk with liraglutide versus placebo (both in combination with standard care) in 9,340 patients with type 2 diabetes monitored for 3.5–5 years. There was a greater total number of neoplasms with liraglutide compared with placebo (470 vs. 419 total [benign, premalignant, or malignant] neoplasms, respectively; HR 1.12 [95% CI 0.99; 1.28]). However, our overall analyses do not suggest a major increase (>25% based on the 95% CI) in the risk of malignant neoplasms with liraglutide, in general terms, versus placebo (HR 1.06 [95% CI 0.90; 1.25]).

Overall cancer rates, although of clinical interest, do not have a known biological relevance because all carcinogens reported to date affect specific cancer subtypes. In our study we have limited power to examine any specific cancer subtype. The primary end point power calculation for LEADER determined that 611 events were required to exclude an HR >1.3 with 90% power. The cancer subtype with the highest number of events in LEADER was nonmelanoma skin cancer, affecting 140 patients (liraglutide, 78 patients [1.7%]; placebo, 62 patients [1.3%]) during the entire study period. This number of events gives a power of 34% to exclude an HR >1.3 for nonmelanoma skin cancer; to exclude an HR >1.3% with a power of 90%, the number of patients required is ~36,000 (assuming the observed rate of nonmelanoma skin cancer events of 0.4% subjects/year and ≥3.5 years' observation time). Beyond these limitations around the power of the trial to detect differences in cancer incidence, the limited time frame (median follow-up of 3.8 years) is inadequate to exclude the carcinogenic potential of a drug.

The proportion of patients with confirmed malignant neoplasms during LEADER was 6.2% (1.92 events per 100 PYO), which is lower than that for the primary composite end point for major adverse CV events (11). To our knowledge, evidence from global epidemiological studies on cancer prevalence in people with type 2 diabetes is lacking. It is therefore difficult to evaluate how overall cancer rates in LEADER compare with those in the general population of patients with type 2 diabetes. Among those patients in LEADER with a confirmed malignant neoplasm, most deaths were due to malignancy. The occurrence of deaths attributable to malignancy was similar with liraglutide and placebo; hence, cause of death seemed to reflect the prognosis of underlying malignant disease, irrespective of treatment group.

There was no suggestion of an association between liraglutide exposure and development of malignant neoplasms in the liraglutide clinical development program for treatment of type 2 diabetes (at doses up to 1.8 mg daily for up to 22 months) (14). Slight imbalances in rates of papillary thyroid cancer and prostate cancer were identified with liraglutide versus a pooled comparator group consisting of an active comparator and placebo; however, rates were similar compared with placebo alone (14).

In LEADER, the frequency of confirmed malignant thyroid neoplasm was similar in the liraglutide and placebo groups, and the only observed case of MTC occurred in a patient assigned to placebo. Fewer participants experienced malignant prostate neoplasms in the liraglutide group than in the placebo group (11). In vitro studies have shown that liraglutide and exenatide significantly inhibit proliferation in human prostate cancer cell lines through GLP-1 receptor–dependent mechanisms (28,29), giving some plausibility to our observation. Alternatively, greater urinary frequency among placebo-treated patients (due to greater hyperglycemia and more diuretic use), and consequently more frequent investigation, could account for the small difference.

We report a numeric imbalance in the frequency of adjudication-confirmed malignant pancreatic neoplasms in the liraglutide group versus placebo group (0.28% [*n* = 13] vs. 0.11% [*n* = 5], respectively; HR 2.59 [95% CI 0.92; 7.27]). Additional details on the capture and adjudication of these cases can be found in the Supplementary Data (Neoplasms of interest: Pancreatic neoplasms). The development of clinically evident pancreatic cancer is a process that takes many years (30). A substantial number of our patients with confirmed malignant pancreatic neoplasms had advanced

Table 2—Confirmed deaths, including deaths not related to cancer, among patients with confirmed malignant neoplasm

