# Influence of antibiotic use on the effectiveness and safety of immune checkpoint inhibitors in Japan.

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## Abstract

**Background**

It has been reported that antibiotic use changes the gut microbiome and alters the outcome of treatment with immune checkpoint inhibitors (ICIs). However, in Asia, this has not been well studied, and there is insufficient evidence to support these reports.

**Methods**

In this study, we investigated the concurrent use of antibiotics and the administration of PD-1 inhibitors in Japanese patients, and examined the relationship between antibiotics and the clinical benefit or safety of PD-1 inhibitors.

**Results**

In total, 152 patients were analyzed: 60 patients received systemic antibiotics within 2 months before or 1 month after the first dose of PD-1 inhibitors (the antibiotic group: ATB) ; the remaining patients comprised the non-antibiotic group (non-ATB). There was a significantly higher proportion of patients under 65 years of age in ATB group. Median overall survival (OS) was not reached in the ATB and non-ATB groups, and there was no statistically significant difference between the two groups (HR = 1.48) (Figure 1). Progression-free survival (PFS) was 3.29 months in the ATB group and was significantly shorter than that in the non-ATB group (5.99 months, HR = 1.75) (Figure 2). Multivariate analysis by Cox regression analysis also showed that PFS was shorter in the ATB group (HR=1.63). As age may be a confounding factor, we performed a stratified analysis, a common method used to adjust for bias. The results of the stratified log-rank test after adjustment for age showed that the PFS was significantly shorter in the ATB group. There were no statistically significant differences between the two groups in the clinical evaluation after 1 year, incidence of adverse events of Grade 3 or above, and laboratory data (Figure 5 and Table 3).

**Conclusions**

Our results suggest that the use of antibiotics may affect the anticancer treatment outcomes of Japanese patients who are administered PD-1 inhibitors.

## Background

- ✓ Resident gut bacteria can affect patient responses to cancer immunotherapy.
- ✓ Previous studies have showed that antibiotic consumption is associated with poor response to immunotherapeutic PD-1 blockade.[1.-4.]
- ✓ It is not well studied in Japanese patients with gut bacteria unique to Japan that the use of antibiotics affect clinical outcomes of PD-1 inhibitors.

## Methods

| | |
|---|---|
| Patients | Japanese patients treated with nivolumab or pembrolizumab alone at Nagoya University Hospital from July 1, 2014 to February 28, 2019. |
| Exclusion criteria | Not Japanese, combination chemotherapy, whose medications are unknown up to 2 months before the start of treatment, or an ECOG performance status of >2. |
| Study design | A retrospective 1-year follow-up study. |
| Ethical approval | Ethical review committee of Nagoya University |

## Results

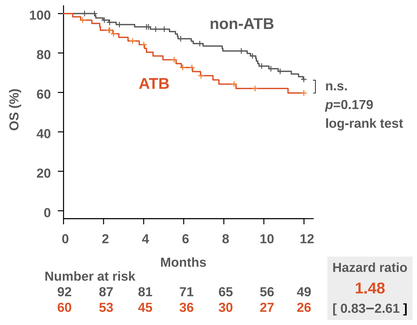
### Table 1. Baseline characteristics

| | non-ATB n=92 | ATB n=60 | *p* value |
|---|---|---|---|
| Median age [range] | 71.2 [ 30-85 ] | 63.1 [ 39-80 ] | <0.001[a] |
| ＜65 yr (n) | 26 | 31 | <0.01[b] |
| ≧65 yr (n) | 66 | 29 | |
| Male (n) | 64 | 43 | 0.857[b] |
| Female (n) | 28 | 17 | |
| PS=2 (n) | 2 | 5 | 0.113[b] |
| PS=1 (n) | 35 | 21 | 0.734[b] |
| PS=0 (n) | 26 | 11 | 0.181[b] |
| PS not listed (＜3) (n) | 29 | 23 | 0.484[b] |
| Median BMI [range] | 22.7 [ 13.0-34.7 ] | 21 [ 14.7-31.1 ] | 0.729[a] |
| BMI≧25 (n) | 15 | 14 | 0.298[b] |
| BMI＜18.5 (n) | 14 | 13 | 0.386[b] |
| Nivolumab (n) | 68 | 48 | 0.331[b] |
| Pembrolizumab (n) | 24 | 12 | |
| MM (n) | 30 | 14 | 0.273[b] |
| NSCLC (n) | 45 | 32 | 0.622[b] |
| RCC (n) | 9 | 4 | 0.568[b] |
| GC (n) | 4 | 2 | 1.000[b] |
| HNC (n) | 4 | 8 | 0.064[b] |
| Median No. of previous anticancer regimens | 1 [ 0-6 ] | 1 [ 0-6 ] | 0.645[a] |

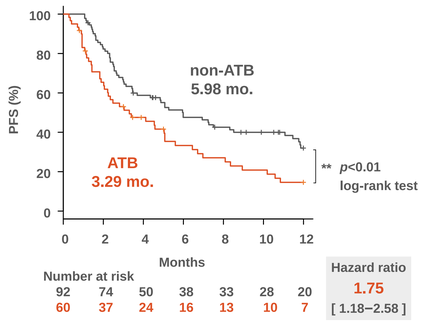
[a] Mann-Whitney's U test, [b] Fisher's exact test

ATB, the antibiotic group; non-ATB, the non-antibiotic group.
MM, malignant melanoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; GC, gastric cancer; HNC, head and neck cancer.

