




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

Alessio Cortellini ^{1,2}, Marco Tucci,^{3,4} Vincenzo Adamo,⁵ Luigia Stefania Stucci,³ Alessandro Russo,⁵ Enrica Teresa Tanda,⁶ Francesco Spagnolo,⁶ Francesca Rastelli,⁷ Renato Bissoni,⁷ Daniele Santini,⁸ Marco Russano,⁸ Cecilia Anesi,⁸ Raffaele Giusti,⁹ Marco Filetti,⁹ Paolo Marchetti,^{9,10,11} Andrea Botticelli,¹⁰ Alain Gelibter,¹¹ Mario Alberto Occhipinti,¹¹ Riccardo Marconcini,¹² Maria Giuseppa Vitale,¹³ Linda Nicolardi,¹⁴ Rita Chiari,¹⁴ Claudia Bareggi,¹⁵ Olga Nigro,¹⁶ Alessandro Tuzi,¹⁶ Michele De Tursi,¹⁷ Nicola Petragnani,¹⁸ Laura Pala,¹⁹ Sergio Bracarda,²⁰ Serena Macrini,²⁰ Alessandro Inno,²¹ Federica Zoratto,²² Enzo Veltri,²² Barbara Di Cocco,²² Domenico Mallardo,²³ Maria Grazia Vitale,²³ David James Pinato ²⁴, Giampiero Porzio,² Corrado Ficorella,^{1,2} Paolo Antonio Ascierto ²³

To cite: Cortellini A, Tucci M, Adamo V, *et al.* Integrated analysis of concomitant medications and oncological outcomes from PD-1/PD-L1 checkpoint inhibitors in clinical practice. *Journal for ImmunoTherapy of Cancer* 2020;**8**:e001361. doi:10.1136/jitc-2020-001361

Accepted 28 August 2020

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



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Alessio Cortellini;
alessiocortellini@gmail.com

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 microbiome³ 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 microenvironment, 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-related 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 used²¹ 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 \geq 70 years),^{25–28} sex (male vs female), Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) (0–1 vs \geq 2), burden of disease (number of metastatic sites \leq 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)

