



HAL
open science

Immune checkpoint inhibitor treatment of a first cancer is associated with a decreased incidence of second primary cancer

P. Heudel, S. Chabaud, D. Perol, A. Flechon, J. Fayette, P. Combemale, O. Tredan, F. Desseigne, C. de la Fouchardiere, H. Boyle, et al.

► To cite this version:

P. Heudel, S. Chabaud, D. Perol, A. Flechon, J. Fayette, et al.. Immune checkpoint inhibitor treatment of a first cancer is associated with a decreased incidence of second primary cancer. *ESMO Open*, 2021, 6 (1), pp.100044. 10.1016/j.esmoop.2020.100044 . hal-03808637

HAL Id: hal-03808637

<https://hal.science/hal-03808637>

Submitted on 22 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Immune checkpoint inhibitor treatment for a first cancer is associated with a decreased incidence of second primary cancer

Pierre Heudel, Sylvie Chabaud, David Perol, Aude Flechon, Jerome Fayette, Patrick Combemale, Olivier Tredan‡, Françoise Desseigne, Christelle de la Fouchardière, Helene Boyle, Maurice Perol, Thomas Bachelot‡, Philippe Cassier, Virginie Avrillon, Catherine Terret, Anne-Sophie Michallet, Eve-Marie Neidhardt-Berard, Emmanuelle Nicolas-Virelizier, Armelle Dufresne‡, Amine Belhabri, Mehdi Brahmi‡, Laure Lebras, Frank Nicolini‡, Mathieu Sarabi‡, Philippe Rey, Alice Bonneville-Levard, Pauline Rochefort, Anne-Marie Provensal, Lauriane Eberst, Souad Assaad, Aurélie Swalduz, Pierre Saintigny‡, Philippe Toussaint, Yann Guillermin, Marie Castets‡, Clelia Coutzac‡, Pierre Meeus, Aurélien Dupré, Thierry Durand, Hugo Crochet, Beatrice Fervers, Frederic Gomez, Michel Rivoire*, Vincent Gregoire, Line Claude, Catherine Chassagne-Clement, Franck Pilleul*, Thomas Mognetti, Bruno Russias, Jean-Luc Soubirou, Christine Lasset*, Gisèle Chvetzoff, Patrick Mehlen*‡, Sophie Beaupère†, Philippe Zrounba, Isabelle Ray-Coquard*, Jean-Yves Blay*,†,‡.

Affiliations :

All : Centre Léon Berard, Rue Laennec , 69008 Lyon, France

* : Centre Léon Bérard & Université Claude Bernard, Lyon, France

† : Unicancer, 101 Rue de Tolbiac 75013 Paris, France

‡ : Cancer Research Center of Lyon (CRCL), Lyon, France

Correspondence to Prof J-Y Blay, Department of Medical Oncology, Centre Léon Bérard, 28 rue Laennec, 69373 Lyon Cedex 08, & Université Claude Bernard Lyon I France. Tel: +33 (0)4 78 78 51 26, jean-yves.blay@lyon.unicancer.fr

Summary

Rationale:

Second primary cancers (SPC) are diagnosed in over 5% of patients after a first primary cancer (FPC). We explored here the impact of ICI given for a FPC on the risk of SPC in different age groups, cancer types and treatments.

Patient, material and methods

The files of the 46829 patients, diagnosed with a FPC in the Centre Leon Berard from 2013 to 2018 were analyzed. Structured data were extracted and electronic patient records were screened using a natural language processing tool, with a validation using manual screening on 2818 files of patients. An univariate and multivariate analysis of the incidence of SPC according to patient characteristics and treatment was conducted.

Results

Among the 46829 patients, 1830 (3.9%) had a diagnosis of SPC with a median interval of 11.1 months (range 0-78 months); 18128 (38.7%) received cytotoxic chemotherapy (CC) and 1163 (2.5%) received ICI for the treatment of the FPC in this period. SPC were observed in 7/1163 (0.6%) patients who had received ICI for their FPC vs 437/16997 (2.6%) patients receiving CC and no ICI for the FPC vs 1386/28669 (4.8%) for patients receiving neither CC nor ICI for the FPC. This reduction was observed at all ages and for all histotypes analyzed. Treatment with ICI and/or cytotoxic for the FPC are associated with a reduced risk of SPC in multivariate analysis.

Conclusion

Immunotherapy with ICI, alone and in combination with CC was found associated with a reduced incidence of SPC for all ages and cancer types.

Keywords: immunotherapy, immune check points, second primary cancer, second malignant neoplasia.

Highlights

- From 2013 to 2018, 3,9% of the 46829 patients diagnosed of a first cancer presented a second primary cancer (SPC)*
- Treatment of the first cancer with immune checkpoint inhibitors (ICI) was associated with a major reduction of SPC
- Cytotoxic chemotherapy given for a FPC was also associated with a lower magnitude of reduction of SPC.
- The reduction of the risk of SPC with ICI was of major magnitude in patients treated in localized phase of their FPC

Introduction

Second primary cancers (SPC) are increasingly diagnosed in the long term follow-up of children and adult patients cured of a first primary cancer (FPC) (1-10). In recent studies, over 10% of all incident cancers are SPC. SPC are among the important causes of early deaths in patients treated and cured of a first cancer, along with cardiovascular diseases and complications of the first cancer treatments (1-10). There are multiple risk factors for SPC including genetic predispositions, carcinogens involved in the FPC (e.g. smoking, alcohol, sun exposure...), lifestyles, overweight, low exercise... The cytotoxic treatments given for the first cancer may also contribute to an excess risk of second primary cancers for cured patients (1-10). This has been largely documented for secondary leukemias after alkylating agents, as well as for solid tumors in the irradiated field (1,2,5,9).

In the recent years, immunotherapy of cancer using immune checkpoint inhibitors (ICI), PD1 or PDL1 Ab as well as anti CTLA-4 have transformed the management of patients with advanced cancers. These antibodies against ICI are now demonstrated to reduce the risk of relapse and to improve survival in localized and advanced phase of the disease, in particular in malignant melanomas, and in lung cancer (11-14).

We recently reported that the administration of immunotherapy with immune checkpoint inhibitors (ICI) for the first primary cancer is associated with a major reduction risk of SPC (15). This was observed in the exhaustive population of cancer patients treated in the cancer center over a 6 year period, screening the patient records of the exhaustive database of patients with a FPC treated in a comprehensive cancer center, the Centre Leon Berard (CLB) (16).

