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Antibiotic Use Does Not Appear to Influence Response to Nivolumab

COURECHE KADERBHAI[1,2], CORENTIN RICHARD[2,3], JEAN DAVID FUMET[1,2], ANNE AARNINK[1], PASCAL FOUCHER[4], BRUNO COUDERT[1], LAURE FAVIER[1], AURÉLIE LAGRANGE[1], EMERIC LIMAGNE[2,3], ROMAIN BOIDOT[2,3] and FRANCOIS GHIRINGHELLI[1,2,3]

[1]*Department of medical oncology, Center GF Leclerc, Dijon, France;*
[2]*Plateform transfer in biological Oncology, Dijon, France;*
[3]*GIMI Genetic and Immunology Medical Institute, Dijon, France;*
[4]*Department of Thoracic Oncology CHU, Dijon, France*

Abstract. *Background: Microbiota is known to influence response to anticancer immunotherapy. We examined whether antibiotic usage could impact nivolumab efficacy in patients treated for non-small-cell lung cancer (NSCLC). Patients and Methods: Seventy-four patients with NSCLC were included in this retrospective study. They received nivolumab between 2015 and 2016 (3 mg/kg i.v. q2w). The association between RECIST response and antibiotic usage was determined using Chi-square and Cox proportional hazard model. Results: A total of 17, 21 and 36 patients experienced response, stable disease and progression disease under nivolumab. Only 15 (20.3%) patients were exposed to antibiotic medication in the 3 months before the first nivolumab injection or during treatment. We found a similar response rate for the two populations, without impact of antibiotic exposure (Chi-square test p=0.75). Moreover, we observed no impact of antibiotic medication on progression-free survival under nivolumab (log-rank test, p=0.72). Conclusion: Microbiota modification induced by antibiotics does not appear to affect the efficacy of nivolumab in patients with NSCLC.*

Lung cancer remains the leading cause of cancer-related death worldwide (1). Non-small-cell lung cancer (NSCLC) is the most frequent histological type, representing 80% of all of cases. NSCLC is often diagnosed at an advanced stage when the treatment is palliative and was, until recently, based on platinum-based doublet chemotherapy with a median overall survival of approximatively 1 year, in the absence of oncogenic driver (2). For about 5 years, the development of new molecules targeting negative co-stimulatory receptor or its ligands such as program death 1 (PD1) and program death ligand 1 (PDL1) offered a second chance to patients with this disease. Indeed, major phase III trials validated the use of these antibodies notably directed against PD1 (nivolumab, pembrolizumab) or PDL1 (atezolizumab) in second line (3-6). However, only approximatively a quarter of treated patients experienced response to these immunotherapies, highlighting important interpatient heterogeneity and the necessity to develop validated biomarkers in order to identify patients with an increased probability of response to these antibodies (7).

One explanation of this variability of response to immunotherapy could come from microbiota of the patient, which can vary significantly from one individual to another. It is well known that the microbiota influences the immune system response (8) and especially antitumor immune response (9). Human microbiota is influenced by several factors such host genetics, lifestyle and exposure to antibiotic medication. It has been shown that imbalance of microbiota ecosystem caused by repeated exposure to antibiotic can increase the frequency of some types of cancer such as lung cancer, suggesting a relationship between microbiota and carcinogenesis (10). Because of its impact on the immune response, the microbiota plays an important role in modulation of chemotherapy efficacy by affecting the tumor immunomicroenvironment (11, 12). More recently, the influence of microbiota on immunotherapy response has been demonstrated in mice. Indeed, Vetizou *et al.* showed that the therapeutic efficiency of another antibody directed against negative co-stimulatory receptor called cytotoxic T-lymphocyte antigen 4 (CTLA4), on fibrosarcomas in mice

Correspondence to: Professor François Ghiringhelli, Centre Georges François Leclerc, Genetic and Immunology Medical Institute GIMI, 1 rue du professeur Marion, 21000 Dijon, France. Tel: +33 380393353, Fax: +33 380393434, e-mail: fghiringhelli@cgfl.fr

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Table I. *General patient and tumor characteristics of the two populations.*

