Letters to the editor

Association between antibiotics use and outcome in patients with NSCLC treated with immunotherapeutics

Conflicting data exist about the impact of antibiotic exposure on clinical outcome during immune-checkpoint blockade (ICB) in advanced non-small-cell lung cancer (aNSCLC). Routy et al. [1] and Derosa et al. [2] described a detrimental effect of antibiotic administration on clinical outcome during ICB in aNSCLC, which is in line with our single-center experience at the tertiary cancer center in Salzburg [3]. Derosa et al. reported an inferior median overall survival (mOS) associated with the use of antibiotics within a time frame of 30 days [hazard ratio (HR) = 4.4] or 60 days (HR = 2.0) preceding ICB initiation in 239 patients with aNSCLC [2]. In contrast, Metges et al. found a survival advantage for patients receiving antibiotics up to 60 days before or during ICB (mOS: 16.2 versus 11.5 months, $P = 0.01$) in 325 aNSCLC patients [4].

In our bi-centric analysis, including 96 non-squamous aNSCLC patients, no influence of antibiotic exposure on mOS from ICB initiation was found (AB^--group: 11.2 versus AB^+-group: 12.2 months, HR = 0.84, $P = 0.546$, Figure 1A). In contrast to Derosa et al. and Metges et al., the defined time frame of antibiotic exposure ranged from one month before to 1 month after ICB start in our analysis. Neither the time point of antibiotic administration (before: 15.5 months, after: 6.3 months, before and after: not reached, $P = 0.060$), nor a distinct antibiotic class applied as monotherapy ($P = 0.954$) was associated with mOS.

While the detrimental effect of antibiotic exposure on clinical outcome with ICB was corroborated in our aNSCLC cohort in Salzburg ($N = 43$, AB^--group: mOS 13.6 versus AB^+-group: 7.5 months, HR = 2.04, $P = 0.046$, Figure 1B) [3], an opposite effect was found at the tertiary cancer center in Linz ($N = 53$; AB^--group: mOS 10.8 months versus AB^+-group: not reached, HR = 0.33, $P = 0.008$, Figure 1C). The imbalance of ECOG performance status (PS) at the time point of ICB initiation between the centers in Salzburg and Linz (ECOG PS $\geq$2: 30% versus 0%, $P < 0.001$, supplementary Table S1, available at *Annals of Oncology* online) might have laid the basis for a confounding bias. It is noteworthy that ECOG PS in our bicentric AB^+-group was worse in comparison to the Derosa study (ECOG PS $\geq$2: 13% versus 1%). However, the antibiotic treatment status and ECOG PS remained independently associated with mOS in multivariate analysis in the latter study [2]. Compared with Derosa et al. (20% within 30 days, 28% within 60 days) and Metges et al. (47% within 60 days), 40% of patients had been exposed to antibiotics in our cohort predominantly as empiric antibiotic therapy and for upper respiratory tract infections.

Despite the high clinical interest in this topic, only a few retrospective studies have reported an inferior outcome with antibiotics use during ICB and the question arises whether a publication bias exists. In consideration of the limited and conflicting data and due to putative heterogeneity between tertiary cancer centers as depicted in our bi-centric approach, prospective stratification according to the antibiotic treatment status is necessitated in future clinical trials to clarify the impact of antibiotic administration on clinical outcome with ICB.

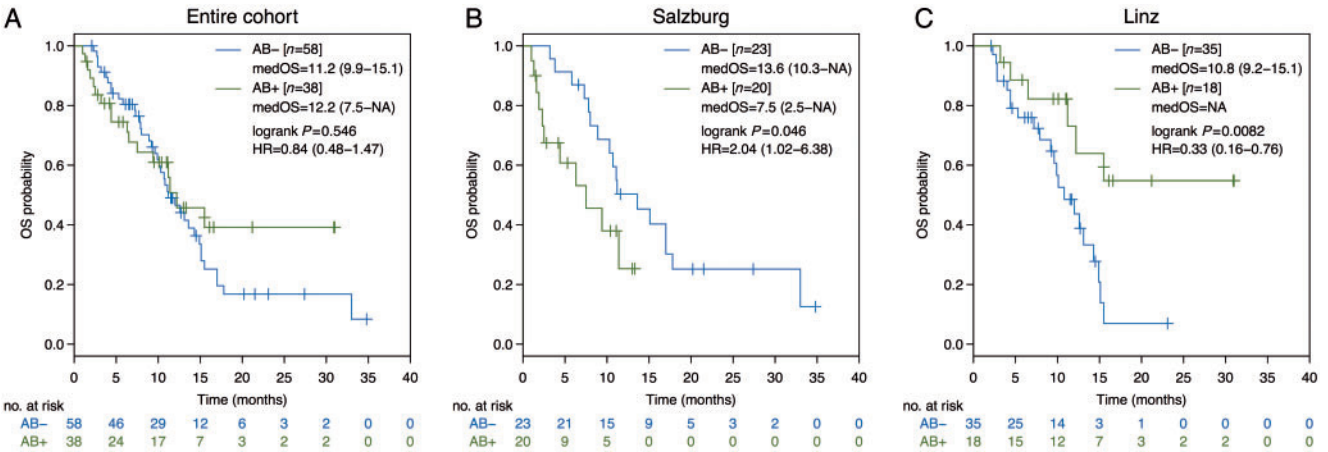

Figure 1. Kaplan–Meier curves for overall survival according to the antibiotic treatment status. Comparison of Kaplan–Meier curves for overall survival between antibiotic-positive and antibiotic-negative group in advanced non-squamous non-small-cell lung cancer for the entire cohort (A), for the tertiary cancer center in Salzburg (B) and for the tertiary cancer center in Linz (C). The 95% confidence interval is shown in brackets. Tick marks represent censored patients. medOS, median overall survival; HR, hazard ratio.