In the present work, we explored the impact of ICI on the reduction of the risk of SPC according to patient characteristics, in different age groups and histotypes, exploring also the interaction with the administration of cytotoxic chemotherapy for the FPC. The incidence of second primary cancer was reduced in all subgroups after the exposure to immunotherapy with ICI and/or cytotoxic chemotherapy cancer in this series of 46829 patients.

Methods

Patients

All patients, adults and children, diagnosed with a primary tumor in the Centre Leon Berard (CLB), Lyon, France, from Jan 2013 to Dec 2018 were considered in this work. Data from patients with a newly diagnosed malignant tumors or locally aggressive rarely metastasizing tumors (e.g giant cell tumor or the bone or desmoid tumors) between January 2013 and December 2018 were collected. Only patients not opposing to the re-analysis of their anonymized health data within internal academic studies were included according to the standard operating procedures of the CLB and to the national and European Union (EU) legislation. Specifically, the study was approved by the national Commission (CNIL Délibération N° 2016-331 du 10 novembre 2016 (N° autorisation 1773637)) and by the local institutional review board of the Centre Leon Berard on May 2019. A limited set of anonymous de-identified patient characteristics, specifically, gender, age, tumor site, stage and histology and treatments administered (surgery, radiotherapy, cytotoxic treatments and immunotherapy with immune check point inhibitors) were collected and analyzed. Records from 46863 patients matching these characteristics were extracted and analyzed. 34 patients with synchronous cancers were excluded for a total population of 46829 patients for this study. 1163 patients in this time period received immunotherapy as part of the treatment of the first cancer. The immune checkpoint inhibitor (ICI) antibodies used for the 1163 patients who received immunotherapy for their first cancer were the following treatments : nivolumab (n=420, 36.6%),

pembrolizumab (n=221, 19.0%), atezolizumab (n=92, 7.9%), durvalumab (n=87, 7.4%), ipilimumab (n=72, 6.1%), or a combination of one of these ICI with cytotoxic chemotherapy, either synchronous, or sequentially (n=271, 23.4%).

Extracting Electronic Patient Records (EPR) with the Consore tool

The electronic patient records (EPR) of the patients of the CLB matching the inclusion criteria, and diagnosed from Jan 2013 to Dec 2018 were first extracted for structured data, eg age gender, histological types of cancers, dates of diagnosis.... The EPR system of the CLB includes a standard set of data (e.g. tumor(s) characteristics, staging, first treatments, dates, follow-up,...), but other information such as subsequent lines of treatment may be present only in unstructured data formats. For these, the EPRs were extracted with the Consore tool (15, <https://www.sword-group.com/en/news/projet-consore>). ConSoRe is an academic data analytics solution aggregating diverse forms of structured and unstructured data extracted from EPR and structuring cancer management for all patients. ConSoRe uses natural language processing to search aggregated data and perform advanced data mining. Both cancers and locally aggressive tumors rarely (<5%) metastasizing, typically desmoid tumors or giant cell tumors of the bones were added. The characteristics extracted included: gender, age, dates, histotype and stages of first and second cancers, surgery, chemotherapy, RT and immunotherapy for the first cancer, relapse (and date) of the first cancer, date of last news, date of death. The extracted relevant structured data was integrated in Excel files. 1455 of the 2119 (68.7%) patients with SPC identified by the Consore program had their SPC formally declared by their responsible physician in the electronic patient record. In addition to this Consore extraction, 2818 electronic patient records were manually screened for confirm immunotherapy use for the first primary cancer and/or for the presence/absence of a diagnosis of second primary cancer. Six additional second primary cancers were identified; 283 possible SPC were reclassified as relapses of the FPC. A total of 1830 confirmed second primary cancers are thus documented in this series of 46829 patients. All 1163 files of patients treated with ICI were screened manually and 7 SPC were identified in this subgroup.

Analysis

A descriptive presentation of the patient characteristics is presented in Table 1. The event considered in this study was the diagnosis of a SPC. To describe the survival time from the FPC to the diagnosis of a SPC, which is the time to event used in the present work, the following methodology was used: survival without second cancer was defined as the time from the date of histological diagnosis of the first cancer to the date of the histological diagnosis of a second cancer. Patient who died without a diagnosis of second cancer were censored at the date of death. Other patients were censored at the date of last contact of the patient. To limit potential biases related to disease severity which could have had an impact on decision of treatment with immunotherapy or chemotherapy, a landmark analysis was conducted with landmark thresholds of 6 months, reducing therefore the number of patients analyzed. All patients with a diagnosis of SPC or last news inferior to this threshold are removed from these specific analyses.

Since immunotherapy with ICI was given mostly to patients with advanced disease, by definition at higher risk of mortality as compared to patients with localized disease and with a possibly shorter life expectancy, a competing risk survival method was used to estimate the risk of being alive without SPC.

Risk of second primary cancer was evaluated using Cox proportional hazard model in an univariate and then multivariate analysis. Parameters tested were those published as risk factors for SPC (1-10), age, gender, cancer types, metastatic disease at diagnosis, as well as the application of

immunotherapy and cytotoxic chemotherapy for the FPC. Backward selection procedure was used to determine the final model by removing non-significant variables ($p>0.05$) one at a time. All statistical analyses will be performed using SAS® software, v 9.4 (SAS institute Inc, Cary, NC, USA).

Results

All 46829 patients with a newly diagnosed cancer treated in the CLB matching the criteria (see Methods) were analyzed. Their characteristics are presented in Table 1. At diagnosis, 7438 patients had metastasis (15.9%) and a total of 11434 (24.4%) had diagnosed metastasis during the observation period (2013-2018). 8513 (18.2%) died during this period. In the same period, 1830 (3.9%) patients had a diagnosis of a SPC (Table 1). The median interval from FPC to SPC of 11.1 months (range 0-78 months). Median follow-up of the series is 19 months. 18128 (38.7%) patients received cytotoxic chemotherapy for the treatment of the FPC and 1163 (2.5%) received immunotherapy with ICI for the treatment of the FPC during this period (Table 1).

