Effect of concomitant medications with immune-modulatory properties on the outcomes of patients with advanced cancer treated with immune checkpoint inhibitors: development and validation of a novel prognostic index

Running title: Prognostication with a microbiota-modulating drug score during cancer immunotherapy

The impact of baseline concomitant medications on the outcome of advanced cancer patients treated with immune checkpoint inhibitors. Development and external validation of a new prognostic "microbiota-modulating drug score".

Abstract

Background: Concomitant medications are known having an impact on the clinical outcomes of patients treated with immune checkpoint inhibitors (ICIs). We aimed weighing the role of different concomitant baseline medications, in order to create a drug-based prognostic score.

Methods: First, we retrospectively recorded concomitant baseline medications at immunotherapy initiation in a single-institution cohort of advanced cancer patients treated with ICIs (training cohort), comparing survival basing on their use. Then, we computed a drug-based prognostic score with the drugs resulting significantly impacting the overall survival (OS). Secondly, we externally validated the score in a large multicenter external cohort.

Results: 217 consecutive advanced cancer patients treated with ICI were included in the training cohort. The median age was 69 years (range: 32 – 89) and the primary tumors were NSCLC (70%), melanoma (14.7%), renal cell carcinoma (9.2%) and others (6%). Among the screened concomitant medication, corticosteroids (HR = 2.3 [95%CI: 1.60-3.30]), systemic antibiotics (HR = 2.07 [95%CI: 1.31 – 3.25]) and proton-pump-inhibitors (PPIs) (HR = 1.57 [95%CI: 1.13 – 2.18]) were significantly related to overall survival (OS). The prognostic score was calculated using these three drug classes, defining good, intermediate and poor prognosis patients. Within the training cohort, also progression-free survival (PFS) ($p < 0.0001$) and objective response rate (ORR) ($p = 0.0297$) were significantly distinguished by the score stratification. The prognostic value of the score was also demonstrated in terms of OS ($p < 0.0001$), PFS ($p < 0.0001$) and ORR ($p = 0.0006$) within the external cohort.

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Conclusion: three likely microbiota-modulating class of drugs such as corticosteroids, systemic antibiotics and proton-pump-inhibitors were identified and effectively combined to create a prognostic score, predicting the outcome of advanced cancer patients undergoing ICIs.

Keywords: concomitant medications; drugs; immunotherapy; corticosteroids; proton-pump inhibitors; antibiotics; immune-checkpoint inhibitors; cancer patients.

Introduction

The concept that concomitant medications could have a negative role on clinical outcomes of cancer patients treated with immune checkpoint inhibitors (ICIs) has been recently raised in the literature [1]. Beyond pharmacodynamic and pharmacokinetic interactions, some drugs could exert both systemic and within-the-tumor microenvironment immune-modulatory effects, including the perturbation of the homeostatic balance and the diversity of the gut microbiota [2], on the one hand, and a drug-induced immunosuppression, on the other hand [3]. Several drug classes have been considered in previous retrospective studies, however, even if the initial biological assumptions underlying their detrimental effects seem consistent and reliable, the question whether such findings have causative or associative correlation is still to be answered [1].

The negative role of concomitant medications has been reported as particularly striking when considering drugs administered prior to the immunotherapy initiation (baseline concomitant medications), compared to those administered after ICIs start.

Corticosteroids have been the first class of medications identified as significantly related to worse clinical outcomes of patients to cancer immunotherapy [4].

Nevertheless, it was showed that corticosteroids administered for non-cancer indications and for treating immune-related adverse events (occurring after the treatment initiation) seem not to affect the clinical outcomes [5-6].

Also, antibiotics were revealed being significantly associated to shortened progression-free survival (PFS) and overall survival (OS) in cancer patients receiving ICIs, possibly due to induced dysbiosis and gut microbiome alterations [7-8]. Lately, it was clarified that antibiotics administered prior of the immunotherapy initiation were related to negative effects, while those administered concurrently were not [9], supporting the hypothesis that baseline medications might more heavily mess up the immune-balance which is required for a proper immunotherapy effect.