Characteristics		Antibiotic exposure	No antibiotic exposure
Age, years	Median (min-max)	69 (51-84)	66 (54-85)
	Mean	68	66
Gender, n (%)	Male	13 (86.7)	47 (79.7)
	Female	2 (13.3)	12 (20.3)
WHO PS, n (%)	0	3 (20.0)	27 (45.8)
	1	12 (80.0)	29 (49.2)
	2	0 (0.0)	3 (5.0)
Histology, n (%)	Adenocarcinoma	7 (46.7)	36 (61.0)
	Squamous cell carcinoma	8 (53.3)	22 (37.3)
	Other	0 (0.0)	1 (1.7)
Smoking history, n (%)	Non-smoking	1 (6.7)	8 (13.6)
	Current or former smoker	14 (93.3)	51 (86.4)
EGFR mutation, n (%)	No	10 (66.7)	34 (57.6)
	Yes	0 (0.0)	4 (6.8)
	Unknown	5 (33.3)	21 (35.6)
KRAS mutation, n (%)	No	9 (60.0)	25 (42.4)
	Yes	1 (6.7)	12 (20.3)
	Unknown	5 (33.3)	22 (37.3)
PDL1 expression, n (%)	Negative	7 (46.6)	22 (37.3)
	≥1%	4 (26.7)	18 (30.5)
	Unknown	4 (26.7)	19 (32.2)
Best response to nivolumab, n (%)	PR + CR	4 (26.7)	13 (22.0)
	SD	5 (33.3)	16 (27.1)
	PD	6 (40.0)	30 (50.9)

EGFR, Epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

was strongly linked to the microbiota, having no efficacy on mice housed in germ-free conditions or treated with antibiotics (13). Sivan *et al*. showed similar results in the context of cancer treatment with anti-PDL1 (14). Replacement of deleterious microbiota by favorable one can restore the efficiency of immunotherapy. Indeed, in the study of Sivan *et al*., comparison in tumor growth of B16 melanomas between two different mice coming from different facilities, highlighted more aggressive tumor and decreased response to anti-PDL1 in mice whose microbiota presented relative loss of *Bifidobacterium* species. Oral feeding of these mice with *Bifidobacterium* or their cohousing with other mice presenting microbiota with *Bifidobacterium* species restored defective processing of tumor control. This difference linked to microbiota was immune-mediated with tumor-specific T-cell responses and intratumoral $CD8^+$ T-cell infiltration significantly higher in mice with *Bifidobacterium* in commensal microbiota. Recently, data started arriving on human with for example, the demonstration of a poorer efficiency of immune checkpoint inhibitor in patients treated for renal cell carcinoma having previously taken antibiotic medication (15). This suggests that modifications of the microbiota, particularly because of exposure to antibiotic medication, can influence responses to immunotherapy in humans. Due to the lack of data on lung cancer and heterogeneity of response to immunotherapy for these patients, we decided to retrospectively search for a link between exposure to antibiotic medication (consequently affecting the microbiota) and response to nivolumab in a cohort of 74 patients with lung cancer treated with this antibody.

Materials and Methods

Patients. This retrospective cohort included 74 patients with locally advanced unresectable or metastatic NSCLC treated with nivolumab in monotherapy at the recommended dose (3 mg/kg *q2* weeks) in second or third line. The patients were taken into care in two French Thoracic Oncology Centers (Dijon Cancer Center Georges-François Leclerc and Dijon University Hospital). Patient and tumor characteristics were collected from medical records and concerned age, sex, WHO performance status (PS), smoking history, histological type, (epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene (KRAS) mutational status, PDL1 expression on tumor biopsy, best RECIST (response evaluation criteria in solid tumours) response to nivolumab and antibiotic medication exposure during immunotherapy or in the 3 months before its use. All computed tomographic scans were reviewed by physicians to validate response to nivolumab, and evaluation was based on RECIST 1.1 (16). Antibiotic and infection's characteristics

Table II. *Antibiotic (ATB) and infection characteristics in the group exposed to antibiotic.*

Characteristic		No. (%)
Type of ATB therapy	Monotherapy	11 (73.3)
	Bi-therapy	4 (26.7)
Route of ATB administration	Oral	11 (73.3)
	Intravenous	4 (26.7)
Duration of ATB treatment	≤7 Days	7 (46.7)
	>7 Days	8 (53.3)
Location of infection	Pulmonary	10 (66.6)
	Urinary	3 (20.0)
	Catheter	1 (6.7)
	Other	1 (6.7)
Time between ATB exposure and first nivolumab	1-3 Months	8 (53.3)
	<1 Month	5 (33.4)
	During nivolumab treatment	2 (13.3)