Despite the large size of the series, the number of patients treated with ICI only for their FPC is limited ($N=32$) (Table 1). We therefore decided to pool them with the group of patients treated with IT and CT for their FPC hereunder. Seven SPC were reported in the group of 1163 (0.6%) patients receiving ICI (with or without cytotoxic chemotherapy) for their FPC vs 437 (2.6%) in the group of 16997 patients receiving cytotoxic chemotherapy (CC) and no immunotherapy for the first cancer, vs 1386 of 28669 (4.8%) for those receiving neither CC nor ICI (Table 2) ($p<0.0001$). The difference was also statistically significant when comparing individually the group receiving immunotherapy vs those receiving cytotoxics only ($p<0.0001$) (Table 2).

Figure 1A presents the time from the diagnosis of the first primary cancer to the date of diagnosis of the second cancer in patients 1) who received immunotherapy with ICI, with or without CC for the FPC, 2) who received CC without ICI, and who received neither ICI nor CC with a landmark analysis at 6 months (see material and methods). The risk to develop a SPC was lower in patients treated by immunotherapy with or without chemotherapy ($HR=0.07$; $CI_{95\%}=0.05-0.20$), and cytotoxic chemotherapy without immunotherapy ($HR=0.36$; $CI_{95\%}=0.32-0.41$), as compared to patients receiving neither cytotoxic chemotherapy, nor immunotherapy both in the whole population (Figure 1A, and Table 3).

When focusing on patients with no diagnosis of metastasis in the observation period, which includes 24356 patients with 1277 SPC, (Figure 1B), a significant reduction in the incidence of SPC was also observed in the group treated with cytotoxic chemotherapy only for the FPC ($HR=0.57$; $CI_{95\%}=0.50-0.65$), and no second cancer was observed in the group treated with ICI (Figure 1B, $p<0.0001$).

Analyzing each individual year of study (from 2013 to 2018), the incidence of SPC was consistently smaller for patients treated with ICI and/or cytotoxics, vs cytotoxics alone vs patients not receiving cytotoxics or ICI (Suppl. Fig. 1). The reduction of the risk of SPC with immunotherapy vs cytotoxics only was observed for children as well as young and older adults (Table 2).

We then analyzed the impact of immunotherapy on the risk of SPC in patients according to the primary site of the FPC (Suppl. Figure 2). Treatment with ICI for the FPC was associated with a reduction of the incidence of SPC in the different subgroups of FPC (e.g. lung, head and neck, colorectal, sarcoma, prostate, skin cancers...). The sites and histotypes of the SPC identified in the group selected for the landmark analysis are presented in Supplementary table 1. The second cancers observed in the group of patients treated with immunotherapy for the FPC were colorectal

adenocarcinoma (n=3), upper digestive tract cancers (N=1), melanoma (n=1), and other site (n=2). Though the number of SPC from the GI tract was overall decreased, 4 of the 7 patients treated with immunotherapy (57,2%) for the FPC had a SPC from the digestive tract vs 145/1270 (11,5%, p=0.0001) for patients not receiving ICI for the FPC.

A multivariate Cox model was conducted to explore the clinical characteristics and therapeutic actions for the FPC associated with the risk to develop a SPC. Of note, the numbers in table 3 are different from those of table 2 because of the 6 months landmark analysis. Gender, age, stage (metastasis at diagnosis), tumor sites, or histotypes (sarcoma) as well as immunotherapy and cytotoxic chemotherapy were introduced in the model. Young age, thyroid, breast and prostate cancer, presence of metastasis at diagnosis, as well as administration of chemotherapy and/or immunotherapy were correlated to a reduced risk of SPC (Table 3A).

A second multivariate Cox model was conducted on the population of patients without documented metastasis of their FPC, and introducing the same parameters (age, gender, tumor sites and histotypes, cytotoxic and/or immunotherapy administration for the FPC. Again, age, tumor type, as well as administration of chemotherapy and/or immunotherapy were correlated to the risk of SPC (Table 3B). No SPC were observed in patients treated with immunotherapy in this subgroup.

Discussion

Second primary cancers (SPC) are an important cause of death for children and adult patients treated for a first primary cancer in long term remission (1-3). The etiological factors of SPC are those of the FPC (e.g. smoking, alcohol, diet), but also the genotoxic treatments used for the first cancer. The hazard ratio associated to the risk of SPC as compared to the general population are reported to range from 1.2 to up to 30 depending on the FPC and its treatment (1-10). We recently reported that the administration of immune checkpoint inhibitors, mostly PD1/PDL1 or CTLA4 antibodies for the FPC was associated with a reduced risk to develop a SPC (15). Only 7 of the 1163 patients treated with immune checkpoint inhibitors for a first cancer had a diagnosis of a SPC in this observation period.

In the present study, we report an analysis of the impact of ICI on the risk of SPC in the different age groups, histotypes and according to the administration of cytotoxic treatments for the FPC. The results presented here indicate that not only immunotherapy but also the administration of cytotoxic chemotherapy was associated with a reduced incidence of SPC in the population and period explored. Cytotoxic treatment for the FPC was also associated with a reduction of the incidence of the SPC, even when immunotherapy was not administered, but the reduction observed was of lower magnitude. This is paradoxical given the abundant literature on the increased risk of SPC in survivors treated with alkylating agents, anthracyclines and others (1,3,17,18). Indeed, cytotoxic agents increase the risk of secondary myeloid malignancy (1-5,17,18), but their impact is less consistent for solid tumors, depending on the drug and organs. The dose of procarbazine correlates to the risk of second solid cancers, but this agent is now less used; cyclophosphamide exposure increases bladder cancer (18). An increased risk of sarcoma was reported after exposure to anthracyclines but not after other cytotoxic agents, including alkylating agents (17). These secondary solid tumors are however diagnosed later at a median of >10 years after the diagnosis of first cancer, i.e much later than the observation period of the present study. Conversely, a 50% reduction of the risk of contralateral breast cancer is observed in patients at high risk who had received adjuvant cytotoxic chemotherapy for the first breast cancer, consistently with the present observations (19).

The reduction of the number of SPC in patients treated with immunotherapy for their FPC is of larger magnitude in this series with a hazard ratio inferior to 0.1. With the limited follow-up, it remains unclear whether treatment with immune check point inhibitors (ICI) for the FPC may either delay or

prevent the emergence of SPC. It is actually striking to observe that the median time between the FPC and the SPC was 11 months (ranging from 0 to 78 months) but this must be considered in the context of a median follow-up of 19 months for this series. This follow-up is relatively short in view of the usual reported delays to the emergence of the second cancer in most series of the literature, frequently exceeding 10 years. The observed short term reduction of risk of SPC may involve the reactivation of an efficient antitumor immune response against an infra-clinical tumor, as shown for the adjuvant treatment of high risk melanoma (12,13). The reduction associated with ICI administration was consistent for each of the individual years, from 2013 to 2018, of this study, and observed in all age group and for all histotypes and primary cancer sites explored.