In addition, cancer patients are used taking several concomitant medications, due both to comorbidities and cancer symptoms or complications. Indeed, in a recent study, polypharmacy has been postulated as a negative prognostic factor for non-small cell lung cancer (NSCLC) patients receiving ICIs [10].

From this perspective, we aimed evaluating whether and how different concomitant baseline medications affect the clinical outcomes of cancer patients receiving ICIs, in order to weigh their putative negative effects and to hypothesize how they could be mitigated/modulated in clinical practice.

With this purpose, we explored the prognostic impact of baseline medications in a single-institution cohort of advanced cancer patients receiving ICI, then creating a drug-based prognostic score, which was subsequently validated in an external multicenter cohort.

Materials and Methods

Study design

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We conducted a single-institution, retrospective, observational data collection, in the Medical Oncology Department of the University Hospital of Parma, (Italy) between April 2014 and February 2019. The primary aim was the evaluation of the impact of concomitant baseline medications at immunotherapy initiation on survival of advanced cancer patients treated with ICIs in a training cohort.

Hypothesizing the confirmation of previous evidence by the literature, with a different weight of concomitant medications on the outcome of patients to cancer immunotherapy, we aimed creating a drug-based prognostic score, including those medications with statistically significant impact on the outcome of patients in the training cohort.

Secondly, in the case of effectiveness of the prognostic tool in the internal cohort, we expected to externally validate the model using a multicenter, real-world cohort of advanced cancer patients receiving PD-1/PD-L1 checkpoint inhibitors (validation cohort) [11].

In the training cohort, we included all consecutive patients with confirmed diagnosis of advanced or metastatic solid malignancies, who underwent treatment with single agent ICI (including CTLA-4 [cytotoxic T-lymphocyte-associated protein 4], PD-1 [programmed death-1] and PD-L1 [programmed death-ligand 1] inhibitors, according to the tumor type indications within clinical practice) in any treatment line, at the University Hospital of Parma, with data availability regarding baseline concomitant medications.

The clinical outcomes of interest were objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). Treatment responses were assessed with radiological imaging according to the clinical practice. RECIST (v. 1.1) criteria were used [12] and a subsequent confirmation imaging was recommended in the case of

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disease progression with clinical benefit; treatment beyond disease progression was allowed when clinically indicated. ORR was defined as the portion of patients experiencing an objective response (complete or partial response) as best response to immunotherapy. PFS was defined as the time from treatment initiation to disease progression or death, whichever occurred first. OS was defined as the time from treatment initiation to death. For PFS as well as for OS, patients without events were considered censored at the time of the last follow-up. The data cut-off period was May 2019.

Commentato [MT1]: Siamo sicuri?

Information about key concomitant medications at the time of immunotherapy initiation was gathered from patient clinical records. According to the previous evidence by the literature about this issue, the following drug classes were evaluated:

- ✓ Corticosteroids (dose ≥ 10 mg prednisone equivalent per day, with a minimum 24 hours of dosing) within 30 days before immunotherapy initiation (yes vs no) [4-6, 13];
- ✓ Systemic antibiotics within 30 days before immunotherapy initiation (yes vs no) [7-9];
- ✓ Proton pump inhibitors (PPIs) (yes vs no) [8, 14];
- ✓ Statins (yes vs no) [15-16];
- ✓ Acetylsalicylic acid (yes vs no) [17];
- ✓ Metformin (yes vs no) [18];
- ✓ Angiotensin Converting Enzyme (ACE) inhibitors (yes vs no) [19].

The drug-based prognostic score was expected to be created by using the drug classes significantly related to OS at the univariate analysis and weighed according to their regression β coefficients. The Harrell's C statistic was used to assess the goodness of calibration of the model. Therefore, ORR, PFS and OS of the training cohort were

evaluated according to the computed score. A fixed multivariable regression model was used to estimate the clinical outcomes according to the computed score [20-22]. The pre-planned covariates were: primary tumor type (NSCLC, melanoma, renal cell carcinoma, others), age (continuous variable), sex (male *vs* female), Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) (0-1 *vs* ≥ 2), burden of disease (number of metastatic sites ≤ 2 *vs* > 2), treatment line (first *vs* non-first), BMI (continuous variable) [23-24], neutrophil to lymphocyte ratio (NLR) (≥ 4 vs < 4) [25], and ICI class (PD-1, PD-L1 or CTLA-4 inhibitors). The computed prognostic score, in the case of confirmation of its prognostic efficacy, was expected to be applied to the validation cohort, following the rules of external validation [26]. A similar fix pre-planned multivariate regression model was used to estimate the clinical outcomes according to the computed score within the validation cohort, including all the covariates with data availability, among those used in the training cohort.