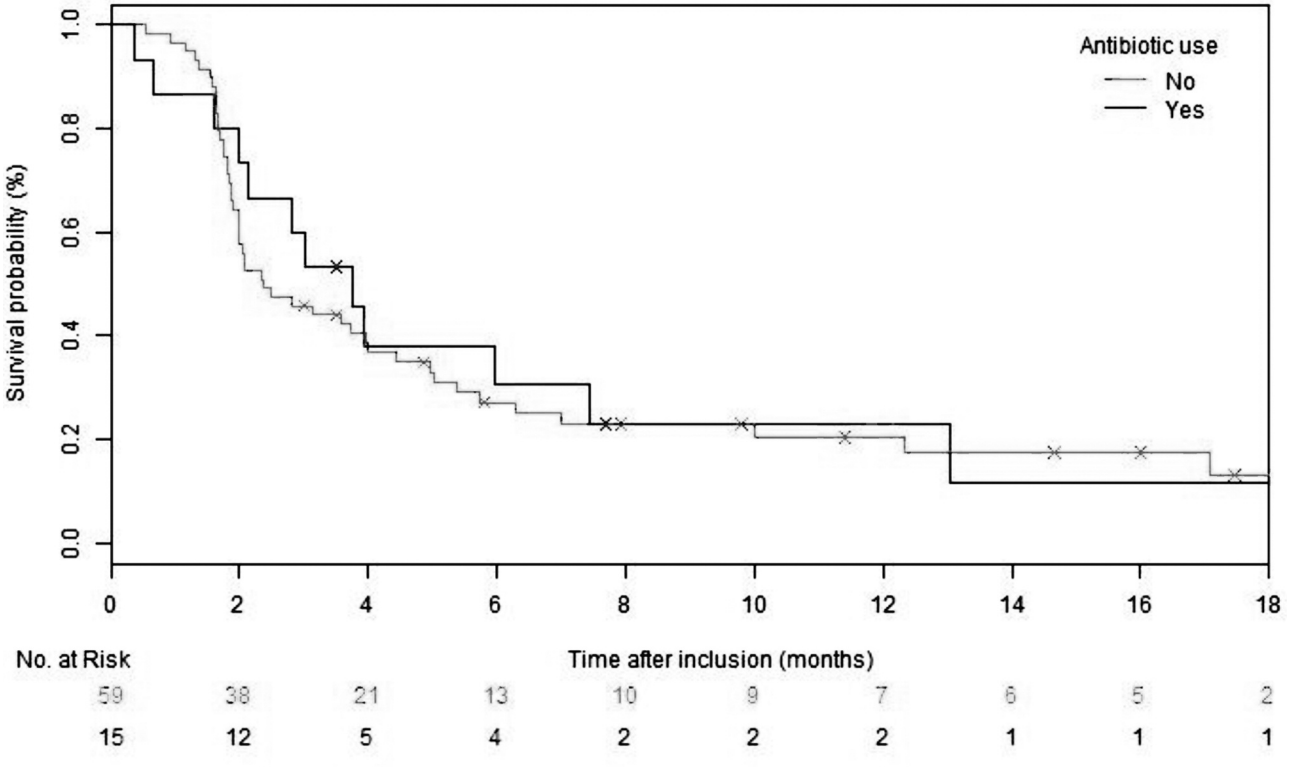

Figure 1. *Kaplan–Meier curves of progression-free survival under nivolumab therapy according to antibiotic use. Log-rank test p=0.72.*

were also collected from medical records and concerned: type of antibiotic medication, route of administration, duration of exposure, infection location, and time between antibiotic exposure and first nivolumab injection. The database was closed on 1 March 2017 and was declared and approved by the French authorities for data protection (CNIL, CCTIRS). PDL1 expression was assessed by immunohistochemistry using SP142 (VENTANA PD-L1).