To our knowledge, the impact of immunotherapy for the FPC on the risk to develop a second primary cancer had not been reported in another series. The analysis of the published literature on large clinical trials of immunotherapy with ICI in the approved indications is not informative on the incidence of SPC. Most often none are reported in these series (20,21). Even in cancers occurring in patients with germline mismatch repair deficiency, who are prone to develop multiple tumor types and where immunotherapy is highly active, this has not been reported to our knowledge (22-29). It will be important to study the incidence of second primary cancer in published randomized clinical trials evaluating ICI in the adjuvant setting of non-metastatic cancers.

Of note, a large proportion of patients in whom immunotherapy was applied for their FPC is known to be at risk for a SPC given the etiological factors of their FPC (e.g. lung and head and neck cancers or melanoma, with sun exposure, smoking, alcohol). We would have expected a higher risk of SPC in this population, even in advanced phase. The opposite was seen, and actually no head and neck carcinomas, lung cancer, bladder nor renal cancers were observed as SPC in the group treated with ICI for the FPC. Actually, histotypes and sites of SPC observed in the group treated with immunotherapy for the FPC were different from those treated without ICI for the FPC, with more digestive tract cancers in the rare SPC observed in patients treated with ICI. An analysis of the genomic and molecular characteristics of these SPC occurring after immunotherapy is ongoing.

This study has several limitations. A part of the data were collected through an automatic extraction using natural language processing of the electronic patient records. To ensure the quality of data extracted through this screening, a second, manual, screening of 2818 files was thus performed by the team on all patients who received immunotherapy and on those where the diagnosis of SPC had not been formally declared by the physician in charge. Only 6 additional SPC were identified by this procedure. Another limitation, is that the follow-up of the series is 19 months; indeed further analysis will be required in the same series in the years to come to determine whether our results point to a reduction of the incidence or only to a prolonged delay to diagnosis. Treatment with radiotherapy for the FPC was not integrated in this report. It was not found associated with an increased risk of SPC over the observation period and did not impact on the conclusion of the multivariate analysis (not shown). Another issue is that patients treated with ICI had often advanced disease, receiving immunotherapy with a short life expectancy. For this reason, a second analysis was conducted on the subgroup of patients who never had metastasis of their primary cancers. Both analyses are consistent in their results. Finally, different histological groups of tumors were grouped to ensure sufficient numbers e.g. in "lung cancer", which gather adenocarcinoma or squamous cell carcinoma or "skin cancers", which gather melanoma, Merkel cell carcinomas, epidermoid carcinoma and others. Specific analysis on given histological subtypes will be required in the future. Though consistent for each individual years here, this early reduction in the risk of SPC requires validation from other large series and datasets. This is a large, exhaustive, but single center study which needs to be confirmed using other exhaustive databases of electronic patient records of comprehensive cancer centers. It must be stressed that this study is not a clinical trial and additional series are needed to confirm this observation.

These results have potentially important consequences, in particular in adolescent and young adults cured of the first cancer and in whom SPC are a too important causes of death. Their long life expectancy may expose to a high cumulative risk of second primary malignancy. Several studies have explored the immunological environment of premalignant lesions, and indicate the presence of active immune responses (27,28, 30,31).

Altogether, these results collected in a large exhaustive database of 46829 patients population treated in a comprehensive cancer center indicates that the risk of second primary cancer is reduced in the years following the treatment of the cancer when immunotherapy with ICI is used for the treatment of the first cancer. These results are consistent in all age groups, for all histotypes and in each of the different years of this study. A longer follow-up will be needed to determine whether this reduction of incidence of SPC is maintained over time. If these observations are confirmed, these results open a novel area of clinical research in tertiary prevention for cancer patients, which could test an active prevention of second primary cancers, in a population of patients at high risk, such as those with germline predisposition to cancer, or with long term exposure to carcinogens such as smoking. A randomized study is in preparation.

Funding

LYRICAN (INCA-DGOS-INSERM 12563), NetSARC (INCA & DGOS) and TMRG (INCA & DGOS), InterSARC (INCA), DEvweCAN (ANR-10-LABX-0061), PIA Institut Convergence François Rabelais PLAsCAN (PLASCAN, 17-CONV-0002), RHU4 DEPGYN (ANR-18-RHUS-0009), EURACAN (EC 739521) Association DAM's, la Fondation ARC, Infosarcome, Ligue de L'Ain contre le Cancer, La Ligue contre le Cancer, funded this study.

Conflict of Interest

David Perol : Research Grant : MSD Avenir ; Honoraria : Roche, BMS, MSD, Astra Zeneca ; Travels : Astra Zeneca

Aude Flechon : grants, personal fees and nonfinancial support from ROCHE, AZ, PFIZER, MSD, BMS

Jerome Fayette : grants, personal fees and nonfinancial support from AZ, MSD, BMS, Merck Serono, Biogen, Rakuten, Roche, Servier

Olivier Tredan : Roche, Astra-Zeneca, Novartis, Pfizer, MSD, BMS, Sandoz

Helene Boyle : received travel expenses from BMS, Pfizer and honoraria from BMS and Pfizer

Maurice Perol : grants, personal fees and nonfinancial support from Roche, Genentech, Eli Lilly, Pfizer, Boehringer-Ingelheim, MSD, Bristol-Myers Squibb, Novartis, Pierre Fabre, AstraZeneca, Takeda, Chugai, Amgen (adboards et symposiums)

Thomas Bachelot : advisory board and travel from Roche, Novartis, Astrazeneca, Pfizer, seattle genetic

Philippe Cassier : Roche/Genentech, AZ, Amgen, EMD/Merck Serono, Novartis (sympo/adboard)

Virginie Avrillon : Honoraria for Advisory Boards: Bristol-Myers Squibb

Eve-Marie Neidhardt-Berard : received travel expenses and honoraria from MSD, BMS, Pierre Favre, Novartis.