Statistical Analysis

Baseline patient characteristics were reported with descriptive statistics. $\chi 2$ test was used for the univariate analyses of ORR. Logistic regression was used to compute the odds radios (OR) with 95% confidence intervals (CI) for the multivariate analyses of ORR. Median PFS and median OS were evaluated using the Kaplan-Meier method, and log-rank test was used for the univariate analyses of PFS and OS. Median period of follow-up was calculated according to the reverse Kaplan-Meier method. Cox proportional hazards regression was used for the fixed multivariate analyses of PFS and OS and to compute the hazard ratios (HR) for disease progression and death with 95% CIs. The drug-based prognostic score was weighed according to the regression β coefficients according to the Schneeweiss's scoring system [27-28]. Cox proportional

hazard regression was also used to compute the predicted probabilities for death according to the computed score, in order to estimate the Harrell's C statistic. All statistical analyses were performed using MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

Patients' characteristics

Two-hundred and seventeen consecutive advanced cancer patients treated with ICI were included in the training cohort. Patients characteristics and baseline medications are summarized in **Table 1**. The median age was 69 years (range: 32 – 89) and the primary tumors were: NSCLC (70%), melanoma (14.7%), renal cell carcinoma (9.2%) and others (6%).

Drug-based prognostic score

The median follow-up in the training cohort was 21.6 months (95%CI: 19.4 – 47.8), while the median OS and PFS (mOS and mPFS) were 8.9 months (6.4 – 12.4; 74 censored patients) and 3.6 months (95%CI: 2.8 – 5.4; 160 progression events), respectively.

Table 2 summarizes the univariate analysis for OS according to the concomitant medications. Corticosteroids (HR = 2.3 [95%CI: 1.60-3.30], p < 0.0001), systemic antibiotics (HR = 2.07 [95%CI: 1.31 – 3.25], p = 0.0016) and PPIs (HR = 1.57 [95%CI: 1.13 – 2.18], p = 0.0071) were those significantly related to an increased risk of death, among the class of drugs considered in the analysis. Supplementary figure 1 reported the Kaplan Meier survival curves of OS according to each baseline medication.

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By combining these three medications, we created the drug-based prognostic score based on regression β coefficients, as follows: to baseline corticosteroids were assigned 2 points, while to baseline systemic antibiotics and PPIs was assigned 1 point each. As a result, the score ranged from 0 (best prognosis, the patient did not take none among corticosteroids, systemic antibiotics and PPIs) to 4 (worse prognosis, the patient was on treatment with corticosteroids, systemic antibiotics and PPIs at the immunotherapy initiation) and the Harrell's C statistic for OS was 0.66 (95% CI:0.59-0.72). We then used a three-risk group stratification as follows: score 0 (good prognosis), score 1-2 (intermediate prognosis), score 3-4 (poor prognosis).