Statistical analysis. All patients were followed-up until death or the end of data recording (1 March 2017). Progression-free survival (PFS) was calculated (for nivolumab treatment) as the time from the date of the treatment start to the date of disease progression by the RECIST criteria or death. Patient and disease characteristics were examined using the chi-square test or Fisher's exact test for qualitative variables, and the Kruskal–Wallis test for continuous

Table III. *Univariate and multivariate analysis (Cox regression) for factors associated with progression-free survival.*

		Univariate analysis			Multivariate analysis		
Characteristic	Subgroup	HR	95%CI	*p*-Value	HR	95% CI	*p*-Value
Age		0.98	0.96-1.01	0.13	0.98	0.95-1.01	0.18
Gender	Female	1			1		
	Male	1.26	0.76-2.1	0.36	1.81	1.02-3.20	0.04
WHO PS	0	1			1		
	1	1.02	0.66-1.59	0.92	1.05	0.62-1.79	0.85
Histology	Adenocarcinoma	1			1		
	Epidermoid	0.87	0.56-1.34	0.52	1.03	0.46-2.31	0.94
Smoking	No	1			1		
	Yes	0.88	0.48-1.63	0.70	1.06	0.55-2.03	0.87
Stage	IIIB	1			1		
	IV	0.87	0.53-1.79	0.93	0.63	0.28-1.40	0.25
Nivolumab line	Second	1			1		
	Third	0.88	0.57-1.34	0.55	0.89	0.55-1.44	0.63
Type of doublet	Pemetrexed	1			1		
	Gemcitabine	0.66	0.36-1.22	0.18	0.58	0.24-1.46	0.25
	Taxane	0.81	0.50-1.30	0.38	0.70	0.0.29-1.71	0.44
Type of platin	Carboplatin	1			1		
	Cisplatin	1.25	0.81-1.92	0.31	1.13	0.64-1.99	0.67
Response to first line	PD	1			1		
	SD	0.55	0.32-0.95	0.03	0.43	0.23-0.80	0.008
	PR	0.39	0.26-0.69	0.001	0.32	0.17-0.59	2.6e-4
KRAS mutation	No	1					
	Yes	0.65	0.35-1.21	0.18			
PDL1	Negative	1					
	>1%	0.97	0.55-1.69	0.90			

HR, Hazard ratio; CI, confidence interval; WHO PS, World Health Organization performance status; PR, partial response; SD, stable disease; PD, progression disease; *KRAS*, Kirsten rat sarcoma viral oncogene; PDL1, program death ligand 1.

variables, as appropriate. Survival probabilities were estimated using the Kaplan–Meier method and survival curves were compared using the log-rank test. A Cox proportional hazard model was used to estimate the impact of response to first-line regimen on PFS. Statistical analyses were performed using R software [R version 3.3.2 (2016-10-31)]. All tests were two-sided, and values of $p<0.05$ were considered statistically significant.

Results

Our retrospective cohort comprised of 74 patients treated with nivolumab monotherapy. There were 60 (81.1%) men and 14 (18.9%) women. The median age at first nivolumab usage was 67 years (51 to 85 years). The most common histological type was adenocarcinoma (43/74; 58.1%), followed by squamous cell carcinoma (30/74; 40.5%) and other histology (1/74; 1.4%). The population mostly comprised of current or former smokers (65/74; 87.8%). The general condition of the patients was good, we found a PS of 0 and 1 for 31 (41.9%) and 43 (58.1%) patients, respectively. PDL1 expression of 1% or more was found in 22 (43.1%) of the patients, and was negative for 29 (56.9%) patients. Concerning best response to nivolumab treatment, 23% of patients (17/74) experienced partial (PR) or complete response (CR), 28.4% (21/74) stable disease (SD), and 48.6% (36/74) progressive disease (PD).

Only 15 (20.3%) patients were exposed to antibiotic medication in the 3 months before first nivolumab injection or during treatment. Table I presents general patient and tumor characteristics of patients exposed to antibiotic and those who were not. We found no significant difference between the two groups for clinical variables, nor for PDL1 expression. Table II presents antibiotic and infection characteristics in the group exposed to antibiotic. We noted that patients principally received antibiotic monotherapy (11/15; 73.3%). Median duration of exposure was 8 days (from 2 days to 17 days). Antibiotic medication was principally administrated by oral route (11/15; 73.3%). Location of infection disease leading to antibiotic prescription was variable but mostly concerned the pulmonary area (10/15; 66.6%), which is frequent in smoker patient populations. Finally, important data concerned the time between antibiotic exposure and first nivolumab

injection. Half of the patients received antibiotic between 1 and 3 months before the first antibody injection (8/15).