Frank Nicolini : grants, personal fees and nonfinancial support from Novartis, Incyte Biosciences, Sun Pharma Ltd, Ylang Pharma Inc

Aurélie Swalduz : Honoraria for Advisory Boards: Roche, Bristol-Myers Squibb ; Symposiums: Roche, AstraZeneca, Bristol-Myers Squibb

Pierre Saintigny : Research grant from BMS and Roche

Patrick Mehlen declares to have interest in Netris Pharma as founder and minority shareholder.

Isabelle Ray-Coquard : Honoria : Abbvie, Agenus, Advaxis, BMS, PharmaMar, Genmab, Pfizer, Astra Zeneca, Roche, GSK, MSD, Deciphera, Mersena, Merck Sereno, Novartis, Amgen, Tesaro, and Clovis. Advisory/consultancy : Abbvie, Agenus, Advaxis, BMS, PharmaMar, Genmab, Pfizer, Astra Zeneca, Roche/Genentech, GSK, MSD, Deciphera, Mersena, Merck Sereno, Novartis, Amgen, Tesaro, and Clovis. Research grant : MSD, Roche, BMS.

JYB :Research support and honoraria from Roche, MSD, BMS, Bayer, Novartis, GSK, Astra-Zeneca

The remaining authors have nothing to declare

References:

- 1: Travis LB, Demark-Wahnefried W, Allan JM, Wood ME, Ng AK. Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. *Nat Rev Clin Oncol*. 2013; 10:289-301.
- 2: Newhauser WD, Durante M. Assessing the risk of second malignancies after modern radiotherapy. *Nat Rev Cancer*. 2011; 11: 438-48.
- 3: Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. *Nat Rev Cancer*. 2002; 2:124-32.
- 4: Eichenauer DA, Becker I, Monsef I, et al. Secondary malignant neoplasms, progression-free survival and overall survival in patients treated for Hodgkin lymphoma: a systematic review and meta-analysis of randomized clinical trials. *Haematologica*. 2017; 102:1748-1757.
- 5: Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N Engl J Med*. 2015; 373:2499-511.
- 6: Chattopadhyay S, Zheng G, Sud A et al. Second primary cancers in non-Hodgkin lymphoma: Family history and survival. *Int J Cancer*. 2020; 146:970-976.
- 7: Vakharia PP, Kelm RC, Orrell KA, et al. Risks for noncutaneous second primary malignancy in cutaneous malignant melanoma survivors: an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) program. *Int J Dermatol*. 2020 Jan 23;10.1111/ijd.14781.
- 8: Li D, Weng S, Zhong C, et al. Risk of Second Primary Cancers Among Long-Term Survivors of Breast Cancer. *Front Oncol*. 2020; 9:1426.
- 9: Mehtälä J, Zong J, Vassilev Z, et al. Overall survival and second primary malignancies in men with metastatic prostate cancer. *PLoS One*. 2020 Feb 21;15(2):e0227552.
- 10: Feller A, Matthes KL, Bordoni A et al. The relative risk of second primary cancers in Switzerland: a population-based retrospective cohort study. *BMC Cancer*. 2020; 20: 51.
11. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer*. 2019; 19:133-150. doi: 10.1038/s41568-019-0116-x. PMID: 30755690; PMCID: PMC6705396.
12. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med*. 2017 Nov 9;377(19):1824-1835.
13. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med*. 2018; 378:1789-1801.

14. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after chemoradiotherapy in Stage III NSCLC. *N Engl J Med.* 2018; 379:2342-2350.
15. Heudel P, Chabaud S, Perol D, Ray-Coquard I, Blay JY. Reduced risk of second primary cancer in patients treated with immune checkpoint inhibitors for a first cancer. *Ann Oncol.* 2020 Sep 8:S0923-7534(20)42429-9. doi: 10.1016/j.annonc.2020.09.001
16. Heudel P, Livartowski A, Arveux P et al. The ConSoRe project supports the implementation of big data in oncology. *Bull Cancer* 2016; 103: 949-5
17. Henderson TO, Rajaraman P, Stovall M, et al. Risk factors associated with secondary sarcomas in childhood cancer survivors: a report from the childhood cancer survivor study. *Int J Radiat Oncol Biol Phys.* 2012; 84:224-30.
18. Morton LM, Swerdlow AJ, Schaapveld M et al. Current knowledge and future research directions in treatment-related second primary malignancies. *EJC Suppl.* 2014; 12:5-17.
19. Reding KW, Bernstein JL, Langholz BM, et al. Adjuvant systemic therapy for breast cancer in BRCA1/BRCA2 mutation carriers in a population-based study of risk of contralateral breast cancer. *Breast Cancer Res Treat.* 2010; 123:491-8.
20. Xu C, Chen YP, Du XJ, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis *BMJ* 2018;363:k4226
<http://dx.doi.org/10.1136/bmj.k4226>
21. Chai Q-Q, Du J-Y, Zhu J and Wu B. The Differences in the Safety and Tolerability of Immune Checkpoint Inhibitors as Treatment for Non-Small Cell Lung Cancer and Melanoma: Network Meta-Analysis and Systematic Review. *Front. Pharmacol.* 2019; 10:1260.
22. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. *Nat Rev Cancer.* 2015; 15:181-94.
23. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 2015; 372:2509-20.
24. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol.* 2018; 36: 773-779.
25. Marabelle A, Le DT, Ascierto PA et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol.* 2020; 38:1-10.
26. Le DT, Kim TW, Van Cutsem E, et al. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. *J Clin Oncol.* 2020; 38:11-19.

27. Mendis S, Gill S. Cautious optimism-the current role of immunotherapy in gastrointestinal cancers. *Curr Oncol*. 2020;27(Suppl 2):S59-S68.
28. Spira A, Yurgelun MB, Alexandrov L, et al. Precancer Atlas to Drive Precision Prevention Trials. *Cancer Res*. 2017 ;77:1510-1541.
29. Spira A, Disis ML, Schiller JT, et al. Leveraging premalignant biology for immune-based cancer prevention. *Proc Natl Acad Sci U S A*. 2016 ; 113:10750-8.
30. Mascaux C, Angelova M, Vasaturo A, et al. Immune evasion before tumour invasion in early lung squamous carcinogenesis. *Nature*. 2019; 571: 570-575.
31. Foy JP, Bertolus C, Ortiz-Cuaran S, et al. Immunological and classical subtypes of oral premalignant lesions. *Oncoimmunology*. 2018 Sep 21;7(12):e1496880.