The mOS according to the drug-based prognostic score was: good prognosis 19.4 months (95%CI: 11.0 – 29.0; 41 censored patients), intermediate prognosis 8.7 months (95%CI: 4.9 – 12.1; 29 censored patients), poor prognosis 2.6 months (95%CI: 1.3 – 5.1; 4 censored patients) (log rank p < 0.0001) (**Figure 1A**), while the mPFS was: good prognosis 6.6 months (95%CI: 3.8 – 17.2; 52 progression events), intermediate prognosis 3.1 months (95%CI: 1.8 – 5.1; 77 progression events), poor prognosis 1.6 months (95%CI: 1.2 – 2.5; 31 progression events) (log rank $p < 0.0001$) (**Figure 1B**). The ORR in the overall training cohort was 28.8% (95%CI: 21.5 – 0.37) and among the poor, intermediate and good prognosis groups was 17.4% (95%CI: 4.7 – 44.5), 22.2% (95%CI: 13.2 – 35.1) and 38.7% (95%CI: 26.3 – 55.0), respectively ($p = 0.0297$). At the multivariate analysis, neither poor prognosis (OR = 0.39 [95%CI: 0.09 – 1.22], $p = 0.0996$), nor intermediate prognosis patients (OR = 0.47 [95%CI: 0.21 – 1.04], $p = 0.0654$), were confirmed to have a significantly lower probability of reaching an objective response, compared to good prognosis group. Nevertheless, both poor prognosis (HR = 2.77 [95%CI: 1.64 – 4.67], $p = 0.0001$) and intermediate prognosis patients (HR = 1.61 [95%CI: 1.11 – 2.33], $p = 0.0130$) were confirmed to have a

significantly shorter PFS compared to the good prognosis group. Poor prognosis patients (HR = 2.69 [95%CI: 1.57 – 4.63], p = 0.0003), were confirmed to have a significantly shortened OS, while a not significant trend toward an increased risk of death was found for intermediate prognosis patients (HR = 1.42 [95%CI: 0.98 – 2.19], p = 0.0603), compared to the good prognosis group. **Table 3** summarized the multivariate analyses of ORR, PFS and OS within the training cohort.

External validation

The validation cohort was constituted of 1012 advanced cancer patients (NSCLC 52.2%, melanoma 26%, renal cell carcinoma 18.3% and others 3.6%) treated with PD-1/PD-L1 checkpoint inhibitors, in the oncology departments of 20 Italian institutions, between June 2014 and March 2020. The median age was 68.5 years, 63.9% were male, 14% had an ECOG-PS ≥ 2, 48.4% had > 2 metastatic sites and 39.1% were treated with ICI in the first line setting. At the immunotherapy initiation, 25.5% were on therapy with corticosteroids, 7.7% were taking systemic antibiotics and 48.5% were on treatment with proton pump inhibitors [10].

Commentato [MT2]: Anti-CTLA4?

Applying the computed score to this external cohort, the Harrell C statistic for OS was 0.61 (95% CI:0.58-0.64). The mOS according to the drug-based prognostic score was: good prognosis 36.2 months (95%CI: 28.4 – 39.8; 258 censored patients), intermediate prognosis 19.2 months (95%CI: 16.4 – 24.6; 201 censored patients), poor prognosis 8.3 months (95%CI: 6.6 –11.0; 61 censored patients) (log-rank p < 0.0001) (**Figure 1C**), while the mPFS was: good prognosis 13.9 months (95%CI: 10.4 – 18.9; 257 progression events), intermediate prognosis 11.2 months (95%CI: 8.7 – 13.9; 273 progression events), poor prognosis 5.1 months (95%CI: 4.0 –37.5; 151 progression events) (log-rank p < 0.0001) (**Figure 1D**). The ORR between poor, intermediate and

good prognosis groups was 26.4% (95%CI: 19.3 – 35.2), 36.7% (95%CI: 30.8 – 43.3) and 43.2% (95%CI: 37.1 – 50.1), respectively (p = 0.0006). At the multivariate analysis, only the poor prognosis group was confirmed having significantly worse ORR (OR = [95%CI: 0.59 – 0.89], p = 0.0124) and shorter PFS (HR = 1.72 [95%CI: 1.39 – 2.13], p < 0.0001) compared to the good prognosis group. At the multivariate analysis of OS, both poor prognosis (HR = 1.95 [95%CI: 1.52 – 2.48], p < 0.0001) and intermediate prognosis patients (HR = 1.27 [95%CI: 1.04 – 1.57], p = 0.0219), were confirmed having a significantly increased risk of death compared to the good prognosis patients. Table 4 summarizes the multivariate analyses of ORR, PFS and OS within the validation cohort.

