BACKGROUND
Preclinical studies have highlighted the existence of metaplasia of ductal cells under the action of incretin-based therapies. Since the marketing of these two new classes of antidiabetic drugs (gliptins and GLP-1 receptor agonists) in 2008-2009, adverse pancreatic effects have been reported through pharmacovigilance systems, suggesting a potential increased risk of pancreatic cancer associated with these treatments. However, to date only few pharmacoepidemiological studies have investigated this association.

OBJECTIVES
To investigate the risk of pancreatic cancer associated with incretin-based therapies in patients with type 2 diabetes.

More specifically, our aims were: 1) to measure the association between exposure to incretin-based therapies and the risk of pancreatic cancer; 2) to characterise this association in terms of dose- and treatment duration-response relationship; 3) to compare this association with that observed between other antidiabetic drugs and the risk of pancreatic cancer.

MATERIAL AND METHODS
Study Design: Observational, longitudinal study
Data source: French national health insurance anonymized claim database matched to the national hospital discharge database (SNIRAM) including individual information on:
- sociodemographic characteristics;
- reimbursement for all outpatient healthcare expenditures;
- hospital discharge diagnoses and medical procedures;
- severe and/or costly long-term diseases (LTD).

Study Population: All beneficiaries of the French national health insurance general scheme, aged 40 to 80 years and with a history type 2 diabetes diagnosis in 2010 were included unless they fulfilled one of the following exclusion criteria:
- history of cancer (any location) or pancreatectomy before inclusion;
- incident;
- cancer (any location) or death in the 3 months following inclusion;
- contraindication to incretin-based therapies (pregnancy, lactation, liver failure).

Follow-up: From the date of first reimbursement for an antidiabetic treatment in 2010 up to 31 December 2013, date of diagnosis of any cancer or death.

Exposure definition: Patients were considered exposed to an antidiabetic treatment starting from 3 months following the date of first reimbursement for this treatment.

Statistical Analysis: Multivariate Cox proportional hazard models
- Exposure to each class of antidiabetic drugs and the risk of pancreatic cancer
- Statistical adjustment for demographic characteristics;
- adjustment for other antidiabetic drugs, complications of diabetes, history of pancreatitis, ulcers, cholecystectomy, smoking status, alcohol consumption and morbid obesity.

RESULTS
Characteristics of the study population
Among the 1,346,055 people included, 41.1% were exposed to gliptins and 7.2% to GLP-1 receptor agonists. Mean follow-up was 44 months, during which 3,113 cases of pancreatic cancer occurred (incidence of 62.9 per 100,000 people per year), 1,107 cases in the group exposed to gliptins and 157 cases in the group exposed to GLP-1 receptor agonists.

Table 1. Baseline characteristics according to exposure to incretin-based therapies

The risk of pancreatic cancer was significantly higher among people ever vs. never exposed to gliptins (adjusted Hazard Ratio [aHR] = 1.30; 95% CI: [1.20-1.40]).

Comparison of the risk of pancreatic cancer between patients exposed versus non-exposed to incretin-based therapies and to other classes of oral antidiabetic drugs

Figures 1 and 2 show the results of the comparison of the risk of pancreatic cancer associated with gliptins and GLP-1 receptor agonists versus with other classes of oral antidiabetic drugs.

CONCLUSION
- The risk of pancreatic cancer is increased in people exposed to gliptins with a recently initiated treatment or a low level of exposure, but not in those with a long-lasting or a high level of exposure to gliptins or in those exposed to GLP-1 receptor agonists.
- The association found between exposure to gliptins and the risk of pancreatic cancer is similar to that observed for other classes of oral antidiabetic drugs.
- A longer follow-up is needed to confirm these reassuring results.

Conflict of Interest: None of the authors have any conflicts of interest to declare.