Legends of the figures :

Figure 1: Time to second primary tumor according to the treatment given for the first primary tumor.

Figure 1A: Time to second primary tumor in pts treated with immunotherapy and/or cytotoxic chemotherapy or none for the first primary cancer (all patients).

Figure 1B: Time to second primary tumor in pts treated with immunotherapy and/or cytotoxic chemotherapy or none for the first primary cancer in patients without documented metastasis.

Survival analysis was performed using competing risk analysis to estimate the risk of being alive without SPC and 6-months landmark analysis to limit analysis to subjects who have survived long enough for treatment to be initiated. Due to this last constraint, 12432 patients (26.5%) with SPC or death before 6 months were excluded from the survival analysis. Thus, the population in this analysis consists of 34397 patients. **CIF est.** : cumulative incidence function with competing risks data.

Figure 1: Time from primary cancer to secondary cancer in different subgroups of patients

Figure 1A : Time to second primary tumor according to systemic treatments given for the FPC

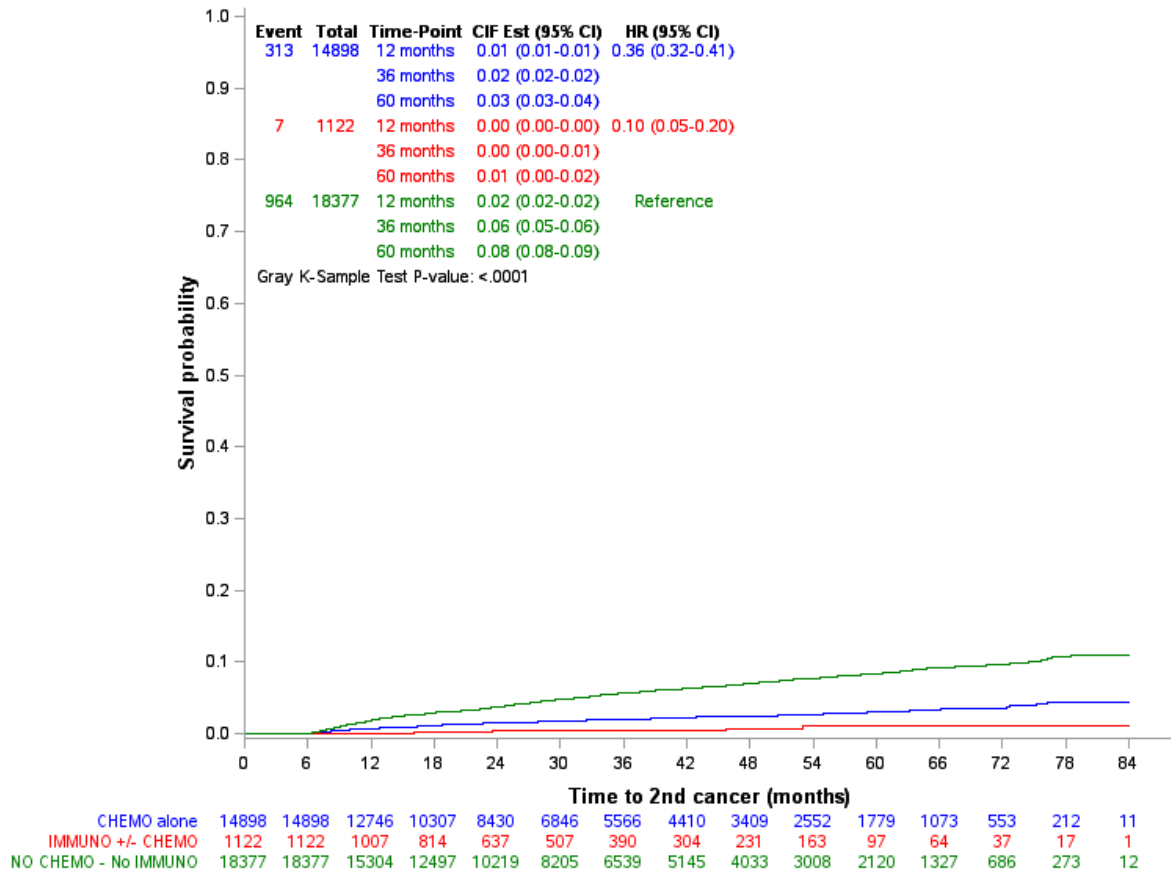


Figure 1B: Time to second primary tumor according to systemic treatments given for the FPC in patients without documented metastasis

