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Integrated analysis of concomitant medications and oncological outcomes from PD-1/PD-L1 checkpoint inhibitors in clinical practice

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ABSTRACT

Background Concomitant medications, such as steroids, proton pump inhibitors (PPI) and antibiotics, might affect clinical outcomes with immune checkpoint inhibitors.

Methods We conducted a multicenter observational retrospective study aimed at evaluating the impact of concomitant medications on clinical outcomes, by weighing their associations with baseline clinical characteristics (including performance status, burden of disease and body mass index) and the underlying causes for their prescription. This analysis included consecutive stage IV patients with cancer, who underwent treatment with single agent antiprogrammed death-1/programmed death ligand-1 (PD-1/PD-L1) with standard doses and schedules at the medical oncology departments of 20 Italian institutions. Each medication taken at the immunotherapy initiation was screened and collected into key categories as follows: corticosteroids, antibiotics, gastric acid suppressants (including proton pump inhibitors - PPIs), statins and other lipid-lowering agents, aspirin, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors/Angiotensin II receptor blockers, calcium antagonists, β-blockers, metformin and other oral antidiabetics, opioids.

Results From June 2014 to March 2020, 1012 patients were included in the analysis. Primary tumors were: non-small cell lung cancer (52.2%), melanoma (26%), renal cell carcinoma (18.3%) and others (3.6%). Baseline statins (HR 1.60 (95% CI 1.14 to 2.25), p=0.0064), aspirin (HR 1.47 (95% CI 1.04 to 2.08, p=0.0267) and β-blockers (HR 1.76 (95% CI 1.16 to 2.69), p=0.0080) were confirmed to be independently related to an increased objective response rate. Patients receiving cancer-related steroids (HR 1.72 (95% CI 1.43 to 2.07), p<0.0001), prophylactic systemic antibiotics (HR 1.85 (95% CI 1.23 to 2.78), p=0.0030), prophylactic gastric acid suppressants (HR 1.29 (95% CI 1.09 to 1.53), p=0.0021), PPIs (HR 1.26 (95% CI 1.07 to 1.48), p=0.0050), anticoagulants (HR 1.43 (95% CI: 1.16 to 1.77), p=0.0007) and opioids (HR 1.71 (95% CI 1.28 to 2.28), p=0.0002) were confirmed to have a significantly higher risk of disease progression. Patients receiving cancer-related steroids (HR 2.16 (95% CI 1.76 to 2.65), p<0.0001), prophylactic systemic antibiotics (HR 1.93 (95% CI 1.25 to 2.98), p=0.0030), prophylactic gastric acid suppressants (HR 1.29 (95% CI 1.06 to 1.57), p=0.0091), PPI (HR 1.26 (95% CI 1.04 to 1.52), p=0.0172), anticoagulants (HR 1.45 (95% CI 1.14 to 1.84), p=0.0024) and opioids (HR 1.53 (95% CI 1.11 to 2.11), p=0.0098) were confirmed to have a significantly higher risk of death.

Conclusion We confirmed the association between baseline steroids administered for cancer-related indication, systemic antibiotics, PPIs and worse clinical outcomes with PD-1/PD-L1 checkpoint inhibitors, which can be assumed to have immune-modulating detrimental effects.

INTRODUCTION

Drug–drug interactions (DDIs) have traditionally played an important role in the safe and effective delivery of systemic anticancer therapy.[1] Concomitant medications can alter efficacy and worsen toxicity from systemic therapies through pharmacodynamic (PK) and pharmacokinetic (PD) interactions, particularly due to interference with absorption, distribution, metabolism and elimination of drugs.[1] The advent of immune checkpoint inhibitors (ICIs) has reignited the interest toward DDIs beyond traditional PK/PD considerations.[2]

ICIs exert their action mainly relying on the restoration/activation of T-cell responses against cancer, and therefore, might be altered by those factors which particularly affect the immune balance prior to the ICIs administration, such as disruption of the homeostatic balance within the gut microbiome[3] and drug-induced immune suppression.[4]

Concomitant medications including steroids, proton pump inhibitors and systemic antibiotics have been postulated to exert immune-modulatory effects within the tumor microenviroment, thus affecting clinical outcomes from ICI therapy.[2]

However, while some degree of biological plausibility exists to justify an immune-mediated basis to the detrimental effect observed on response and survival from ICIs, the strength and reliability of the association has been largely derived from retrospective/post hoc analyzes and the dispute between causative instead of associative relationship has not been fully resolved.[2] Given their immunosuppressive action, steroids were the first class of medications which was significantly related to worse clinical outcomes with cancer immunotherapy.[5] Nevertheless, a significant association with worse outcome was later confirmed for baseline steroids administered for palliation of cancer-rleated symptoms but not for other indications including treatment of immune-related adverse events.[6 7]

In the case of systemic antibiotics, the evidence for a causative effect seems stronger and more plausible in view of their capacity to perturbate the gut microbiome, a renown determinant of response to ICIs.[8–10] Nevertheless, the risk of collinearity with the underlying cause for the antibiotics prescription (eg, infections which might subtend to poorer clinical condition), has yet to be fully discriminated.

Proton pump inhibitors were associated to decreased progression-free survival (PFS) and overall survival (OS) in non-small-cell-lung-cancer (NSCLC) and melanoma patients receiving programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) checkpoint inhibitors,[9 11] while some studies investigated the impact of other concomitant medication, such as non-steroidal anti-inflammatory drugs (NSAIDs), metformin, aspirin, β-blockers and statins, without conclusive results.[12 13]

While a growing body of evidence underscores the importance of concomitant medications in affecting outcome from ICI, a key limitation affecting most of the published evidence is the lack of an integrated analysis of multiple classes of concomitant therapies. This is of particular importance to determine whether the influence on clinical outcomes might be driven by associative rather than causative links, especially given the high prevalence of polypharmacy in patients with cancer.[14]

Recently, we created a large multicenter, observational study of patients receiving PD-1/PD-L1 checkpoint inhibitors in clinical practice, already subject of several analyzes,[15–20] and we now gathered the baseline concomitant medication information for the same population, in order to evaluate their impact on clinical outcomes.

MATERIALS AND METHODS

Study design

We conducted a real-world, multicenter, retrospective observational data collection aimed at evaluating the impact of concomitant medications at immunotherapy initiation on clinical outcomes, by weighing their associations with baseline clinical characteristics (including performance status, burden of disease and body mass index (BMI)) and the underlying indication for steroids, antibiotics and gastric acid suppressants prescription. This study included consecutive patients with confirmed diagnosis of stage IV solid cancer, who underwent treatment with single agent anti-PD-1/PD-L1 as first or subsequent line, with data availability regarding baseline concomitant medication. The data collection was further implemented and updated involving patients treated at the medical oncology departments of 20 Italian institutions (online supplemental table 1), between June 2014 and March 2020. Patients were treated according to the tumor type indication with pembrolizumab, nivolumab, atezolizumab and other PD-1/PD-L1 prescribed at doses and schedules indicated in the respective product SPCs.

Clinical outcomes of interest included objective response rate (ORR), PFS and OS. Patients were assessed with radiological imaging in clinical practice, with a frequency ranging from 12 to 16 weeks, according to the monitoring requirements for high-cost drugs of the respective national drug regulatory agencies (the on-line monitoring dashboard of the 'Agenzia Italiana del Farmaco' requires a disease assessment at least every 16 weeks; available at: https://servizionline.aifa.gov.it/). RECIST (V. 1.1) criteria were used[21] and a subsequent confirming imaging was recommended. However, 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 as censored at the time of the last follow-up. Data cut-off period was May 2020.