	Liraglutide *n* (%)	Placebo *n* (%)
All malignant neoplasms	296 (100.0)	279 (100.0)
All-cause mortality	75 (25.3)	70 (25.1)
Known cause of death	73 (24.7)	64 (22.9)
CV death	8 (2.7)	1 (0.4)
Non-CV death	65 (22.0)	63 (22.6)
Malignancy	58 (19.6)	55 (19.7)
Malignant pancreatic neoplasms	13 (100.0)	5 (100.0)
All-cause mortality	11 (84.6)	5 (100.0)
Known cause of death	11 (84.6)	5 (100.0)
CV death	0 (0.0)	0 (0.0)
Non-CV death	11 (84.6)	5 (100.0)
Malignancy	11 (84.6)	5 (100.0)
Malignant thyroid neoplasms	5 (100.0)	3 (100.0)
All-cause mortality	0 (0.0)	0 (0.0)
Malignant colorectal neoplasms	28 (100.0)	28 (100.0)
All-cause mortality	6 (21.4)	6 (21.4)
Known cause of death	6 (21.4)	4 (14.3)
CV death	0 (0.0)	0 (0.0)
Non-CV death	6 (21.4)	4 (14.3)
Malignancy	3 (10.7)	4 (14.3)
Malignant breast neoplasms (female only)	21 (100.0)	20 (100.0)
All-cause mortality	1 (4.8)	1 (5.0)
Known cause of death	1 (4.8)	1 (5.0)
CV death	1 (4.8)	0 (0.0)
Non-CV death	0 (0.0)	1 (5.0)
Malignancy	0 (0.0)	1 (5.0)
Malignant prostate neoplasms (male only)	26 (100.0)	47 (100.0)
All-cause mortality	0 (0.0)	6 (12.8)
Known cause of death	–	6 (12.8)
CV death	0 (0.0)	0 (0.0)
Non-CV death	0 (0.0)	6 (12.8)
Malignancy	0 (0.0)	3 (6.4)
Malignant nonmelanoma skin neoplasm	78 (100.0)	62 (100.0)
All-cause mortality	3 (3.8)	3 (4.8)
Known cause of death	3 (3.8)	3 (4.8)
CV death	1 (1.3)	0 (0.0)
Non-CV death	2 (2.6)	3 (4.8)
Malignancy	1 (1.3)	1 (1.6)
Malignant melanoma	13 (100.0)	5 (100.0)
All-cause mortality	2 (15.4)	1 (20.0)
Known cause of death	2 (15.4)	0 (0.0)
CV death	0 (0.0)	0 (0.0)
Non-CV death	2 (15.4)	0 (0.0)
Malignancy	2 (15.4)	0 (0.0)
Malignant lung and bronchus neoplasms	28 (100.0)	33 (100.0)
All-cause mortality	21 (75.0)	22 (66.7)
Known cause of death	20 (71.4)	20 (60.6)
CV death	2 (7.1)	0 (0.0)
Non-CV death	18 (64.3)	20 (60.6)
Malignancy	17 (60.7)	20 (60.6)

The EAC CV subcommittee classified deaths with a known cause into CV or non-CV deaths. The sponsor further categorized the deaths according to plausible cause.

stages, suggesting the tumors originated well before the patients were recruited into LEADER.

Although earlier studies, subject to criticism on methodological grounds, suggested an increased risk for pancreatic tumors with incretin-based therapy (18,20,21), a recent large, international registry study did not confirm an increased risk of pancreatic cancer versus sulfonylureas (median follow-up 1.3–2.8 years) (23), in line with a U.S. insurance claims database study that compared liraglutide with non–GLP-1–based therapy (median follow-up 15 months) (22). Monitoring of pancreatic cancer in CV outcome trials (such as LEADER) has been cited as a strategy for increasing knowledge in this area (26). To date, CV outcome trials have consistently reported pancreatic cancer occurs in similar or fewer numbers of patients receiving GLP-1RAs than placebo: semaglutide (SUSTAIN-6 [Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes]), with a mean observation time of 2.1 years; lixisenatide (ELIXA [Evaluation of Lixisenatide in Acute Coronary Syndrome]), with a median follow-up of 25 months; and exenatide once weekly (EXSCEL [Exenatide Study of Cardiovascular Event Lowering]), with a median follow-up of 3.2 years (12,31,32). A recent meta-analysis of all GLP-1RA CV outcome trials (including LEADER) also reported an absence of a significant effect for GLP-1RA on rates of pancreatic cancer and MTC, albeit with significant heterogeneity between the four eligible trials (33).