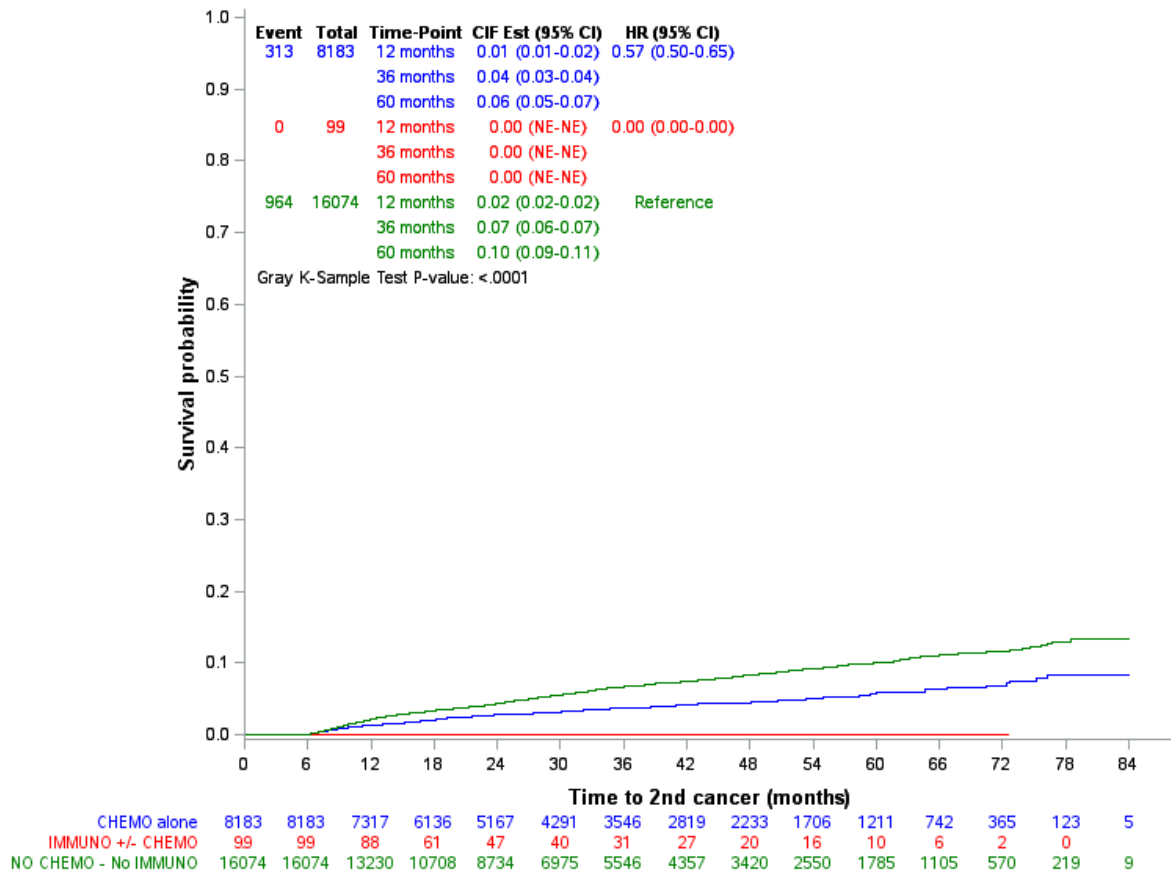


Table 1 Description of the patients and treatments received for the first primary cancer before the second primary cancer

	Cytotoxics only N=16997		Cytotoxics and Immunotherapy N=1131		Immunotherapy only N=32		Neither Cytotoxics nor immunotherapy N=28669		All patients N=46829	
	N	%	N	%	N	%	N	%	N	%
Gender										
F	9657	(56.8%)	426	(37.7%)	14	(43.8%)	16628	(58.0%)	26725	(57.1%)
M	7340	(43.2%)	705	(62.3%)	18	(56.3%)	12041	(42.0%)	20104	(42.9%)
Age of cancer1										
N	16997		1131		32		28669		46829	
Mean(Et)	57.7 (18.6)		59.6 (12.6)		50.8 (19.0)		57.2 (18.8)		57.5 (18.6)	
Médian (min; max)	60.9 (0; 100)		60.9 (0; 90)		54.9 (10; 77)		60.0 (0; 115)		60.4 (0; 115)	
Q1-Q3	48.1-70.4		52.0-67.8		43.8-65.1		46.1-70.5		47.1-70.4	
Classes of age for first cancer\$										
<30	1436	(8.4%)	24	(2.1%)	5	(15.6%)	2597	(9.1%)	4062	(8.7%)
[30-60[6737	(39.6%)	509	(45.0%)	14	(43.8%)	11717	(40.9%)	18977	(40.5%)
>=60	8824	(51.9%)	598	(52.9%)	13	(40.6%)	14355	(50.1%)	23790	(50.8%)
Cancer sites										
Breast	4809	(28.3%)	33	(2.9%)	1	(3.1%)	6857	(23.9%)	11700	(25.0%)
Lung	2125	(12.5%)	486	(43.0%)	11	(34.4%)	2084	(7.3%)	4706	(10.0%)
Head & Neck	929	(5.5%)	167	(14.8%)	5	(15.6%)	2286	(8.0%)	3387	(7.2%)
Gyneco.	1105	(6.5%)	62	(5.5%)	0	(0.0%)	1967	(6.9%)	3134	(6.7%)
Digestive	1445	(8.5%)	53	(4.7%)	1	(3.1%)	1498	(5.2%)	2997	(6.4%)
Connective tissue	646	(3.8%)	19	(1.7%)	0	(0.0%)	2253	(7.9%)	2918	(6.2%)
Colorectal	1099	(6.5%)	30	(2.7%)	1	(3.1%)	1545	(5.4%)	2675	(5.7%)
Prostate	643	(3.8%)	11	(1.0%)	0	(0.0%)	1732	(6.0%)	2386	(5.1%)
Urothelial	434	(2.6%)	142	(12.6%)	1	(3.1%)	837	(2.9%)	1414	(3.0%)
Thyroid	220	(1.3%)	7	(0.6%)	0	(0.0%)	1106	(3.9%)	1333	(2.8%)
Skin cancer	149	(0.9%)	57	(5.0%)	0	(0.0%)	713	(2.5%)	919	(2.0%)
Others	3393	(20.0%)	64	(5.7%)	12	(37.5%)	5791	(20.2%)	9260	(19.8%)
Metastatic at diagnosis										
No	10199	(60.0%)	492	(43.5%)	31	(96.9%)	28669	(100.0%)	39391	(84.1%)
Yes	6798	(40.0%)	639	(56.5%)	1	(3.1%)	0	(0.0%)	7438	(15.9%)
Second primary cancer										
No	16560	(97.4%)	1125	(99.5%)	31	(96.9%)	27283	(95.2%)	44999	(96.1%)
Yes	437	(2.6%)	6	(0.5%)	1	(3.1%)	1386	(4.8%)	1830	(3.9%)
Histotypes (2nd cancer)										
Head&Neck	47	(0.3%)	0	(0.0%)	0	(0.0%)	185	(0.6%)	232	(0.5%)
Sarcoma	43	(0.3%)	0	(0.0%)	0	(0.0%)	153	(0.5%)	196	(0.4%)

Lung	40	(0.2%)	0	(0.0%)	0	(0.0%)	140	(0.5%)	180	(0.4%)
Breast	54	(0.3%)	0	(0.0%)	0	(0.0%)	104	(0.4%)	158	(0.3%)
Digestive*	36	(0.2%)	0	(0.0%)	1	(3.1%)	99	(0.3%)	136	(0.3%)
Skin	30	(0.2%)	1	(0.1%)	0	(0.0%)	83	(0.3%)	114	(0.2%)
Colorectal	22	(0.1%)	3	(0.3%)	0	(0.0%)	69	(0.2%)	94	(0.2%)
Gyneco	19	(0.1%)	0	(0.0%)	0	(0.0%)	70	(0.2%)	89	(0.2%)
Urothelial	12	(0.1%)	0	(0.0%)	0	(0.0%)	53	(0.2%)	65	(0.1%)
Thyroid	11	(0.1%)	0	(0.0%)	0	(0.0%)	38	(0.1%)	49	(0.1%)
Prostate	4	(0.0%)	0	(0.0%)	0	(0.0%)	31	(0.1%)	35	(0.1%)
Other	119	(0.7%)	2	(0.2%)	0	(0.0%)	361	(1.3%)	482	(1.0%)