We investigated whether antibiotic medication exposure influenced the response rate (CR plus PR) and PFS on therapy with nivolumab. We recorded similar response rates to nivolumab for the two populations, without impact of antibiotic exposure (chi-square test p=0.75). Indeed, in the group not exposed to antibiotic, we found response, SD and PD rates were 22%, 27.1% and 50.9%, respectively. In the group exposed to antibiotic, corresponding rates were 26.7%, 33.3% and 40%, respectively. Moreover, we found no impact of antibiotic medication on PFS under nivolumab (log-rank test p=0.72) (Figure 1). Univariate Cox proportional hazards model indicated that no clinical factor was significantly associated with improved PFS (Table III).

Discussion

To our knowledge, this study is the first exploration of the role of antibiotics in patients with lung cancer treated with anti-PD1. In contradiction to results for patients with renal carcinoma and in mouse models, we found no link between exposure to antibiotic medication (and consequently of the microbiota) and response to nivolumab. Indeed, the response rate to nivolumab and PFS under it for our population of patients exposed to antibiotic medication during or in the 3 months before first anti-PD-1 injection was similar to the population without exposure. We therefore prudently consider that dysbiosis caused by antibiotics have no major influence on response to this immunotherapy.

These results contradict previous data obtained on mice. Indeed, several studies have already highlighted a pejorative impact of unfavorable microbiota and response to cytotoxic chemotherapy (17) or immunotherapy such as anti-CTLA4 (13) or anti-PDL1 (14). Concerning response to chemotherapy, the efficiency of some drugs is known to depend on immune components (18, 19). It is in this case that microbiota, and more precisely gut microbiota, can play an important role. For example, Viaud *et al*. have shown that immune effects of cyclophosphamide (an alkylating cytotoxic drug) are modulated by gut microbiota. Cyclophosphamide induced the translocation of specific bacteria (in particularly *Lactobacillus johnsonii*, *Lactobacillus murinus* and *Enterococcus hirae*) into mesenteric lymph nodes allowing to accumulation of type 17 T-helper (T_H17) cell and T_H1 cell responses. Moreover tumor-bearing mice that were germ-free or exposed to broad-spectrum antibiotic medication able to kill these bacteria presented a reduced T_H17 response and led to resistance to cyclophosphamide (12). Concerning immunotherapy and more specially immune checkpoint inhibitors, microbiota were also found to play an important part in its efficacy. Vetizou *et al*. found that progression of fibrosarcoma was controlled by antibody to CTLA4 in specific pathogen-free mice, but not in germ-free mice or those treated with broad-spectrum antibiotics. The explanation for this comes from a faulty immune response in the latter group where there was a decrease in activation of splenic effector $CD4^+$ T-cells and tumor-infiltrating lymphocytes (13). Finally, evaluation of melanoma tumor growth in two mouse groups from two different facilities, which differed only in the composition of their gut microbiota, produced interesting data. Tumor grew more aggressively in the group with a failing microbiota (lacking in *Bifidobacterium* spp), but it could be ablated by co-housing with mice with favorable microbiota, or by transferring fecal material from one group to the other. Moreover, response to anti-PDL1 was better in the group with favorable microbiota. These data were explained by a T-cell response in the tumor microenvironment largely being better in the group with favorable microbiota (14).

Our observations also contradict data recently obtained in patients treated with immune checkpoint inhibitor for metastatic renal cell carcinoma (mRCC). The group of 80 patients exposed to antibiotic in the month before first antibody injection (n=16) had decreased PFS compared to the group without exposure (2.3 *vs*. 8.1 months, p<0.001). This statistical association was maintained after multivariate analysis adjusted for age, gender, International mRCC Database Consortium risk groups, tumor burden and proton pomp inhibitors (15).

It is clear that our study suffers from several limits: it was a retrospective analysis, with a limited number of patients [which is nevertheless equivalent to the cohort of patients with metastatic renal cell carcinoma (15)] and lack of power. However, our contradictory data compared with analysis of the mouse model could be explained by different microbiota between patients and mice, and the fact that tumor cells used in these models were melanoma or fibrosarcoma and not lung carcinoma. We believe that differences in observation obtained on metastatic renal cell carcinoma could be linked to the fact that in this cohort of patients, not all patients were treated with anti-PD1 or PDL1 monotherapy. Indeed, 12.5% were treated with combined immune checkpoint inhibitor (anti-PD1 plus anti-CTLA4) and consequently represent a more heterogeneous population.

In conclusion, under these observations, we provide reassuring data about the use of antibiotic medication in the months before first injection of nivolumab in patients with NSCLC. However, this conclusion has to be confirmed in a larger cohort of patients with prospective collection of data.

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