Fixed multivariable regression models were used to estimate clinical outcomes according to each concomitant medication category following adjustment for preplanned adjusting covariates that might represent confounders.[22–24] The key covariates were: primary tumor type (NSCLC, melanoma, renal cell carcinoma and others), age (<70 vs ≥70 years),[25–28] 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) and BMI. BMI was used given to its alleged role in affecting immunotherapy clinical outcomes[15 16] and as a surrogate of cardiovascular/metabolic conditions which might have influenced the prescription of certain concomitant medications.

Table 1 Patients characteristics

	N (%) 1012
Age, (years)	
Median	68.5
Range	21–91
Elderly (≥70)	452 (44.7)
Sex	
Male	647 (63.9)
Female	365 (36.1)
ECOG PS	
0–1	870 (86.0)
≥2	142 (14.0)
Primary tumor	
NSCLC	528 (52.2)
Melanoma	263 (26.0)
Renal cell carcinoma	185 (18.3)
Others	36 (3.6)
No of metastatic sites	
≤2	522 (51.6)
>2	490 (48.4)
Type of anti-PD-1/PD-L1 agent	
Pembrolizumab	343 (33.9)
Nivolumab	613 (60.6)
Atezolizumab	32 (3.2)
Others	24 (2.3)
Treatment line of Immunotherapy	
First	396 (39.1)
Non-first	616 (60.9)
BMI (kg/m^2)	
Median (range)	25.1 (13.5–50.8)
Mean	25.6
Underweight	38 (3.8)
Normal weight	460 (45.5)
Overweight	377 (37.3)
Obese	137 (13.5)
Baseline steroids	
Non-cancer related	52 (5.1)
Cancer related	211 (20.8)
Systemic antibiotics	
Prophylaxis	30 (3.0)
Infection	48 (4.7)
Gastric acid suppressant	
Prophylaxis	100 (9.9)
Gastritis/GERD	447 (44.2)
Gastric acid suppressant	
H2 antagonists	56 (5.5)
Proton pump inhibitors	491 (48.5)
Statins	
Yes	196 (19.4)
Other lipid lowerings	
Yes	48 (4.7)
Aspirin	
Yes	189 (18.7)
Anticoagulants	
Yes	145 (14.3)
NSAIDs	
Yes	59 (5.8)
ACE inhibitors/ARBs	
Yes	313 (30.9)
Calcium antagonist	
Yes	140 (13.8)
Beta blockers*	
Yes	114 (12.1)
Metformin	
Yes	114 (11.3)
Other oral antidiabetics	
Yes	46 (4.5)
Opioids†	
Yes	68 (7.4)

*Available for 943 patients
†Available for 921 patients
ARBs, AngiotensinII receptor blockers; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; GERD, gastroesophageal reflux disease; NSCLC, non-small cell lung cancer; PD-1/PD-L1, programmed death-1/programmed death ligand-1.

Weight and height were obtained from patients' medical records at the time of immunotherapy initiation. BMI was calculated using the formula of weight/height^2 (kilograms per square meter) and categorized according to WHO categories: underweight, BMI <18.5 kg/m^2; normal-weight, 18.5 kg/m^2≤ BMI ≤24.9 kg/m^2; overweight, 25 kg/m^2≤ BMI ≤29.9 kg/m^2; obese, BMI ≥30 kg/m^2. In order to properly weighing the role of baseline concomitant medication, their association with ECOG-PS, burden of disease and with BMI were evaluated.

Concomitant medications

Information on prescribing of concomitant medications was gathered from patients' clinical records. Each medication prescribed at the time of immunotherapy initiation was screened and categorized as follows:

Table 2 Univariate and multivariate analyzes of ORR

Variable (Comparator)	ORR		
	Univariarte analysis		Multivariate analysis
	Response/ratio—ORR (%) (95% CI)	OR (95% CI); p value	aOR (95% CI); p value
Baseline steroids			
(No)	293/715–41.0 (36.4 to 45.9)		
Non-cancer indications	20/50–40.0 (24.4 to 61.7)	0.96 (0.53 to 1.72); p=0.8917	1.18 (0.65 to 2.17); p=0.5836
Cancer indications	48/195–24.6 (18.1 to 32.6)	0.47 (0.32 to 0.67); p<0.0001	0.55 (0.38 to 0.81); p=0.0020
Systemic antibiotics			
(No)	340/883–38.5 (34.5 to 42.8)		
Prophylaxis	5/29–17.2 (5.6 to 40.2)	0.33 (0.12 to 0.88); p=0.0266	0.39 (0.14 to 1.05); p=0.0631
Infection	16/48–33.3 (19.1 to 54.1)	0.79 (0.43 to 1.48); p=0.4735	0.89 (0.47 to 1.69); p=0.7314
Gastric acid suppressant			
(No)	185/446–41.5 (35.7 to 47.9)		
Prophylaxis	146/422–34.6 (29.2 to 40.7)	0.74 (0.56 to 0.97); p=0.0342	0.85 (0.64 to 1.14); p=0.3057
Gastritis/GERD	30/92–32.6 (22.0 to 46.5)	0.68 (0.42 to 1.09); p=0.1135	0.75 (0.46 to 1.24); p=0.2750
Gastric acid suppressant			
(No)	185/446–41.5 (35.7 to 47.9)		
H2 antagonists	19/51–37.3 (22.4 to 58.1)	0.84 (0.46 to 1.53); p=0.5700	1.03 (0.55 to 1.93); p=0.9196
Proton pump inhibitors	157/463–33.9 (28.8 to 39.6)	0.72 (0.55 to 0.95); p=0.0214	0.82 (0.62 to 1.09); p=0.1725
Statins			
(No)	275/774–35.5 (31.4 to 39.9)	1.56 (1.13 to 2.15); p=0.0070	1.60 (1.14 to 2.25); p=0.0064
Yes	86/186–46.2 (36.9 to 57.1)		
Other lipid lowerings			
(No)	345/915–37.7 (33.9 to 41.9)	1.22 (0.66–2.24); p=0.5130	1.11 (0.59 to 2.09); 0.7271
Yes	19/45–42.2 (25.4 to 65.9)		
Aspirin			
(No)	281/780–36.0 (31.9 to 40.5)	1.42 (1.02 to 1.97); p=0.0361	1.47 (1.04 to 2.08); 0.0267
Yes	80/180–44.4 (35.2 to 55.3)		
Anticoagulants			
(No)	319/826–38.6 (34.5 to 43.1)	0.72 (0.49 to 1.07); p=0.1078	0.79 (0.53 to 1.19); 0.2774
Yes	42/134–31.3 (22.6 to 42.3)		
NSAIDs			
(No)	346/905–38.2 (34.3 to 42.4)	0.61 (0.32 to 1.11); p=0.1064	0.64 (0.34 to 1.20); 0.1667
Yes	15/55–27.3 (15.2 to 44.9)		
ACE inhibitors/ARBs			
(No)	235/666–35.3 (30.9 to 40.1)	1.37 (1.04 to 1.82); p=0.0258	1.26 (0.93 to 1.71); p=0.1241
Yes	126/294–42.9 (35.7 to 51.0)		
Calcium antagonist			
(No)	307/828–37.1 (33.0 to 41.5)	1.17 (0.81 to 1.71); p=0.3990	1.07 (0.72 to 1.59); p=0.7188
Yes	54/132–40.9 (30.7 to 53.4)		
β-blockers*			
(No)	293/794–36.9 (32.8 to 41.4)	1.71 (1.14 to 2.56); p=0.0092	1.76 (1.16 to 2.69); p=0.0080
Yes	54/108–50.0 (37.5 to 65.2)		
Metformin			
(No)	318/849–37.5 (33.4 to 41.8)	1.06 (0.70 to 1.58); p=0.7930	1.02 (0.67 to 1.56); p=0.9081
Yes	43/111–38.7 (28.0 to 52.2)		
Other oral antidiabetics			