- \$: adults and children treated in the CLB were all included in this analysis.
- * : digestive : non colorectal carcinomaCRC

Table 2: Second primary cancers in the different age classes according to the treatment of the primary cancer

Systemic treatment for the first primary cancer										
	Cytotoxics only		Cytotoxics and immunotherapy		Immunotherapy only		No cytotoxics, no immunotherapy		All Patients	
	N=16997	(%)	N=1131	(%)	N=32	(%)	N=28669	(%)	N=46829	(%)
Age at first cancer										
[0-30[38/1436	2.6%	0/24	0.0%	0/5	0.0%	123/2597	4.7%	161/4062	4.0%
[30-60[151/6737	2.2%	1/509	0.2%	0/14	0.0%	496/11717	4.2%	648/18977	3.4%
>=60	248/8824	2.8%	5/598	0.8%	1/13	7.7%	767/14355	5.3%	1021/23790	4.3%
All	437/16997	2.6%	6/1131	0.5%	1/32	3.1%	1386/28669	4.8%	1830/46829	3.9%

Table 3: Multivariate analysis of predictive factors for second primary cancer.

Table 3A : Entire series

Parameter	Univariate analysis			Multivariate analysis	
	Events/competing events/N (landmark population)	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Sex			<.0001		
Male	654 / 4439 / 15087	1		NS	
Female	630 / 2157/19310	0.791 (0.709-0.882)			
Age at FCD			<.0001		<.0001
<30	93 / 239 /3062	1		1	
[30-60[451 / 2223 / 14069	1.056 (0.844-1.321)		1.516 (1.200-1.913)	
>=60	740 / 4134 / 17266	1.468 (1.182-1.822)		1.887 (1.496-2.381)	
Metastasis at diagnosis			<.0001		<.0001
No	1280 / 3952 / 28311	1		1	
Yes	4 / 2644 / 6086	0.011 (0.005-0.024)		0.01 (0.005-0.020)	
Localisation of FC			<.0001		<.0001
Lung	107 / 1447 / 3381	1		1	
Melanoma	31 / 98 / 604	1.924 (1.290-2.869)		0.919 (0.616-1.369)	
Head & Neck	145 / 711 / 2730	1.685 (1.313-2.163)		0.944 (0.736-1.211)	
Prostate	67 / 271 / 1828	1.143 (0.843-1.55)		0.622 (0.459-0.843)	
Colorectal	81 / 504 / 2091	1.202 (0.901-1.604)		1.070 (0.802-1.427)	
Breast	199 / 422 / 8619	0.717 (0.567-0.907)		0.408 (0.321-0.518)	
Sarcoma	122 / 320 / 1976	2.044 (1.576-2.653)		1.311 (0.999-1.720)	
Gynae	79 / 386 / 2353	1.157 (0.865-1.548)		0.886 (0.662-1.185)	
Urological	68 / 427 / 1072	1.889 (1.393-2.560)		1.996 (1.474-2.702)	
Gastro-intestinal	68 / 993 / 2172	1.007 (0.743-1.364)		0.872 (0.644-1.182)	
Thyroid	17 / 97 / 796	0.771 (0.463-1.285)		0.454 (0.272-0.759)	
Other	300 / 920 / 6775	1.386 (1.111-1.728)		0.777 (0.621-0.972)	
Treatment for the FPC			<.0001		<.0001
No Chemo / No Immuno	964 / 2517 / 18377	1		1	
Chemo alone	313 / 3634 / 14898	0.364 (0.320-0.413)		0.698 (0.609-0.799)	
Immuno +/- Chemo	7 / 545 / 1122	0.097 (0.046-0.203)		0.770 (0.388-1.53)	

Table 3B: Patients without metastasis of the first cancer during the observation period

Univariate analysis				Multivariate analysis	
Parameter	Events/competing events/N (landmark population)	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Sex			<.0001		
Male	647 / 1762 / 9851	1		NS	
Female	630 / 590 / 14505	0.682 (0.611-0.761)			
Age at FPC			<.0001		<.0001
<30	93 / 93 2506	1		1	
[30-60[450 / 557 / 9941	1.252 (1.000-1.566)		1.522 (1.205-1.921)	
>=60	734 / 1702 / 11909	1.773 (1.427-2.202)		1.887 (1.495-2.381)	
Anatomic site of FPC			<.0001		<.0001
Lung	100 / 422 / 1396	1		1	
Melanoma	31 / 53 / 336	1.016 (0.679-1.521)		0.951 (0.635-1.424)	
Head & Neck	145 / 336 / 2015	0.988 (0.766-1.275)		0.978 (0.757-1.264)	
Prostate	67 / 79 / 1333	0.701 (0.515-0.954)		0.639 (0.469-0.871)	
Colorectal	81 / 127 / 1061	1.106 (0.825-1.483)		1.108 (0.826-1.487)	
Breast	199 / 88 / 7198	0.365 (0.287-0.464)		0.416 (0.325-0.531)	
Sarcoma	122 / 86 / 1482	1.201 (0.920-1.567)		1.349 (1.022-1.782)	
Gynae	79 / 89 / 1408	0.891 (0.664-1.198)		0.913 (0.679-1.229)	
Urological	68 / 88 / 462	2.140 (1.573-2.911)		2.090 (1.536-2.844)	
Gastro-intestinal	68 / 319 / 1074	0.912 (0.670-1.242)		0.910 (0.669-1.240)	
Thyroid	17 / 34 / 606	0.451 (0.270-0.754)		0.466 (0.278-0.781)	
Other	300 / 631 / 5816	0.680 (0.542-0.853)		0.798 (0.632-1.006)	
Treatment for the FPC			<.0001		<.0001
No Chemo / No Immuno	964 / 1624 / 16074	1		1	
Chemo alone	313 / 694 / 8183	0.571 (0.502-0.648)		0.706 (0.617-0.808)	
Immuno +/- Chemo	0 / 34 / 99	0.000 (0.000-0.000)		0.000 (0.000-0.000)	