F. Huemer[1,2†], G. Rinnerthaler[1,2,3†], D. Lang[4], H. Hackl[5], B. Lamprecht[4] & R. Greil[1,2,3*]

[1]Department of Internal Medicine III, Paracelsus Medical University Salzburg, Salzburg; [2]Salzburg Cancer Research Institute, Salzburg; [3]Cancer Cluster Salzburg, Salzburg; [4]Department of Pulmonology, Kepler University Hospital, Linz; [5]Division of Bioinformatics, Biocenter, Medical University of Innsbruck, Innsbruck, Austria
(*E-mail: r.greil@salk.at)
† Both authors contributed equally as co-first authors.

Funding

None declared.

Disclosure

FH received travel grants from BMS, Roche and MSD. GR has acted as scientific advisor for Roche, obtained speakers' honoraria from BMS and Roche, received travel grants from Roche and received research funding from Roche. DL received travel grants from Roche. BL has acted as scientific advisor for, or obtained speakers' honoraria from BMS, MSD, and Roche. RG received speakers' honoraria from Roche, Merck/MSD and BMS, has acted as scientific advisor for Roche and BMS, received research funding from Roche, Merck/MSD and BMS, and obtained travel grants from Roche. HH has declared no conflicts of interest.

References

1. Routy B, Le Chatelier E, Derosa L et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2017; 359(6371): 91–97.
2. Derosa L, Hellmann MD, Spaziano M et al. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol 2018; 29(6): 1437–1444.
3. Huemer F, Rinnerthaler G, Westphal T et al. Impact of antibiotic treatment on immune-checkpoint blockade efficacy in advanced non-squamous non-small cell lung cancer. Oncotarget 2018; 9(23): 16512–16520.
4. Metges J, Michaud E, Lagadec DD et al. Impact of anti-infectious and corticosteroids on immunotherapy: nivolumab and pembrolizumab follow-up in a French study. Ann Oncol 2018; 29(Suppl 8): viii400–viii441.

doi:10.1093/annonc/mdz021
Published online 24 January 2019

Sex-based differences of the tumor mutational burden and T-cell inflammation of the tumor microenvironment

It has been recently reported the validation of a new biomarker, with strong predictive value for response to pembrolizumab, based on the tumor mutational burden (TMB) and a gene expression signature of 18 genes (T-cell-inflamed GEP) [1].

TMB is an indirect measure of tumor antigenicity generated by somatic tumor mutations [2]. T-cell-inflamed GEP signature includes genes indicative of an ongoing Th1 and cytotoxic CD8+ T-cell-driven immune response, including IFN-γ signaling, cytolytic activity, antigen presentation, and T-cell trafficking, as well as adaptive inhibitory molecules such as programmed cell death protein 1 (PD-1)/programmed death-ligand 1 and indoleamine 2,3-dioxygenase 1, that are co-regulated within tumor microenvironment [3].

Both tumor antigenicity and a T-cell-driven inflammation of the tumor microenvironment are necessary elements to obtain a response to immune-checkpoint inhibitors [4]. Jointly analyzing these two variables, the new biomarker categorizes tumors in four different groups [(i) GEP low and TMB low, (ii) GEP low and TMB high, (iii) GEP high and TMB low, (iv) GEP high and TMB high], characterized by a different degree of responsiveness to pembrolizumab, regardless of tumor histotype. The predictive value of this new biomarker has been validated in three independent cohorts of patients with 22 different tumor histotypes, treated with pembrolizumab.

We previously described that the modality through which women and men with cancer respond to immunotherapies is different, with men obtaining a significantly larger benefit than women from anti-CTLA4 or anti-PD-1 monotherapy compared with chemotherapy, regardless of tumor type [5]. We therefore re-analyzed available patient-level data, used to validate the new biomarker [1], according with patients' sex.

We found that tumors of male and female patients were differently distributed among the four biomarker-defined groups (Figure 1A). In the whole patient population, the percentage of tumors with low levels of either TMB and GEP score—a condition that strongly predicts for absence of response to pembrolizumab—was nearly double in women as compared with men (GEP^{lo} TMB^{lo} 29% in women versus 15% in men, prevalence ratio 1.9, 95% confidence interval 1.22–2.96). By contrast, the percentage of tumors characterized by high TMB and GEP score—that is associated with a high probability of response to pembrolizumab—was almost halved in women compared with men (GEP^{hi} TMB^{hi} 26% in women versus 42% in male, prevalence ratio 0.61, 95% confidence interval 0.43–0.88).

These differences were observed in all the three independent cohorts of patients analyzed to validate the biomarker [1] (i.e. melanoma, head and neck squamous cell carcinoma and the pan-cancer cohort, that includes 20 different cancer types; *P*-heterogeneity: 0.47), with the largest difference observed in the cohort of patients with melanoma (Figure 1B). Sex retained a significant association with the biomarker-defined groups after controlling for age and tumor histotype in a logistic multivariable model ($P = 0.032$).

Such large sex-based differences in both TMB and T-cell inflammation of the tumor microenviroment, which are key elements of the anticancer immune-response and are strongly associated with responsiveness to pembrolizumab, further confirm the relevance of sex-dimorphism in spontaneous as well as drug-enhanced anticancer immune responses. Confirmation of the predictive value for response to pembrolizumab of the new