Discussion

Commentato [MT3]: Dlirei che va tagliata un pò

In the era of the immunomodulation in cancer treatment, the issue of concomitant medications has been retrospectively explored in many patient cohorts, reporting the outcome of ICIs according to the clinical characteristics of patients [1, 4-5, 7-10]. The majority of prognostic factors emerged in the field of advanced cancer immunotherapy are represented by immutable baseline variables, such as sex or age, or by historical long-term conditions, like obesity and smoking status, very hard to modify in the short time frame before ICI start [23, 29-31]. Otherwise, the intake of concomitant drugs could be easily interrupted in the case of non-vital symptomatic medications, such as PPIs, or replaced for antihypertensive or antiplatelet agents, as well as in the case of contingent drugs, prescribed to manage impromptu clinical conditions (e.g. corticosteroids or antibiotics). From this point of view, our results about the impact of PPIs, systemic antibiotics and corticosteroids becomes truly interesting for clinical

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practice, offering for the first time the possibility to actively intervene on a prognostic factor, aside from merely exploiting the information for the patient counseling.

The interpretative reading of our findings, showing a negative impact of certain class of drugs, which use is mostly related to temporary symptoms (dyspepsia, infections, inflammation), and denying the role of long-term medications, such as statins, metformin, ACE-inhibitors and acetylsalicylic acid, might be driven by two main strands.

The first is represented by the effect of concomitant medications on the gut microbiota of the individual. The second is constituted by the "comorbidity bias", namely the comorbidity or condition leading the individual to the assumption of such medications.

In the first case, we can postulate a non-casual finding about the exclusive impact, among the class of drugs investigated herein, of those influencing the host microbiota. The gut microbiome, notably, has been demonstrated as a crucial factor potentially responsible for the outcome to cancer immunotherapy [2], and medications as corticosteroids have been demonstrated able of determining its alterations [32]. Glucocorticoids affects mucus production and secretion, resulting in a shift of the bacterial floral composition. In addition, recent evidence showed a significant decrease in mucin gene expression after treatment with dexamethasone, possibly decreasing the protective effect of the mucins [33]. From a systemic perspective, prolonged exposure to corticosteroids can result in metabolic disorders like insulin resistance, leading to further consequences on the microbiome composition. A wider crosstalk between steroid hormones and gut microbiota has been suggested by the observation of substantial shifts in the hypothalamic–pituitary–adrenal axis response to stress associated with altered gut microbiota [34].

In the case of antibiotics, the unexpected impact of a single week of medications administered before a long-term immunotherapy in cancer patients is subtended by a striking rationale. Long-term impacts on the human throat and gut microbiome have been demonstrated also after short-term administration of such drugs. In a case-control study in subjects with dyspeptic disorders, the microbial composition of untreated control subjects was relatively stable over time; on the contrary, dramatic shifts were observed one week after antibiotic treatment, with reduced bacterial diversity. Moreover, the microbiota remained perturbed in some cases for up to four years after antibiotic treatment [35]. Along this line, the perturbation exerted by antibiotic administration has even been demonstrated to alter the immune response to vaccines [36].

Eventually, PPIs have been already deemed to alter the intestinal bacterial flora [37-38]. The influence of PPIs on the gastrointestinal microbiome depends not only on their capacity to increase gastric pH, but also on the potential to influence the microbiota through pH-independent mechanisms, inducing hormonal changes and interfering with nutrient absorption, changing the pattern of bacterial food substrates [38]. Interestingly, omeprazole treatment has been demonstrated to result in decreased Akkermansia muciniphila in mice models [39], and we know that correlations between clinical responses to ICIs and the abundance of A. muciniphila have been revealed by metagenomic studies of baseline patient stool samples before ICI start [40]. It has even been suggested that oral supplementation with A. muciniphila can restore the efficacy of PD-1 blockade, by increasing the recruitment of T lymphocytes [40].

Basing on these evidences, the link between the influence of concomitant medications on microbiome and the response to immunotherapy seems to strengthen, suggesting

careful consideration of the true risk-benefit balance before prescribing microbiota-modulating concomitant drugs to our patients who are candidate to immunotherapy.