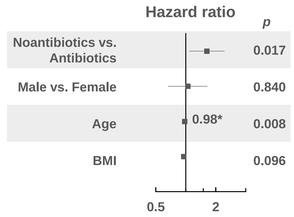
### Figure 1. Overall survival




### Figure 2. Progression-free survival

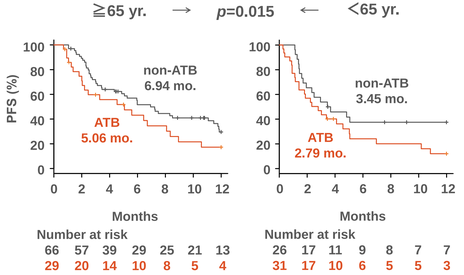



### Figure 3. Multivariate analysis of PFS

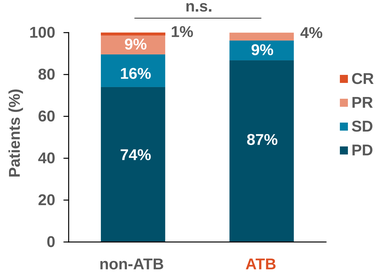



Cox proportional hazard model *$p$<0.05

### Figure 4. Stratified analysis of PFS




### Figure 5. Clinical evaluation after 1 year




Fisher's exact test
† Does not include 22 unevaluable (non-ATB: 15, ATB: 7).
RECISTv1.1
CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate (CR+PR), DCR: disease control rate (CR+PR+SD)

### Table 2. ATB classification

| | | PO | IV | Total |
|---|---|---|---|---|
| β-lactams | 1st generation cephems | 2 | 9 | 11 |
| | 2nd generation cephems | 0 | 7 | 7 |
| | 3rd generation cephems | 7 | 6 | 13 |
| | 4th generation cephems | 0 | 1 | 1 |
| | Penicillins | 3 | 16 | 19 |
| | Carbapenems | 0 | 2 | 2 |
| | Penems | 0 | 0 | 0 |
| | Aminoglycosides | 0 | 0 | 0 |
| | Tetracyclines | 6 | 0 | 6 |
| | Macrolides | 14 | 0 | 14 |
| | Lincomycin | 0 | 0 | 0 |
| | Glycopeptides | 0 | 1 | 1 |
| Quinolones | New quinolones | 16 | 0 | 16 |
| Sulfonamides | TMP-SMX | 7 | 0 | 7 |
| | Oxazolidinones | 0 | 0 | 0 |
| | Metronidazole | 1 | 0 | 1 |

### Table 3. Adverse events

| | non-ATB n=92 | | ATB n=60 | | *p* value | |
|---|---|---|---|---|---|---|
| | All Grade | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 |
| Any adverse event | 75 | 11 | 50 | 9 | 0.831 | 0.629 |
| Infusion reaction | 0 | 0 | 2 | 0 | 0.154 | |
| Fatigue | 26 | 0 | 17 | 0 | 1.000 | |
| Itching | 25 | 1 | 13 | 1 | 0.566 | |
| Rash | 27 | 3 | 11 | 0 | 0.179 | |
| Diarrhea | 9 | 0 | 5 | 0 | 1.000 | |
| Nausea | 7 | 0 | 3 | 0 | 0.741 | |
| Decreased appetite | 14 | 0 | 10 | 0 | 0.823 | |
| Joint pain | 6 | 0 | 4 | 0 | 1.000 | |
| Muscle pain | 6 | 0 | 2 | 0 | 0.480 | |
| Fever | 10 | 0 | 13 | 0 | 0.104 | |
| Anemia | 10 | 3 | 8 | 1 | 0.798 | |
| Pneumonitis | 9 | 1 | 10 | 3 | 0.221 | |
| Hyperthyroidism | 10 | 1 | 3 | 0 | 0.248 | |
| Hypothyroidism | 17 | 0 | 9 | 0 | 0.663 | |
| Hypophysitis | 4 | 3 | 2 | 0 | 1.000 | |
| Type 1 DM | 1 | 1 | 0 | 0 | 1.000 | |
| Myocarditis | 0 | 0 | 1 | 1 | 0.395 | |
| Joint inflammation | 0 | 0 | 2 | 0 | 0.154 | |
| Increase in AST level | 12 | 0 | 14 | 4 | 0.124 | |
| Increase in ALT level | 12 | 0 | 13 | 2 | 0.183 | |
| Increase in γ-GTP level | 17 | 1 | 16 | 1 | 0.236 | |
| Increase in SCr level | 7 | 0 | 5 | 0 | 1.000 | |
| Otherwise | 5 | 0 | 7 | 0 | 0.220 | |

CTCAE v4.0, Fisher's exact test

## Conclusion

- ✓ ATB administration was associated with worse PFS even in Japanese patients.
- ✓ The response rate was tended to be higher in the non-ATB group.
- ✓ There was no significant difference in the number of episodes for adverse events of all Grade and Grade 3 or above.

**More rigorous monitoring of proper antibiotic use is important for patients planning anti-PD-1 antibody therapy.**

## References

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