Continued

Table 1 Continued

	N (%) 1012
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/height² (kilograms per square meter) and categorized according to WHO categories: underweight, BMI <18.5 kg/m²; normal-weight, 18.5 kg/m² ≤ BMI ≤24.9 kg/m²; overweight, 25 kg/m² ≤ BMI ≤29.9 kg/m²; obese, BMI ≥30 kg/m². 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		
	Univariate 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		
	Univariate 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)	1.68 (1.23 to 2.29); 0.0010	—
Melanoma	114/254—44.9 (37.0 to 53.9)		
Kidney	74/180—41.1 (32.3 to 51.6)		
Others	13/35—37.1 (19.7 to 63.5)		
BMI			
(Normal weight)	12/36—33.3 (17.2 to 58.2)	0.83 (0.41 to 1.67); 0.6038	—
Underweight	167/435—38.4 (32.8 to 44.7)		
Overweight	128/352—36.3 (30.3 to 43.2)		
Obese	54/136—39.7 (29.8 to 51.8)		
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 ≥10mg 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 <10mg 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 analysis
	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	0.88 (0.73 to 1.07); p=0.2329	0.87 (0.72 to 1.06); p=0.1944
Yes versus no		
Other lipid lowerings	1.06 (0.73 to 1.52); p=0.7498	1.21 (0.83 to 1.75); p=0.3061
Yes versus no		
Aspirin	0.86 (0.71 to 1.06); p=0.1630	0.79 (0.64 to 0.98); p=0.0318
Yes versus no		
Anticoagulants	1.49 (1.21 to 1.83); p=0.0001	1.43 (1.16 to 1.77); p=0.0007
Yes versus no		
NSAIDs	1.17 (0.86 to 1.59); p=0.3120	1.07 (0.78 to 1.47); p=0.6594
Yes versus no		
ACE inhibitors/ARBs	0.90 (0.76 to 1.07); p=0.2378	0.94 (0.79 to 1.12); p=0.5113
Yes versus no		
Calcium antagonists	1.03 (0.83 to 1.28); p=0.7540	1.07 (0.86 to 1.34); p=0.5261
Yes versus no		
β-blockers*	1.06 (0.84 to 1.35); p=0.6151	0.95 (0.75 to 1.22); p=0.7003
Yes versus no		
Metformin	1.16 (0.92 to 1.47); p=0.1868	1.13 (0.89 to 1.42); p=0.3059
Yes versus no		
Other oral anti-diabetics	1.24 (0.89 to 1.75); p=0.1981	1.24 (0.88 to 1.74); p=0.2098
Yes versus no		
Opioids†	2.05 (1.56 to 2.71); p<0.0001	1.71 (1.28 to 2.28); p=0.0002
Yes versus no		
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 analysis
	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	0.81 (0.64 to 1.02); p=0.0810	0.79 (0.62 to 1.01); p=0.0622
Yes versus no		
Other lipid lowerings	1.01 (0.65 to 1.57); p=0.9534	1.31 (0.84 to 2.05); p=0.2275
Yes versus no		
Aspirin	0.94 (0.75 to 1.19); p=0.6548	0.85 (0.67 to 1.07); p=0.1713
Yes versus no		
Anticoagulants	1.61 (1.27 to 2.03); p=0.0001	1.45 (1.14 to 1.84); p=0.0024
Yes versus no		
NSAIDs	1.51 (1.07 to 2.11); p=0.0167	1.30 (0.92 to 1.83); p=0.1337
Yes versus no		
ACE inhibitors/ARBs	0.88 (0.72 to 1.07); p=0.2204	0.91 (0.74 to 1.11); p=0.3798
Yes versus no		
Calcium antagonists	1.12 (0.87 to 1.44); p=0.3648	1.19 (0.92 to 1.54); p=0.1728
Yes versus no		
β-blockers*	1.03 (0.77 to 1.36); p=0.8554	0.90 (0.68 to 1.20); p=0.4938
Yes versus no		
Metformin	1.31 (1.02 to 1.70); p=0.0413	1.24 (0.95 to 1.61); p=0.1040
Yes versus no		
Other oral antidiabetics	1.34 (0.91 to 1.97); p=0.1304	1.26 (0.85 to 1.85); p=0.2475
Yes versus no		
Opioids†	2.14 (1.58 to 2.91); p<0.0001	1.53 (1.11 to 2.11); p=0.0098
Yes versus no		
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