Continued

Table 2 Continued

Variable (Comparator)	ORR		
	Univariarte analysis		Multivariate analysis
	Response/ratio—ORR (%) (95% CI)	OR (95% CI); p value	aOR (95% CI); p value
(No)	342/919–37.2 (33.3 to 41.4)	1.45 (0.77 to 2.73); p=0.2402	1.34 (0.69 to 2.8); p=0.3808
Yes	19/41–46.3 (27.9 to 72.3)		
Opioids†			
(No)	317/822–38.6 (34.4 to 43.1)	0.75 (0.43 to 1.33); p=0.3325	0.90 (0.49 to 1.63); p=0.7325
Yes	19/59–32.2 (19.4 to 50.3)		
Primary tumor			–
(NSCLC)	160/491–32.6 (27.8 to 38.1)		
Melanoma	114/254–44.9 (37.0 to 53.9)	1.68 (1.23 to 2.29); 0.0010	
Kidney	74/180–41.1 (32.3 to 51.6)	1.44 (1.02 to 2.05); 0.0406	
Others	13/35–37.1 (19.7 to 63.5)	1.22 (0.60 to 2.49); 0.5799	
BMI			–
(Normal weight)	12/36–33.3 (17.2 to 58.2)		
Underweight	167/435–38.4 (32.8 to 44.7)	0.83 (0.41 to 1.67); 0.6038	
Overweight	128/352–36.3 (30.3 to 43.2)	0.91 (0.68 to 1.22); 0.5226	
Obese	54/136–39.7 (29.8 to 51.8)	1.03 (0.69 to 1.53); 0.8709	
Gender			–
(Female)	128/348–36.8 (30.7 to 43.7)	1.06 (0.81 to 1.39); p=0.6638	
Male	233/612–38.1 (33.3 to 43.3)		
Age			–
(Non-elderly)	190/535–35.5 (30.6 to 40.9)	1.22 (0.94 to 1.59); p=0.1338	
Elderly	171/425–40.2 (34.5 to 46.7)		
Treatment line			–
(First)	181/373–48.5 (41.7 to 56.1)	0.46 (0.39 to 0.61); p<0.0001	
Non-first	180/587–30.7 (26.3 to 35.5)		
No of metastatic sites			–
(≤2)	203/503–40.4 (35.0 to 46.3)	0.78 (0.60 to 1.01); p=0.0648	
>2	158/457–34.6 (29.4 to 40.4)		
ECOG PS			–
(0–1)	322/828–38.9 (34.8 to 43.4)	0.66 (0.44 to 0.98); p=0.0406	
≥2	39/132–29.5 (21.0 to 40.4)		

At the multivariate analysis, each drug category was adjusted for the preplanned key covariates separately.
*Available for 902 patients.
†Available for 881 patients.
ARBs, AngiotensinII receptor blockers; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; GERD, gastroesophageal reflux disease; NSCLC, non-small cell lung cancer; ORR, objective response rate.

- Corticosteroids administration (dose ≥10 mg prednisone equivalent per day, with a minimum 24 hours of dosing) within the 30 days before immunotherapy initiation, classified according to their indication as: no (including those patients receiving <10 mg prednisone equivalent) versus cancer indications (administration for symptoms palliation, radiation therapy, central nervous system metastases) versus non-cancer indications (eg, other inflammation processes non related to cancer).
- Systemic antibiotics within the 30 days before immunotherapy initiation, classified according to their indication as: no versus prophylaxis (eg, to prevent COPD exacerbation or diverticulitis prevention) versus infection (in case of a diagnosed infective disease).
- Baseline gastric acid suppressant, classified according to their indication as: no vs gastritis/gastroesophageal reflux disease (GERD) versus prophylaxis (eg, to prevent gastritis due to other concomitant

Table 3 Univariate and multivariate analyzes of PFS

Variable (Comparator)	PFS	
	Univariate analysis	Multivariate aanalysis
	HR (95% CI); p value	aHR (95% CI); p value
Baseline steroids		
(No)		
Non-cancer indications	1.08 (0.77 to 1.52); p=0.6370	0.96 (0.68 to 1.36); p=0.9681
Cancer indications	2.02 (1.69 to 2.40); p<0.0001	1.72 (1.43 to 2.07); p<0.0001
Systemic antibiotics		
(No)		
Prophylaxis	2.27 (1.52 to 3.39); p=0.0001	1.85 (1.23 to 2.78); p=0.0030
Infection	1.12 (0.79 to 1.59); p=0.4953	0.99 (0.70 to 1.41); p=0.9772
Gastric acid suppressant		
(No)		
Prophylaxis	1.51 (1.29 to 1.76); p<0.0001	1.29 (1.09 to 1.53); p=0.0021
Gastritis/GERD	1.05 (0.79 to 1.39); p=0.7432	1.01 (0.75 to 1.33); p=0.9683
Gastric acid suppressant		
(No)		
H2 antagonists	1.33 (0.96 to 1.86); p=0.0843	1.05 (0.75 to 1.48); p=0.7435
Proton pump inhibitors	1.41 (1.21 to 1.65); p<0.0001	1.26 (1.07 to 1.48); p=0.0050
Statins Yes versus no	0.88 (0.73 to 1.07); p=0.2329	0.87 (0.72 to 1.06); p=0.1944
Other lipid lowerings Yes versus no	1.06 (0.73 to 1.52); p=0.7498	1.21 (0.83 to 1.75); p=0.3061
Aspirin Yes versus no	0.86 (0.71 to 1.06); p=0.1630	0.79 (0.64 to 0.98); p=0.0318
Anticoagulants Yes versus no	1.49 (1.21 to 1.83); p=0.0001	1.43 (1.16 to 1.77); p=0.0007
NSAIDs Yes versus no	1.17 (0.86 to 1.59); p=0.3120	1.07 (0.78 to 1.47); p=0.6594
ACE inhibitors/ARBs Yes versus no	0.90 (0.76 to 1.07); p=0.2378	0.94 (0.79 to 1.12); p=0.5113
Calcium antagonists Yes versus no	1.03 (0.83 to 1.28); p=0.7540	1.07 (0.86 to 1.34); p=0.5261
β-blockers* Yes versus no	1.06 (0.84 to 1.35); p=0.6151	0.95 (0.75 to 1.22); p=0.7003
Metformin Yes versus no	1.16 (0.92 to 1.47); p=0.1868	1.13 (0.89 to 1.42); p=0.3059
Other oral anti-diabetics Yes versus no	1.24 (0.89 to 1.75); p=0.1981	1.24 (0.88 to 1.74); p=0.2098
Opioids† Yes versus no	2.05 (1.56 to 2.71); p<0.0001	1.71 (1.28 to 2.28); p=0.0002
Primary tumor		
(NSCLC)		–
Melanoma	0.60 (0.49 to 0.72); p<0.0001	
Kidney	0.75 (0.61 to 0.91); p=0.0050	
Others	0.92 (0.59 to 1.44); p=0.7288	
BMI		
(Normal-weight)		–
Underweight	1.23 (0.83 to 1.83); p=0.2966	
Overweight	0.95 (0.81 to 1.13); p=0.6090	
Obese	0.80 (0.63 to 1.02); p=0.0761	