About the second interpretative strand, namely the "comorbidity bias", our findings are burdened by the lack of data and analyses about the comorbidities and the reason for the concomitant drug prescription in the two patient populations. ~~and about the reason for the concomitant drug prescription in the two patient populations.~~The use of medications is driven by comorbidities and clinical conditions, for which it must be controlled. A key challenge, in this and other prior analyses from the literature, is inferring causal relationships in retrospective cohorts, often biased by closely interconnected characteristics, such as comorbidities and medications. The "causation or association" issue has already been raised in this field [1]. Other authors have attempted to correct the bias by using a comorbidity index to capture and simplify several disease states [41]. Nevertheless, we believe that the final effect can depend on single clinical conditions, rather than on the overall comorbidity burden.

However, even assuming that in our case series the comorbidities had affected the outcomes, such detrimental effect should have been resulted in a shortened OS only. Nevertheless, our drug-based prognostic score significantly predicted PFS (in both cohorts) and ORR (in the validation cohort). Moreover, looking at the three drug classes included in the score, we can recognize that the underlying reasons subtending their prescription, likely do not represent historical comorbidities. Corticosteroids prescription is usually related to cancer-related symptoms palliation, to such an extent that the crucial element of a negative selection of subjects, with worse prognosis, might be based mainly on this association [5], beside to the effect of these drugs on the gut microbiome. In clinical practice, PPIs are often over-prescribed, and gastritis/

gastroesophageal reflux disease (GERD) not always represents the underlying reason [42].

Also, the cancer patient population receiving antibiotics could have been negatively selected among individuals with impaired immune responses, indeed suffering from infections yet before initiating immunotherapy. Beyond the possible negative effect on their microbiota, antibiotic use could mark a subgroup with less efficient immune system, negatively influencing both the response to immune checkpoint blockade and the overall clinical outcome of the patient [43].

On the other hand, clinical conditions associated with the use of statins, acetylsalicylic acid, metformin, and ACE inhibitors, could be related with improved outcome to immunotherapy. All these class of drugs are often used in obese individuals, characterized by the propensity of being affected by hypertension, vasculopathy and metabolic disorders [44]. Of note, we previously found that overweight, as a tumorigenic immune dysfunction that could be effectively reversed by ICIs, can be a favorable prognostic factor in cancer patients treated with immunotherapy [23-24]. Consistently, higher BMI was associated with improved PFS and OS to ICI in the validation cohort of the present analysis, confirming the favorable effect of overweight in our study population. Also, in the case of metabolic disorders, we previously reported that hypercholesterolemia was associated with better outcomes in ICI-treated cancer patients. We interpreted our finding as an expression of low-grade inflammation state, marking patients more likely to respond to immunotherapy. Interestingly, the effect of blood cholesterol on OS was irrespective of statin use, which was in turn an independent favorable predictor of survival in our study population [16]. This latter data was also confirmed by other authors [45]. Eventually, even the smoking status, often associated with hypertension and vasculopathy, has been classified as a predictive

marker for survival benefits to ICIs [31]. These evidences, taken together, contribute to justify a possible positive selection bias of patients taking statins, acetylsalicylic acid, metformin, and ACE inhibitors, which putative role (either favorable or detrimental) could be masked by coexistent clinical characteristics associated with the outcome of patients to ICI.

Our study acknowledges a number of limitations, mainly related to the retrospective design. The heterogeneity of tumor types evaluated might have affected the analyses, even if we included the primary tumor type in the pre-specified fixed multivariate model. Also, we must consider the lack of data availability regarding the comorbidities and the possible missing concomitant baseline medications of patients. Instead, considering that the control cohort was used for external validation, the unbalanced patient characteristics (e.g. higher percentages of NSCLC patients, patients with high disease burden, patients receiving ICI as further line and patients on corticosteroids/systemic antibiotics in the training cohort compared to the control cohort; the presence of patients receiving CTLA-4 inhibitors) do not represent an actual limitation.