We also report a numeric imbalance in the occurrence of adjudication-confirmed malignant melanoma with liraglutide (0.28% [*n* = 13]) vs. placebo (0.11% [*n* = 5], HR 2.59 [95% CI 0.92; 7.27]). Only one patient developed malignant melanoma after 1 year of receiving placebo. The low numbers of patients led to wide CIs for the HRs for malignant melanoma, thus precluding firm conclusions. The HR for skin neoplasms with semaglutide versus placebo in SUSTAIN-6 was 1.41 (95% CI 0.76; 2.63), though the relevance of comparison with our analysis is very limited, with only one of the six skin neoplasms reported in SUSTAIN-6 being classified as malignant melanoma (12). The primary reports for ELIXA and EXSCEL did not include data specific to skin neoplasms (31,32). A meta-analysis of randomized clinical trials of 24 weeks' to 5 years' duration showed that DPP-4 inhibitors were not associated with a significantly increased risk of developing malignant melanoma (25).

Preclinical data suggest that GLP-1RAs may have GLP-1 receptor-dependent intestinotrophic effects (19). Treatment with exenatide for 4 weeks significantly increased polyp number and size, primarily in the distal small bowel (19), an atypical location for human gastrointestinal adenomas.

In clinical trials of liraglutide at higher doses (up to 3.0 mg daily for the weight management indication), small imbalances between treatment groups were noted in the number of patients with benign colorectal neoplasm events (n = 17 [0.52%] with liraglutide vs. n = 4 [0.22%] with placebo; odds ratio 2.39 [95% CI 0.78; 9.76]) (15). These findings were not reproduced in LEADER, where the liraglutide dose was lower (up to 1.8 mg daily).

Furthermore, in clinical trials of liraglutide for weight management (up to 3.0 mg daily), an imbalance was reported in the number of women with malignant or premalignant breast neoplasms in the liraglutide (n = 14 [0.59%]) versus placebo group (n = 3 [0.23%]; odds ratio 2.56 [95% CI 0.71; 13.91]) (15). It was speculated that weight loss may have led to enhanced detection of breast neoplasms in liraglutide-treated women (15). Similar findings were reported from an observational study in GLP-1RA users (34). In LEADER, with longer exposure in a larger population with more cases reported, the overall incidence of confirmed malignant breast neoplasms was similar across the liraglutide and placebo groups.

Our study has limitations. First, LEADER was not primarily designed or powered to provide conclusive data regarding occurrence of neoplasms with liraglutide. A relatively low frequency of neoplasms was observed for most tissues, precluding firm conclusions. In addition, the median follow-up time in LEADER was 3.8 years (11), and longer-term neoplasm risk could not be assessed.

Second, neoplasms in some tissue types may have been subject to detection bias (e.g., due to gastrointestinal adverse events or weight loss observed with liraglutide), and a role for detection or surveillance bias in the relationship between diabetes and cancer has been suggested previously (35,36).

Third, a relatively low proportion of potential neoplasms captured were confirmed by adjudication. These events were reported and sent for adjudication according to a broad study definition to help ensure a robust process. The emphasis on a histological or cytological diagnosis during neoplasm adjudication provided high specificity in confirmed cases but may also have decreased sensitivity. To address this, we also examined cases based on clinical reporting, which generally confirmed the adjudicated findings.