Continued

Table 3 Continued

Variable (Comparator)	PFS	
	Univariate analysis	Multivariate aanalysis
	HR (95% CI); p value	aHR (95% CI); p value
Gender Male versus female	1.11 (0.94 to 1.30); p=0.1920	–
Age Elderly versus non-elderly	0.98 (0.84 to 1.14); p=0.7948	–
Treatment line Non-first versus first	1.45 (1.23 to 1.70); p<0.0001	–
No of metastatic sites >2 vs ≤2	1.51 (1.29 to 1.75); p<0.0001	–
ECOG PS ≥2 vs 0–1	1.94 (1.58 to 2.38); p<0.0001	–

At the multivariate analysis, each drug category was adjusted for the preplanned key covariates separately.
*Available for 943 patients.
†Available for 921 patients.
ARBs, AngiotensinII receptor blockers; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; GERD, gastroesophageal reflux disease; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

medication); no versus H2 Antagonists (such as ranitidine) vs proton pump inhibitors.
- Baseline statins (yes vs no).
- Other baseline lipid-lowering agents (fibrates, ezetimibe and similar) (yes vs no).
- Baseline aspirin (considered as low-dose daily assumption of aspirin for cardiovascular prevention) (yes vs no).
- Baseline anticoagulants (including new oral anticoagulants, low molecular weight heparin and cumarinic anticoagulant drugs) (yes vs no).
- NSAIDs within the 30 days before treatment initiation, including COX-2 inhibitors (including both chronic and PRN administration) (yes vs no).
- Baseline ACE inhibitors/angiotensin II receptor blockers (ARBs) (yes vs no), calcium antagonists (yes vs no), β-blockers (yes vs no).
- Baseline metformin (yes vs no) and other oral antidiabetics (yes vs no).
- Baseline opioids (yes vs no).

Statistical analysis

Baseline patient characteristics were reported with descriptive statistics. χ^2 test was used for the univariate analysis of ORR. Logistic regression was used for the multivariate analysis of ORR and to compute the ORs with 95% CIs. Median PFS and median OS were evaluated using the Kaplan-Meier method. Median period of follow-up was calculated according to the reverse Kaplan-Meier method. Cox proportional hazards regression was used for the univariate analysis, for the fixed multivariate analysis of PFS and OS and to compute the HRs for disease progression and death with 95% CIs. The alpha level for all analyzes was set to p<0.05. χ^2 test was also used to evaluate the associations between baseline concomitant medication and ECOG-PS (0–1 vs ≥2), burden of disease (number of metastatic sites≤2 vs>2) and BMI (underweight, normal-weight, overweight and obese). In order to properly evaluate the role of some baseline medications, a further analysis using the BMI as a continuous covariate was performed, through the one-way analysis of variance (ANOVA). All statistical analyzes were performed using MedCalc Statistical Software V.19.3.1 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2020).

RESULTS

Patients' characteristics

In total, 1012 consecutive advanced cancer patients were evaluated. Patients characteristics are and baseline medication are summarized in table 1. The median age was 68.5 years (range: 21–92), male/female ratio was 647/365. Primary tumors were: NSCLC (52.2%), melanoma (26%), renal cell carcinoma (18.3%) and others (3.6%).

Efficacy analysis

The median follow-up was 24.2 months (95% CI 23.3 to 67.2); in the study population ORR was 37.6% (95% CI 33.8%% to 41.7) (361 responses out of 960 evaluable patients), while median PFS and median OS were 10.2 months (95% CI 9.2 to 11.4; 681 progression events) and 19.7 months (95% CI 17.5 to 24.6; 520 censored patients), respectively. Table 2 reports the univariate and multivariate analyzes of ORR. Compared with patients who did not received baseline steroids, patients receiving them for cancer-related symptoms were confirmed to have a significantly lower ORR compared with patients who did not receive baseline steroids (HR 0.55 (95% CI 0.38 to 0.81), p=0.0020), while not patients who received steroids for non-cancer indications. Also baseline statins (HR 1.60 (95% CI 1.14 to 2.25), p=0.0064), aspirin (HR 1.47 (95% CI 1.04 to 2.08), p=0.0267) and β-blockers (HR

Table 4 Univariate and multivariate analyzes of OS

Variable (Comparator)	Overall survival	
	Univariate analysis	Multivariate analysis
	HR (95% CI); p value	aHR (95% CI); p value
Baseline steroids		
(No)		
Non-cancer indications	0.95 (0.62 to 1.47); p=0.8477	0.85 (0.54 to 1.31); p=0.4691
Cancer indications	2.76 (2.27 to 3.36); p<0.0001	2.16 (1.76 to 2.65); p<0.0001
Systemic antibiotics		
(No)		
Prophylaxis	2.68 (1.74 to 4.13); p<0.0001	1.93 (1.25 to 2.98); p=0.0030
Infection	1.51 (1.04 to 2.18); p=0.0301	1.20 (0.82 to 1.75); p=0.3288
Gastricacid suppressant		
(No)		
Prophylaxis	1.57 (1.31 to 1.89); p<0.0001	1.29 (1.06 to 1.57); p=0.0091
Gastritis/GERD	1.07 (0.76 to 1.49); p=0.7066	0.98 (0.69 to 1.38); p=0.9309
Gastric acid suppressant		
(No)		
H2 antagonists	1.30 (0.87 to 1.93); p=0.1919	1.04 (0.69 to 1.56); p=0.8444
Proton pump inhibitors	1.49 (1.23 to 1.79); p<0.0001	1.26 (1.04 to 1.52); p=0.0172
Statins Yes versus no	0.81 (0.64 to 1.02); p=0.0810	0.79 (0.62 to 1.01); p=0.0622
Other lipid lowerings Yes versus no	1.01 (0.65 to 1.57); p=0.9534	1.31 (0.84 to 2.05); p=0.2275
Aspirin Yes versus no	0.94 (0.75 to 1.19); p=0.6548	0.85 (0.67 to 1.07); p=0.1713
Anticoagulants Yes versus no	1.61 (1.27 to 2.03); p=0.0001	1.45 (1.14 to 1.84); p=0.0024
NSAIDs Yes versus no	1.51 (1.07 to 2.11); p=0.0167	1.30 (0.92 to 1.83); p=0.1337
ACE inhibitors/ARBs Yes versus no	0.88 (0.72 to 1.07); p=0.2204	0.91 (0.74 to 1.11); p=0.3798
Calcium antagonists Yes versus no	1.12 (0.87 to 1.44); p=0.3648	1.19 (0.92 to 1.54); p=0.1728
β-blockers* Yes versus no	1.03 (0.77 to 1.36); p=0.8554	0.90 (0.68 to 1.20); p=0.4938
Metformin Yes versus no	1.31 (1.02 to 1.70); p=0.0413	1.24 (0.95 to 1.61); p=0.1040
Other oral antidiabetics Yes versus no	1.34 (0.91 to 1.97); p=0.1304	1.26 (0.85 to 1.85); p=0.2475
Opioids† Yes versus no	2.14 (1.58 to 2.91); p<0.0001	1.53 (1.11 to 2.11); p=0.0098
Primary tumor		
(NSCLC)		–
Melanoma	0.45 (0.36 to 0.57); p<0.0001	
Kidney	0.49 (0.38 to 0.63); p<0.0001	
Others	0.60 (0.33 to 1.10); p=0.0992	
BMI		

Continued

Table 4 Continued

Variable (Comparator)	Overall survival	
	Univariate analysis	Multivariate analysis
	HR (95% CI); p value	aHR (95% CI); p value
(Normal weight)		–
Underweight	1.51 (0.98 to 2.32); p=0.0590	
Overweight	0.97 (0.79 to 1.17); p=0.7592	
Obese	0.78 (0.59 to 1.04); p=0.0981	
Gender Male versus no	0.97 (0.81 to 1.16); p=0.7499	–
Age Elderly versus non-elderly	1.11 (0.90 to 1.36); p=0.3138	–
Treatment line Non-first versus first	1.49 (1.23 to 1.80); p<0.0001	–
No of metastatic sites >2 vs ≤2	1.51 (1.26 to 1.79); p<0.0001	–
ECOG PS ≥2 vs 0–1	2.44 (1.96 to 3.05); p<0.0001	–