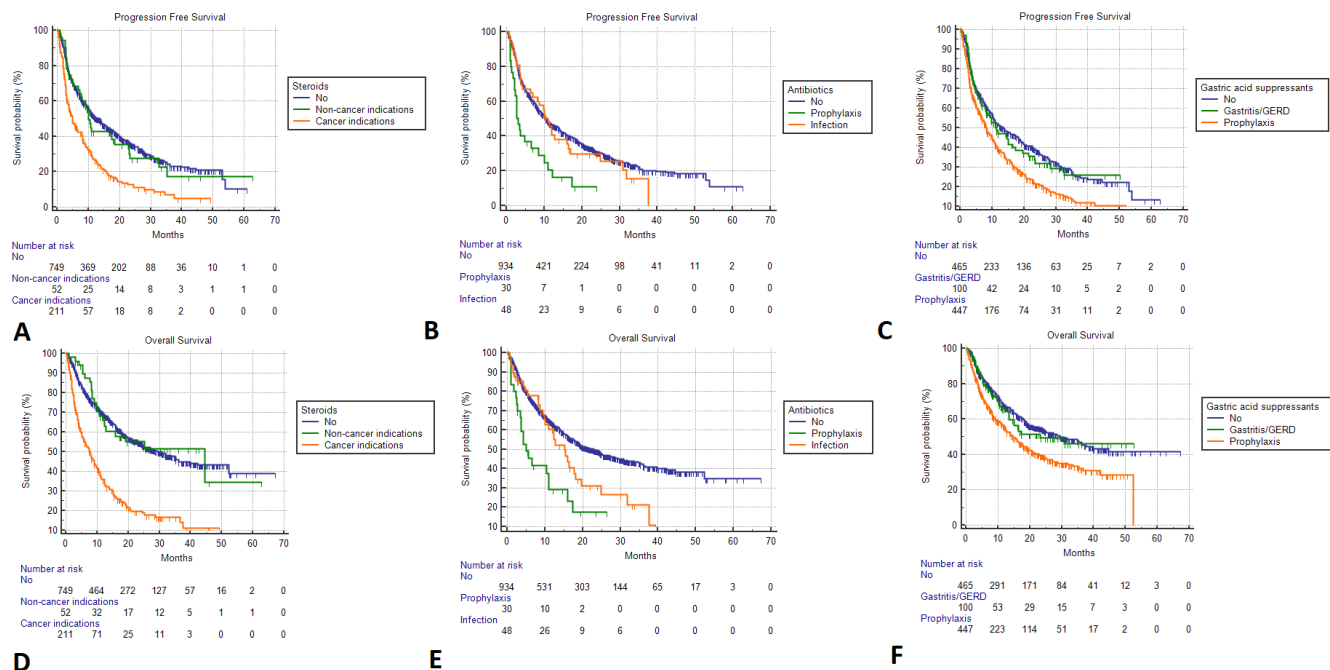


Figure 1 Kaplan-Meier survival estimates. Progression-free survival; (A) Steroids. No: 13.5 months (95% CI 10.8 to 15.4; 472 events); non-cancer indications: 10.0 months (95% CI 7.2 to 18.3; 36 events); cancer indications: 4.9 months (95% CI 3.6 to 6.5; 247 events); (B) Systemic antibiotics. No: 10.5 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.