Fourth, although of scientific and clinical interest, our subgroup analyses and sensitivity analyses excluding neoplasms occurring $<$1 year or $<$2 years after randomization were based on lower numbers of patients than the main analyses, further reducing the precision of the HRs and complicating data interpretation. In addition, LEADER was conducted in a population at high CV risk and excluded patients based on a history of malignancy, which could potentially limit the generalizability of the findings (37).

Finally, the generalizability of our findings to GLP-1RAs other than liraglutide up to doses of 1.8 mg daily is unclear.

In conclusion, overall safety analyses of data from the LEADER trial do not suggest a major increase in the risk of malignant neoplasms with liraglutide, in general terms, versus placebo. Based on small numbers, imbalances with uncertain significance were observed for neoplasms of some tissue types, without allowing firm conclusions. We cannot comment on the longer-term neoplasm risk beyond a median follow-up time of 3.8 years. Only long-term, larger, prospective, pragmatic, or observational registry studies may help to answer questions about the longer-term safety of liraglutide and other GLP-1RAs.

Acknowledgments. The authors thank Helle Frimer-Larsen (Novo Nordisk A/S) for statistical support and for reviewing the manuscript. Medical writing assistance was provided by Watermeadow Medical, an Ashfield Company, part of UDG Healthcare plc, funded by Novo Nordisk A/S. Editorial support was provided by Helen Marshall of Watermeadow Medical, funded by Novo Nordisk A/S. The authors are grateful to the LEADER trial participants, investigators (available in the Supplementary Data), and trial-site staff and the leadership, employees, and contractors of the sponsor who were involved in the conduct of the trial.

Funding. J.B.B. received support from the U.S. National Institutes of Health award UL1-TR-001111.

Duality of Interest. This study was supported by Novo Nordisk. M.A.N. reports receiving fees for serving on advisory boards from AstraZeneca, Berlin-Chemie, Eli Lilly and Co., Fractyl, Hanmi, Merck Sharp & Dohme, Novo Nordisk, and Intarcia Therapeutics/Servier; lecture fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Eli Lilly and Co., Medscape, Merck Sharp & Dohme, and Novo Nordisk; travel support from Berlin-Chemie, Eli Lilly and Co., Merck Sharp & Dohme, Novo Nordisk, and Intarcia Therapeutics/Servier; and grant support (to his institution) from AstraZeneca, Eli Lilly and Co., GlaxoSmithKline, Intarcia Therapeutics/Servier, Merck Sharp & Dohme, Novartis, and Novo Nordisk. T.J.J., C.R., and S.C. are employees and shareholders of Novo Nordisk. J.B.B. reports receiving contracted consulting fees, paid to his institution, and travel support from Adocia, AstraZeneca, Dance Biopharm, Dexcom, Elcelyx Therapeutics, Eli Lilly and Co., Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, Merck, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Shenzhen HighTide, and vTv Therapeutics and grant support from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Co., GI Dynamics, GlaxoSmithKline, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, Merck, Novo Nordisk, Orexigen, Sanofi, Scion NeuroStim, Takeda, and Theracos. J.B.B. also reports receiving fees and holding stock options in Insulin Algorithms and PhaseBio and reports serving on the board of the AstraZeneca Healthcare Foundation.

Author Contributions. M.A.N., T.J.J., C.R., S.C., and J.B.B. participated in analysis and interpretation of the data, edited the manuscript for important intellectual content, approved the final version, and take full responsibility for its contents. M.A.N. and J.B.B. participated in the development of the protocol and in the conduct and oversight of the protocol. M.A.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented as oral presentations at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016, and at the 52nd Annual Meeting of the European Association for the Study of Diabetes, Munich, Germany, 12–16 September 2016.