At the multivariate analysis, each drug category was adjusted for the pre-planned key covariates separately.
*Available for 943 patients.
†Available for 921 patients.
ARBs, Angiotensin II receptor blockers; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group-Performance Status; GERD, gastroesophageal reflux disease; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

1.76 (95% CI 1.16 to 2.69), p=0.0080) were confirmed to be independently related to an increased ORR. Table 3 summarizes the univariate and multivariate analyzes of PFS. Patients receiving cancer-related steroids (HR 1.72 (95% CI 1.43 to 2.07), p<0.0001), prophylactic systemic antibiotics (HR 1.85 (95% CI 1.23 to 2.78), p=0.0030), prophylactic gastric acid suppressants (HR 1.29 (95% CI 1.09 to 1.53), p=0.0021), proton pump inhibitors (HR 1.26 (95% CI 1.07 to 1.48), p=0.0050), anticoagulants (HR 1.43 (95% CI 1.15 to 1.76), p=0.0009) and opioids (HR 1.54 (95% CI 1.11 to 2.12), p=0.0083), were confirmed to have a significantly higher risk of disease progression. On the contrary, patients who assumed aspirin were confirmed to have a significantly lower risk of disease progression (HR 0.79 (95% CI 0.64 to 0.98), p=0.0318). Table 4 summarizes the univariate and multivariate analyzes of OS. Patients receiving cancer-related steroids (HR 2.16 (95% CI 1.76 to 2.65), p<0.0001), prophylactic systemic antibiotics (HR 1.93 (95% CI 1.25 to 2.98), p=0.0030), prophylactic gastric acid suppressants (HR 1.29 (95% CI 1.06 to 1.57), p=0.0091), proton pump inhibitors (HR 1.26 (95% CI 1.04 to 1.52), p=0.0172), anticoagulants (HR 1.45 (95% CI 1.14 to 1.84), p=0.0024) and opioids (HR 1.53 (95% CI 1.11 to 2.11), p=0.0098) were confirmed to have a significantly higher risk of death. Figures 1 and 2 report the Kaplan-Meier survival curves for PFS and OS according to baseline steroids, systemic antibiotics, gastric acid suppressants, anticoagulants and opioids.

Baseline associations

All the baseline associations are summarized in online supplemental table 5; the administration of baseline steroids (p<0.0001), systemic antibiotics (p=0.0001), gastric acid suppressant (both according to their indication (p<0.0001) and drug class (p=0.0002)), anticoagulants (p=0.0011), antidepressants (p=0.0002) and opioids (p=0.0123) was significantly associated to a poorer ECOG-PS. Similarly, the administration of baseline steroids (p=0.0014), gastric acid suppressant (both according to their indication (p<0.0001) and drug class (p<0.0001)), β-blockers (p=0.0166), and opioids (p=0.0014) was significantly associated to a higher burden of disease.

The administration of statins (p=0.005), anticoagulants (p=0.001), ACE inhibitors/ARBs (p=0.002), calcium antagonists (p=0.008), β-blockers (p=0.008), and other oral antidiabetics (p=0.036) was significantly associated to a higher BMI, while the administration of NSAIDs (p=0.003), and opioids (p=0.004) to a lower BMI at the ANOVA analysis. Using WHO categories for BMI, we confirmed the association with anticoagulants (p=0.0438), NSAIDs (0.0069) and opioids (p=0.0153).

DISCUSSION

Identification of factors that prelude to immune-refractoriness is an area of high unmet need in cancer immunotherapy. A number of non-oncological medical therapies have been postulated to render the tumor

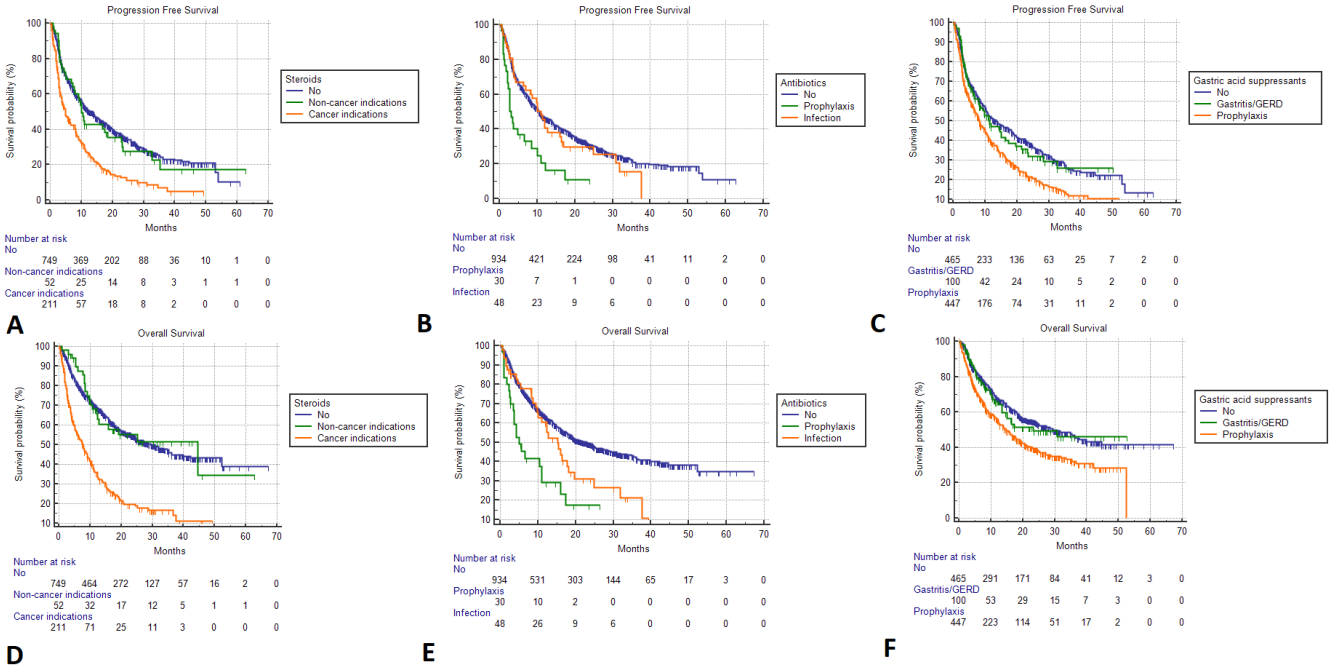

Figure 1 Kaplan-Meier survival estimates. Progression-free survival; (A) Steroids. No: 13.5 months (95% CI 10.8 to 15.4; 472 events); non-cancer indications: 10.0 months (95% CI 7.2 to 18.3; 36 events); cancer indications: 4.9 months (95% CI 3.6 to 6.5; 247 events); (B) Systemic antibiotics. No: 10.5 months (95% CI 9.2 to 11.9, 622 events); prophylaxis: 2.8 months (95% CI 2.1 to 6.7, 25 events); infections: 10.9 months (95% CI 6.4 to 37.5, 34 events); (C) Gastric acid suppressants. No: 13.5 months (95% CI 10.5 to 18.2, 288 events); gastritis/GERD: 11.2 months (95% CI 7.9 to 17.3, 60 events); prophylaxis: 8.2 months (95% CI 6.9 to 9.9, 333 events). Overall survival; (D) Steroids. No: 30.8 months (95% CI 24.4 to 36.3; 432 censored); non-cancer indications: 44.6 months (95% CI 12.0 to 44.6; 30 censored); cancer indications: 7.8 months (95% CI 5.4 to 9.8; 58 censored); (E) Systemic antibiotics. No: 22.8 months (95% CI 18.9 to 27.4, 494 censored); prophylaxis: 4.9 months (95% CI 3.5 to 11.0, 8 censored); infections: 15.2 months (95% CI 9.8 to 18.1, 18 censored); (F) Gastric acid suppressants. No: 29.4 months (95% CI 22.8 to 39.8, 266 censored); gastritis/GERD: 23.2 months (95% CI 13.4 to 30.8, 59 censored); prophylaxis: 14.8 months (95% CI 12.3 to 52.3, 195 censored). GERD, gastroesophageal reflux disease.

microenviroment more tolerogenic, therefore exerting detrimental effects on depth, duration of response and survival of patients treated with ICI.[2] Our purpose was to provide a more comprehensive analysis with a large population of patients with different malignancies receiving PD-1/PD-L1 inhibitors, in order to gain reliable results about the putative immune-modulating effects of concomitant medication most usually taken by patients with cancer.

