NIVOLUMAB SERUM CONCENTRATION IN METASTATIC MELANOMA PATIENTS COULD BE RELATED TO ANTI-TUMOR ACTIVITY GENE AND OUTCOME

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Background Nivolumab (nivo) is a monoclonal antibody that targets programmed death-1 (PD-1) molecule and has been approved for the treatment of several solid tumors; in the treatment of adjuvant and metastatic melanoma had better efficacy compared with chemotherapy or ipilimumab (anti-CTLA4).¹⁻⁴ The classical dosage of nivo tested in the phase III trials was 3 mg/kg every 2 weeks (Q2W). However, in order to make easier the administration, it was introduced the flat dosage at 240mg every 2 weeks (Q2W) or 480mg every 4 weeks (Q4W).⁵⁻⁶ The purpose of this study was to investigate retrospectively the relationships between the different nivo dosages and their serum concentration; in addition, we also investigated possible relationship with the expression of pro/antitumor activity genes.

Methods From July 2016 to December 2018 at INT IRCCS Pascale, Naples, we collected serum and RNA samples from 88 patients with metastatic melanoma at week 12 from the first administration of nivo. All patients have appropriately signed informed consent. The ORR among the 88 patients was 25% (patients baseline characteristics are listed in table 1). Commercial ELISA assay were performed in 96 well plates following the protocol procedures. Gene expression profiling was performed using NanoString® IO360 panels on 37 patients (CR: 4, PR: 10, SD: 11, PD: 12). Statistical analysis was performed through the Student's t-test and via Spearman's rho correlation coefficient. Gene profiling analysis was performed via Bonferroni correction.

Results We observed that patients with complete response (CR) have a higher nivo concentration ($p=0.003$) compared to other groups. No correlation was observed with the most important markers of renal and hepatic function: eGFR, creatinine, AUC, albumin, ALT, AST and gamma GT. Data from gene expression profile shown that patients with CR had a higher expression of anti-tumor and immune activation genes such as: TAPBP, CD47, HDC, IL12RB2 and HLA-DQA1 ($P < 0.05$). Furthermore, genes with pro-tumor or immunosuppressive activity such as MMP9, GOR160, HK2 and LILRA5 ($P < 0.05$) were found to be inversely related with drug concentration while CD1C, a T-cell surface glycoprotein involved in antigen-presenting, it is directly related ($p=0.005$).

Conclusions In this retrospective study we found that higher serum concentration of nivo was correlated with a better outcome and higher frequency of CR. Moreover, in patients with a CR there was an enhancing of the immune activation with an increase of HLA-DQA, TAPBP and IL12RB2. Further investigations are needed to get additional information.

Acknowledgements The study was supported by the Institutional Project 'Ricerca Corrente' of Istituto Nazionale Tumori IRCCS Fondazione 'G. Pascale' of Napoli, Italy.

Abstract 24 Table 1 Patients clinical parameters

Table 1. patients clinical parameters.

Patients Characteristic	N = 88
Median age	60 (range 27-91)
Gender: female/male, n (%)	45 (51)/43 (49)
Melanoma AJCC Stage 8 ed.	
Stage IV, n (%)	84 (96)
Stage IIIC, n (%)	3 (3)
Stage IIIB, n (%)	1 (1)
CNS metastases at baseline, n (%)	25 (22)
BRAF Status	
Wilde type, n (%)	57 (65)
Mutation, n (%)	26 (29)
NA, n (%)	5 (6)
BMI	
Normal weight ($18.5 < \text{BMI} \leq 24.9$), n (%)	24 (27)
Overweight ($25 < \text{BMI} \leq 29.9$), n (%)	36 (41)
Obese ($\text{BMI} \geq 30$), n (%)	28 (32)
Response rate at 1° assessment	
Complete response (CR), n (%)	6 (7)
Partial response (PR), n (%)	16 (18)
Stable disease (SD), n (%)	30 (34)
Progression disease (PD), n (%)	36 (41)
Nivolumab dosage	
Flat dose 240 mg, n (%)	11 (12)
Flat dose 480 mg, n (%)	19 (22)
Dose 3 mg /Kg, n (%)	58 (66)
LDH level	
High	30 (34)
Normal	33 (38)
NA	25 (28)

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Ethics Approval The study was approved by the internal ethics board of the Istituto Nazionale Tumori IRCCS Fondazione ‘G. Pascale’ of Napoli Italy, approval number of registry 33/17 OSS.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.024>