CONCLUSION

With the present analyses, we have addressed three major issues. First, we have confirmed the role of some microbiota-modulating drugs towards the outcome of patients to cancer immunotherapy, surely demonstrating an association with OS correlation, and possibly identifying a direct causative impact. Second, we created and validated a drug-based prognostic score, clinically effective in discriminating the outcome and characterized by a demonstrative utility, considering the likely more useful recommendation for a washout from the accused drugs before immunotherapy initiation. Last, as suggested by the findings on PFS and ORR, we generated the

premises for the verification of a possible predictive role of the model in prospective cohorts of cancer patients receiving ICIs. With this purpose, we are planning comparative analyses in two matched cohort of NSCLC patients receiving first line ICIs or chemotherapy.

Ethics approval and consent to participate

All patients alive at the time of data collection provided an informed consent for the present retrospective analysis. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (University of L'Aquila, Internal Review Board protocol number 32865, approved on July 24th, 2018).

Authors' contributions

All authors contributed to the publication according to the ICMJE guidelines for the authorship. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AC, PAS: conception/design of the study;

MT, VA, LSS, AR, ETT, FS, FR, RB, DS, MR, CA, RG, MF, PM, AB, AG, MAO, RM, MGV, LN, RC, CB, ON, AT, MDT, NP, LP, SB, SM, AI, FZ, EV, BDC, DM, MGV, GP, CF : data acquisition;

MT, VA, LSS, AR, ETT, FS, FR, RB, DS, MR, CA, RG, MF, PM, AB, AG, MAO, RM, MGV, LN, RC, CB, ON, AT, MDT, NP, LP, SB, SM, AI, FZ, EV, BDC, DM, MGV, GP, CF: analysis and interpretation of data;

AC, DJP, PAS: drafting the work or revising it critically for important intellectual content;

AC, MT, VA, LSS, AR, ETT, FS, FR, RB, DS, MR, CA, RG, MF, PM, AB, AG, MAO, RM, MGV, LN, RC, CB, ON, AT, MDT, NP, LP, SB, SM, AI, FZ, EV, BDC, DM, MGV, DJP, GP, CF, PAS: final approval of the version to be published.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials: the datasets used during the present study will not be made available.

Consent for publication

Not applicable.

Conflicts of Interest:

Dr Alessio Cortellini received speaker fees and grant consultancies from Roche, MSD, BMS, AstraZeneca, Novartis, Astellas. Dr Raffaele Giusti received speaker fees and grant consultancies from AstraZeneca and Roche. Dr Maria G Vitale received speaker fees, grant consultancies and travel support from BMS, Ipsen, Novartis, Pfizer, Astellas, Jansen and Pierre-Fabre. Dr Alessandro Russo received grant consultancies from AstraZeneca and MSD. Dr Riccardo Marconcini received grant consultancies from Pierre-Fabre, MSD, Incyte, BMS, and Roche. Dr Francesco Spagnolo received speaker fees and grant consultancies from Roche, Novartis, BMS, MSD, Pierre-Fabre, Sanofi, Merck and Sunpharma. Dr David J. Pinato received lecture fees from ViiV Healthcare, Bayer Healthcare and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, Astra Zeneca; received research funding (to institution) from MSD, BMS. Dr Paolo A. Ascierto received speaker fees and grant consultancies from BMS, Roche-Genentech, MSD, Dohme, Array, Novartis, Merck-Serono, Pierre-Fabre, Incyte, New Link Genetics, Genmab, Medimmune, AstraZeneca, Syndax, SunPharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes,

Italfarmaco, Nektar, Boehringer-Ingelheim; he also received research funds from BMS, Roche-Genentech, Array. All other authors declared no competing interests

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Table and Figure legends:

Figure 1: Kaplan-Meier survival estimates according to the drug-based prognostic score. **(A) Overall survival and (B) progression-free survival in the training cohort. (C) Overall survival and (D) progression-free survival in the validation cohort.**

Table 1: Patient characteristics.

Table 2: Univariate analyses for overall survival (OS) in the training cohort.

Table 3: Multivariate analyses for objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) in the training cohort.

Table 4: Multivariate analyses objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) in the validation cohort.

Supplementary figure 1: Overall survival curves according to baseline medication within the training cohort. (A) Corticosteroids, (B) Systemic antibiotics, (C) Proton

pump inhibitors, (D) Statins, (E) Metformin, (F) ACE inhibitors, (G) Acetylsalicylic acid.