References

1. Cohen DH, LeRoith D. Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. Endocr Relat Cancer 2012;19:F27–F45
2. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607
3. García-Jiménez C, Gutiérrez-Salmerón M, Chocarro-Calvo A, García-Martinez JM, Castaño A, De la Vieja A. From obesity to diabetes and cancer: epidemiological links and role of therapies. Br J Cancer 2016;114:716–722
4. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017;356:j477
5. Chen Y, Wu F, Saito E, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. Diabetologia 2017;60:1022–1032
6. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–1705

7. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132:2131–2157
8. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology 2014;155:1280–1290
9. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771
10. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Diabetes Obes Metab 2016;18:203–216
11. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
12. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
13. Dalsgaard NB, Brønden A, Vilsbøll T, Knop FK. Cardiovascular safety and benefits of GLP-1 receptor agonists. Expert Opin Drug Saf 2017;16:351–363
14. Novo Nordisk. Liraglutide (injection) for the treatment of patients with type 2 diabetes. NDA 22-341 Briefing Document. Endocrine and Metabolic Drug Advisory Committee, 2 April 2009 [Internet], 2009. Available from https://wayback.archive-it.org/7993/20170405221128/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM148659.pdf. Accessed 6 April 2018
15. Novo Nordisk. Liraglutide 3.0 mg for weight management. NDA 206-321 Briefing Document. Endocrinologic and Metabolic Drug Advisory Committee, September 11, 2014 [Internet], 2014. Available from https://wayback.archive-it.org/7993/20170405215636/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM413318.pdf. Accessed 6 April 2018
16. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation [published correction appears in Endocrinology 2012;153:1000]. Endocrinology 2010;151:1473–1486
17. Matveyenko AV, Dry S, Cox HI, et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. Diabetes 2009;58:1604–1615
18. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013;62:2595–2604
19. Koehler JA, Baggio LL, Yusta B, et al. GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7. Cell Metab 2015;21:379–391
20. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 2011;141:150–156
21. Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? Diabetes Care 2013;36:2118–2125
22. Funch D, Gydesen H, Tornøe K, Major-Pedersen A, Chan KA. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. Diabetes Obes Metab 2014;16:273–275
23. Azoulay L, Filion KB, Platt RW, et al.; Canadian Network for Observational Drug Effect Studies Investigators. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. BMJ 2016;352:i581
24. Htoo PT, Buse JB, Gokhale M, Marquis MA, Pate V, Stürmer T. Effect of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors on colorectal cancer incidence and its precursors. Eur J Clin Pharmacol 2016;72:1013–1023
25. Zhao M, Chen J, Yuan Y, et al. Dipeptidyl peptidase-4 inhibitors and cancer risk in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. Sci Rep 2017;7:8273
26. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. N Engl J Med 2014;370:794–797
27. Marso SP, Poulter NR, Nissen SE, et al. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. Am Heart J 2013;166:823–830.e5
28. Nomiyama T, Kawanami T, Irie S, et al. Exendin-4, a GLP-1 receptor agonist, attenuates prostate cancer growth. Diabetes 2014;63:3891–3905
29. Li XN, Bu HM, Ma XH, et al. Glucagon-like peptide-1 analogues inhibit proliferation and increase apoptosis of human prostate cancer cells in vitro. Exp Clin Endocrinol Diabetes 2017;125:91–97
30. Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 2010;467:1114–1117
31. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257
32. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–1239
33. Bethel MA, Patel RA, Merrill P, et al.; EXSCEL Study Group. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol 2018;6:105–113
34. Hicks BM, Yin H, Yu OH, Pollak MN, Platt RW, Azoulay L. Glucagon-like peptide-1 analogues and risk of breast cancer in women with type 2 diabetes: population based cohort study using the UK Clinical Practice Research Datalink. BMJ 2016;355:i5340
35. Dankner R, Boffetta P, Balicer RD, et al. Time-dependent risk of cancer after a diabetes diagnosis in a cohort of 2.3 million adults. Am J Epidemiol 2016;183:1098–1106
36. Lega IC, Wilton AS, Austin PC, Fischer HD, Johnson JA, Lipscombe LL. The temporal relationship between diabetes and cancer: a population-based study. Cancer 2016;122:2731–2738
37. Rinde LB, Småbrekke B, Hald EM, et al. Myocardial infarction and future risk of cancer in the general population-the Tromsø Study. Eur J Epidemiol 2017;32:193–201