We produce important confirmatory evidence regarding the association between exposure to steroids, systemic antibiotics and proton pump inhibitors and worse outcomes from ICI. In addition, we provide novel evidence for a shorter survival in patients on anticoagulants and opioids at ICIs initiation, a finding that was not previously reported in large populations. Similarly, a significant association between improved ORR/PFS and baseline aspirin, and between improved ORR and statins and β-blockers, had never been reported in the context of cancer patients receiving PD-1/PD-L1 inhibitors.

Intriguingly, among the baseline medication which resulted to be significantly related to clinical outcomes in our study population, the common thread might be somehow considered the immune modulating effects, particularly exerted through the modifying pressure on the gut-microbiome.

Steroids were the only baseline medication concordantly related to ORR, PFS and OS in our study population. Glucocorticoids can affect the gut microbiome, the intestinal mucosa and synthesis/secretion of mucins.[29–31] Nevertheless, we have to consider the possible associative (and not causative) effect played by the significant relation between steroids assumption and poorer PS/higher burden of disease. In fact, patients receiving baseline steroids for symptoms palliation were confirmed to have significantly worse ORR, PFS and OS, compared with patients who did not received steroids, while not patients who received steroids for non-cancer indications, similarly to what reported by Ricciuti *et al*.[6]

It is also well known that antibiotics might affect immunity by inducing gut microbiome alterations.[32] In our study, only systemic antibiotics administered for prophylaxis were confirmed to be significantly related to shortened PFS and OS at the multivariate analysis, while not antibiotics administered to treat active infections. Interestingly, it was further revealed that antibiotics administered prior of the immunotherapy initiation was confirmed to be related to worse outcomes, while not those

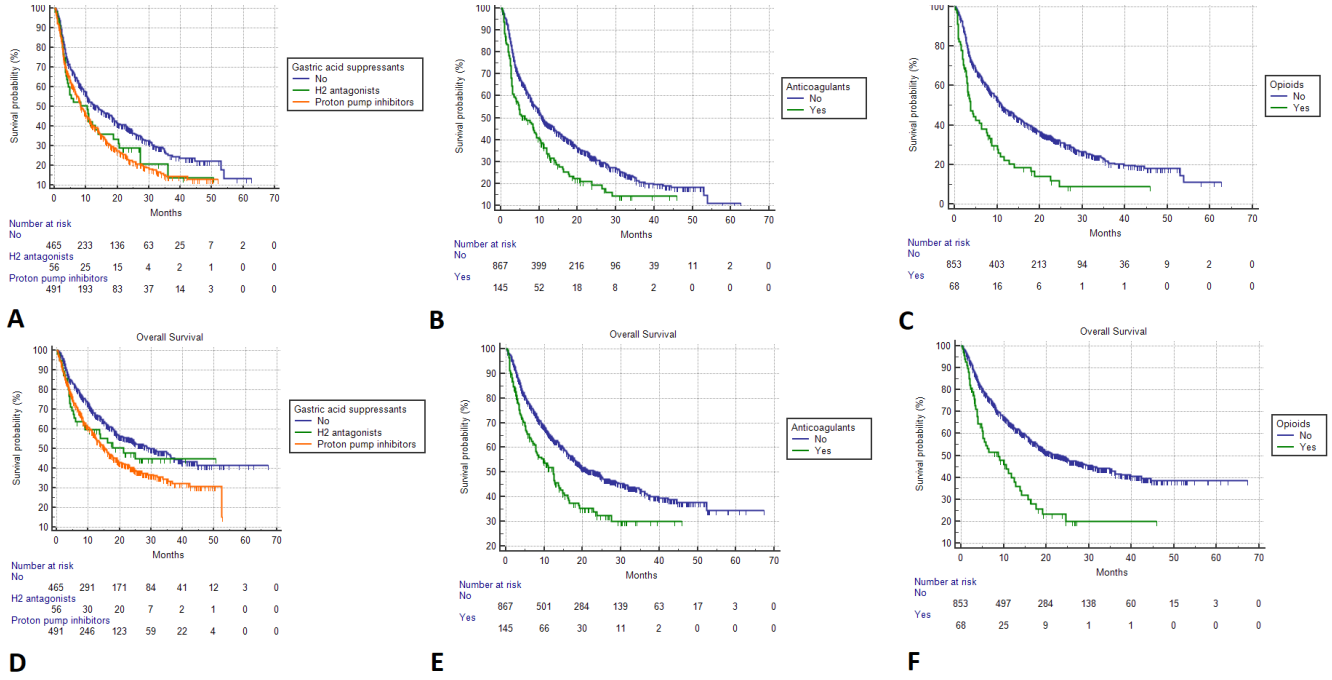

Figure 2 Kaplan-Meier survival estimates. Progression-free survival; (A) Gastric acid suppressants. No: 13.5 months (95% CI 10.5 to 18.2, 288 events); H2 antagonists: 10.3 months (95% CI 3.8 to 13.9; 40 events); proton pump inhibitors: 8.4 months (95% CI 7.5 to 10.0; 353 events); (B) Anticoagulants. No: 10.9 months (95% CI 9.9 to 13.0, 573 events); yes: 6.3 months (95% CI 3.9 to 9.2, 108 events); (C) Opioids. No: 11.0 months (95% CI 10.0 to 13.5, 564 events); yes: 3.8 months (95% CI 2.9 to 6.4, 56 events). Overall survival (D) Gastric acid suppressants. No: 29.4 months (95% CI 22.8 to 39.8, 266 censored); H2 antagonists: 21.1 months (95% CI 6.1 to 25.0; 28 censored); proton pump inhibitors: 15.4 months (95% CI 12.5 to 18.1; 226 censored); (E) Anticoagulants. No: 23.9 months (95% CI 18.9 to 28.6, 460 censored); yes: 12.4 months (95% CI 7.8 to 15.1; 60 censored); (F) Opioids No: 23.2 months (95% CI 18.9 to 28.8, 452 censored); yes: 8.6 months (95% CI 4.7 to 12.7; 22 censored).

administered concurrently,[10] supporting the hypothesis that the underlying modulating effects on the gut microbiome can affect the immunotherapy clinical outcomes only when the modifying pressure is exerted on the prior immune-balance, and not during the treatment. From this perspective, antibiotics administered for prophylactic indications might exert the same negative effect of those administered to treat active infections. However, we have to consider that patients receiving antibiotics have poorer clinical conditions overall and looking at the table 5 we can noticed that those on prophylactic antibiotics had the highest percentage of ECOG-PS ≥2 patients.

Previous studies investigated the role of proton pump inhibitors exclusively,[9 11] while this is the first analysis which evaluated the role of gastric acid suppressants overall. Proton pump inhibitors could negatively affect the gut microbiome due to both the changes of the gastric pH and to bacterial species selections,[33 34] but also H2 antagonists are known to have modifying gut microbiome functions and to induce intestinal barrier dysfunctions.[35 36] Curiously, proton pump inhibitors administration was confirmed to be associated to shortened PFS and OS, but not H2 antagonists and patients receiving gastric acid suppressants for prophylactic purpose experienced significantly shorter PFS and OS, while patients who received these agents to treat gastritis/GERD achieved similar outcomes to patients who did not receive them. In this case, the highest percentage of patients with ECOG-PS ≥2 is among the patients with gastritis/GERD and among the patients on H2 antagonists, but to proper weigh our results, we must take into account the significant association between baseline gastric acid suppressants and burden of disease (online supplemental table 3). Therefore, we are not able to recommend H2 antagonists prescription instead of proton pump inhibitors for patients with cancer who are in need of a gastric acid suppressant treatment and are going to receive a PD-1/PD-L1 checkpoint inhibitor, even more considering the recent alerts from drug regulatory agencies regarding the possible contamination with N-nitrosodimethylamine of some of these agents.[37 38]

Anticoagulants have been assumed to modulate the immune balance, affecting the antibacterial innate immune response,[39] while chronic opioid dosing has been already associated to shift of the gut microbiome and intestinal barrier dysfunction.[40–43] Nevertheless, it should be considered that patients requiring anticoagulation therapy and opioids are often frailer than patients who do not: a point that should be emphasized when evaluating PFS and OS where poorer PS and higher disease burden may confound the analyzes.

The relationship between aspirin and cancer prevention/progression have been historically known,[44 45] but in the setting of immunotherapy of cancer, few studies have been published. Wang *et al*[12] evaluated a cohort of 330 melanoma patients receiving PD-1 inhibitors, without

Table 5 Summary of the associations between each drug category and ECOG-PS, burden of disease and BMI

	ECOG-PS (%)		χ^2	No of metastatic sites (%)		χ^2	BMI				χ^2	BMI (continuous)	One-way ANOVA
	0–1	≥2	P value	≤2	>2	P value	≤18.5	18.5–25	25–30	≥30	P value	Mean (SD)	F-ratio; P value
Baseline steroids													F(21 005)=3.16; p=0.043
(No)	671 (89.6)	78 (10.4)	p<0.0001	410 (54.7)	339 (45.3)	p=0.0014	27 (3.6)	330 (44.1)	288 (38.5)	104 (13.9)	p=0.3548	25.8(4.5)	
Non-cancer indications	43 (82.7)	9 (17.3)		18 (34.6)	34 (65.4)		1 (1.9)	22 (42.3)	19 (36.5)	10 (19.2)		26.9(4.3)	
Cancer indications	156 (73.9)	55 (26.1)		94 (44.5)	117 (55.5)		10 (4.7)	108 (51.2)	70 (33.2)	23 (10.9)		24.9(4.4)	
Systemic antibiotics													F(21 005)=0.94; p=0.388
(No)	815 (87.3)	78 (10.4)	p=0.0001	482 (51.6)	452 (48.4)	p=0.9826	37 (4.0)	416 (44.5)	352 (37.7)	129 (13.8)	p=0.3921	25.7(4.5)	
Prophylaxis	19 (63.3)	9 (17.3)		15 (50.0)	15 (50.0)		1 (3.3)	16 (53.3)	11 (36.7)	2 (6.7)		24.5(3.5)	
Infection	36 (75.0)	55 (26.1)		25 (52.1)	23 (47.9)		–	28 (58.3)	14 (29.2)	6 (12.5)		25.5(3.4)	
Gastric acid suppressant													F(21 005)=2.66; p=0.070
(No)	422 (90.8)	43 (9.2)	p<0.0001	275 (59.1)	190 (40.9)	p<0.0001	21 (4.5)	211 (45.4)	174 (37.4)	59 (12.7)	p=0.7860	25.5(4.5)	
Prophylaxis	93 (93.0)	7 (7.0)		189 (42.3)	258 (57.7)		13 (2.9)	201 (45.0)	166 (37.1)	67 (15.0)		24.9(4.3)	
Gastritis/GERD	355 (79.4)	92 (20.6)		58 (58.0)	42 (42.0)		4 (4.0)	48 (48.0)	37 (37.0)	11 (11.0)		25.9(4.5)	
Gastric acid suppressant													F(21 005)=0.77; p=0.462
(No)	422 (90.8)	43 (9.2)	p<0.0001	275 (59.1)	190 (40.9)	p<0.0001	21 (4.5)	211 (45.4)	174 (37.4)	59 (12.7)	p=0.7860	25.5(4.5)	
H2 antagonists	44 (78.6)	7 (7.0)		189 (42.3)	258 (57.7)		13 (2.9)	201 (45.0)	166 (37.1)	67 (15.0)		25.3(3.4)	
Proton pump inhibitors	404 (82.3	92 (20.6)		58 (58.0)	42 (42.0)		4 (4.0)	48 (48.0)	37 (37.0)	11 (11.0)		25.8(4.6)	
Statins													F(11 006)=7.87; p=0.005
(No)	697 (85.4)	119 (14.6)	p=0.3027	415 (50.9)	401 (49.1)	p=0.3478	36 (4.4)	377 (46.2)	296 (36.3)	107 (13.1)	p=0.0718	25.4(4.4)	
Yes	173 (88.3)	23 (11.7)		107 (54.6)	89 (45.4)		2 (1.0)	83 (42.3)	81 (41.3)	30 (15.3)		26.4(4.7)	
Other lipid lowerings													F(11 006)=3.81; p=0.051
(No)	830 (86.1)	134 (13.9)	p=0.5904	491 (50.9)	473 (49.1)	p=0.0649	36 (3.7)	447 (46.4)	353 (36.6)	128 (13.3)	p=0.0727	25.5(4.5)	
Yes	40 (83.3)	8 (16.7)		31 (64.6)	17 (35.4)		2 (4.2)	13 (27.1)	24 (50.0)	9 (18.8)		26.9(4.2)	
Aspirin													F(11 006)=0.47; p=0.493
(No)	710 (86.3)	113 (13.7)	p=0.5648	421 (51.2)	402 (48.8)	p=0.5710	35 (4.3)	371 (45.1)	305 (37.1)	112 (13.6)	p=0.3756	25.6(4.5)	
Yes	160 (84.7)	29 (15.3)		101 (53.4)	88 (46.6)		3 (1.6)	89 (47.1)	72 (38.1)	25 (13.2)		25.8(4.1)	
Anticoagulants													F(11 006)=11.44; p=0.001
(No)	758 (87.4)	109 (12.6)	p=0.0011	444 (51.2)	423 (48.8)	p=0.5649	36 (4.2)	405 (46.7)	314 (36.2)	112 (12.9)	p=0.0438	25.4(4.5)	
Yes	112 (77.2)	33 (22.8)		78 (53.8)	67 (46.2)		2 (1.4)	55 (37.9)	63 (43.4)	25 (17.2)		26.8(4.6)	
NSAIDs													F(11 006)=9.03; p=0.003
(No)	819 (85.9)	134 (14.1)	p=0.9143	490 (51.4)	463 (48.6)	p=0.6741	33 (3.5)	424 (44.5)	364 (38.2)	132 (13.9)	p=0.0069	25.7(4.4)	
Yes	51 (86.4)	8 (13.6)		32 (54.2)	27 (45.8)		5 (8.5)	36 (61.0)	13 (22.0)	5 (8.5)		23.9(4.8)	
ACE inhibitors/ARBs													F(11 006)=9.42; p=0.002
(No)	604 (45.9)	95 (13.6)	p=0.5465	352 (50.4)	347 (49.6)	p=0.2448	30 (4.3)	333 (47.6)	247 (35.3)	89 (12.7)		25.3(4.3)	
Yes	266 (54.1)	47 (15.0)		170 (54.3)	143 (45.7)		8 (2.6)	127 (40.6)	130 (41.5)	48 (15.3)		26.3(4.7)	

Continued

Table 5 Continued

	ECOG-PS (%)		χ^2	No of metastatic sites (%)		χ^2	BMI			χ^2	BMI (continuous)	One-way ANOVA
	0–1	≥2	P value	≤2	>2	P value	≤18.5	18.5–25	25–30	≥30	P value	Mean (SD)	F-ratio; P value
Calcium antagonist													F(11 006)=7.01; p=0.008
(No)	755 (86.6.9)	117 (13.4)	p=0.1605	446 (51.5)	426 (48.9)	p=0.4905	36 (4.1)	401 (46.0)	322 (36.9)	113 (13.0)	p=0.2146	25.5(4.4)	
Yes	115 (82.1)	25 (17.9)		76 (54.3)	64 (45.7)		2 (1.4)	59 (42.1)	55 (39.3)	24 (17.1)		26.6(4.9)	
β-blockers*													F(1937)=9.96; p=0.008
(No)	713 (86.0)	116 (14.0)	p=0.3118	441 (53.2)	388 (46.8)	p=0.0166	35 4.2)	388 (46.8)	303 (36.6)	103 (12.4)	p=0.1493	25.4(4.5)	
Yes	94 (82.5)	20 (17.5)		47 (41.2)	67 (58.8)		1 (0.9)	47 (41.2)	48 (42.2)	18 (15.8)		26.6(4.1)	
Metformin													F(11 006)=0.37; p=0.542
(No)	777 (86.5)	121 (13.5)	p=0.1522	456 (50.8)	442 (49.2)	p=0.1524	36 (4.0)	407 (45.3)	331 (36.9)	124 (13.8)	p=0.5393	25.6(4.5)	
Yes	93 (81.6)	21 (18.4)		66 (57.9)	48 (42.1)		2 (1.8)	53 (46.5)	46 (40.4)	13 (11.4)		25.9(4.6)	
Other oral antidiabetics													F(11 006)=4.42; p=0.036
(No)	831 (86.0)	135 (14.0)	p=0.8127	495 (51.2)	471 (48.8)	p=0.3233	38 (3.9)	443 (45.9)	356 (36.9)	129 (13.4)	p=0.2597	25.6(4.5)	
Yes	39 (84.8)	7 (15.2)		27 (58.7)	19 (41.3)		–	17 (37.0)	21 (45.7)	8 (17.4)		26.9(4.8)	
Opioids†													F(1915)=8.26; p=0.004
(No)	735 (86.2)	118 (13.8)	p=0.0123	448 (52.5)	405 (47.5)	p=0.0014	29 (3.4)	389 (45.6)	320 (37.5)	115 (13.5)	p=0.0153	25.6(4.4)	
Yes	51 (75.0)	17 (25.0)		22 (32.4)	46 (67.6)		6 (8.8)	37 (54.4)	22 (32.4)	3 (4.4)		24.0(4.1)	

ANOVA, analysis of variance; ARBs, Angiotensin II receptor blockers; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; GERD, gastroesophageal reflux disease.

reporting any association between ORR, PFS, OS and NSAIDs use (including aspirin). Even if (cyclooxygenase) COX-2 expression was known to be positively associated with PD-L1 tumor expression,[46] we did not find associations between baseline NSAIDs (excluding aspirin) and immunotherapy clinical outcomes, but the significant association between improved ORR and baseline aspirin, allows to speculate about the possible synergistic effects of COX inhibition in antitumor immunity.[47] To our knowledge, the association between statins administration and improved clinical outcomes of patients with cancer receiving ICIs have never been described, however, it is well known that cholesterol metabolism plays a role in CD8+T cell function and might be modulated in order to enhance antitumor immunity.[48–51] β-blockers have already been known to improve recurrence-free survival in patients with radically resected melanoma and to have synergistic effects with immunotherapy in mice models.[52 53] In our cohort baseline β-blockers are significantly associated to improved ORR, while in the study of Wang *et al* no significant associations were found.[12] Intriguingly, the inhibition of β-adrenoceptors in the intestinal mucosa and gut lymphatic tissue has been linked with changes in type and virulence of the intestinal microbiome and to reduced bacterial translocation trough the intestinal barrier.[54] Finally, to properly weighing the ORR analysis results, we have to consider the significant association between β-blockers and low burden of disease and between β-blockers, aspirin, lipid-lowering agents and higher baseline BMI. However, contrary to what we previously reported,[15 16] BMI was not significantly associated to improved outcomes in this population, even though a trend toward better ORR, PFS and OS for increased BMI levels was found. Considering that the most robust evidence of an association between improved outcomes and obesity came from NSCLC,[55] this finding might be related to the internal distribution of the study population, which after the update and the addition of data from some new institutions passed form 65.1% and 18.7% of NSCLC and melanoma patients to 52.2% and 26%, respectively.

Despite the suggestion that metformin administration might exert a synergistic antitumor role with ICIs,[2 56] we did not find any significant association between ORR, PFS, OS and baseline metformin, in keeping with previously published evidence.[12]

Beyond the dispute between association and causation, we have to consider that there are some other potential mechanisms by which concomitant medications could affect clinical outcomes during immunotherapy, in addition to gut microbiome alteration. It is well known that corticosteroids can exert immune-suppressive effects through several mechanisms, such as activation of glucocorticoid response elements with the inhibition of interleukin 1 (IL-1) and IL-6 transcription,[57 58] induction of T-cell suppression and diminishing naïve T cell proliferation.[59] Gastric acid suppressants can cause immune-suppressive effects through the inhibition of adhesion molecules of inflammatory cells and affecting cytokines secretion.[60] Aspirin can exert several effects on both innate and adaptive immune responses. It can modulate proliferation/maturation of immune cells, regulate the cytokine production, and induce the lipoxin-driven immune counter-regulation. Nevertheless, aspirin can also have the immune suppressive ability of inducing tolerogenic dendritic cells, therefore expanding Treg cells.[61]

Our study acknowledges a number of limitations, including the retrospective design and the lack of central radiology review. The heterogeneity of tumor types evaluated might had affected the analysis even if we included the primary tumor in the preplanned fixed multivariate model. We have to also consider the small sample size of some subgroups as patients receiving steroids for non-cancer indication, gastric acid suppressants to treat gastritis/GERD and receiving H2 antagonists. Moreover, we are planning to investigate the possible detrimental effect on immunotherapy clinical outcomes of specific polypharmacy patterns. To confirm our results, interactions between concomitant baseline medications and immunotherapy clinical outcomes should be assessed prospectively.

CONCLUSION

This is the largest study to provide a broad, integrated analysis of multiple concomitant medications as determinants of response and survival to immunotherapy in patients with solid tumors. While unable to discriminate between a mechanistic and an associative effect, our study strengthens the knowledge around the association between baseline steroids administered for cancer-related indications, systemic antibiotics, proton pump inhibitors and worse clinical outcomes with PD-1/PD-L1 checkpoint inhibitors, which can be assumed to have immune-modulating detrimental effects. To correctly weight the association between anticoagulants/opioids and worse PFS/OS we must consider their statistical association with poorer PS/higher burden of disease, while the significant association between the administration of aspirin, β-blockers, statins and improved ORR deserves further investigations.

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Ethics approval 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 24 2018).

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