microenvironment 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

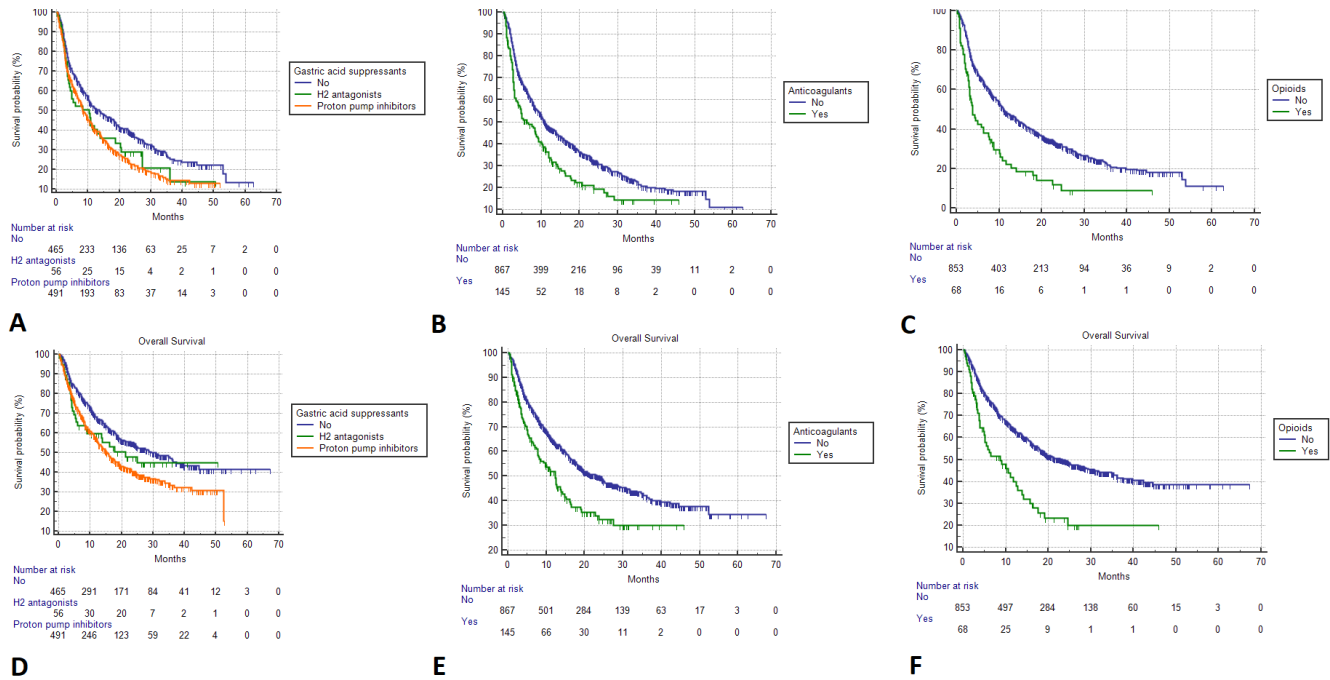


Figure 2 Kaplan-Meier survival estimates. Progression-free survival; (A) Gastric acid suppressants. No: 13.5 months (95% CI 10.5 to 18.2, 288 events); H2 antagonists: 10.3 months (95% CI 3.8 to 13.9; 40 events); proton pump inhibitors: 8.4 months (95% CI 7.5 to 10.0; 353 events); (B) Anticoagulants. 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 (%)			No of metastatic sites (%)			BMI			BMI (continuous)			One-way ANOVA F-ratio; P value	
	0-1		≥2	≤2		>2	≤18.5		18.5-25	25-30	≥30	χ ²		P value
Baseline steroids														
(No)	671 (89.6)	78 (10.4)	410 (54.7)	339 (45.3)	27 (3.6)	330 (44.1)	288 (38.5)	104 (13.9)					F(21 005)=3.16; p=0.043	
Non-cancer indications	43 (82.7)	9 (17.3)	18 (64.6)	34 (65.4)	1 (1.9)	22 (42.3)	19 (36.5)	10 (19.2)					p=0.3548	
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)						
Systemic antibiotics														
(No)	815 (87.3)	78 (10.4)	482 (51.6)	452 (48.4)	37 (4.0)	416 (44.5)	352 (37.7)	129 (13.8)					F(21 005)=0.94; p=0.388	
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)					p=0.3921	
Infection	36 (75.0)	55 (26.1)	25 (52.1)	23 (47.9)	-	28 (58.3)	14 (29.2)	6 (12.5)						
Gastric acid suppressant														
(No)	422 (90.8)	43 (9.2)	275 (59.1)	190 (40.9)	21 (4.5)	211 (45.4)	174 (37.4)	59 (12.7)					F(21 005)=2.66; p=0.070	
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)					p=0.7860	
Gastritis/GERD	355 (79.4)	92 (20.6)	58 (68.0)	42 (42.0)	4 (4.0)	48 (48.0)	37 (37.0)	11 (11.0)						
Gastric acid suppressant														
(No)	422 (90.8)	43 (9.2)	275 (59.1)	190 (40.9)	21 (4.5)	211 (45.4)	174 (37.4)	59 (12.7)					F(21 005)=0.77; p=0.462	
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)					p=0.7860	
Proton pump inhibitors	404 (82.3)	92 (20.6)	58 (68.0)	42 (42.0)	4 (4.0)	48 (48.0)	37 (37.0)	11 (11.0)						
Statins														
(No)	697 (85.4)	119 (14.6)	415 (50.9)	401 (49.1)	36 (4.4)	377 (46.2)	296 (36.3)	107 (13.1)					F(11 006)=7.87; p=0.005	
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)						
Other lipid lowering														
(No)	830 (86.1)	134 (13.9)	491 (50.9)	473 (49.1)	36 (3.7)	447 (46.4)	353 (36.6)	128 (13.3)					F(11 006)=3.81; p=0.051	
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)						
Aspirin														
(No)	710 (86.3)	113 (13.7)	421 (51.2)	402 (48.8)	35 (4.3)	371 (45.1)	305 (37.1)	112 (13.6)					F(11 006)=0.47; p=0.493	
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)						
Anticoagulants														
(No)	758 (87.4)	109 (12.6)	444 (51.2)	423 (48.8)	36 (4.2)	405 (46.7)	314 (36.2)	112 (12.9)					F(11 006)=11.44; p=0.001	
Yes	112 (77.2)	33 (22.8)	78 (63.8)	67 (46.2)	2 (1.4)	55 (37.9)	63 (43.4)	25 (17.2)						
NSAIDs														
(No)	819 (85.9)	134 (14.1)	490 (51.4)	463 (48.6)	33 (3.5)	424 (44.5)	364 (38.2)	132 (13.9)					F(11 006)=9.03; p=0.003	
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)						
ACE inhibitors/ARBs														
(No)	604 (45.9)	95 (13.6)	352 (50.4)	347 (49.6)	30 (4.3)	333 (47.6)	247 (35.3)	89 (12.7)					F(11 006)=9.42; p=0.002	
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)						

Continued

Table 5 Continued

	ECOG-PS (%)				No of metastatic sites (%)				BMI				χ^2		BMI (continuous)		One-way ANOVA F-ratio; P value		
	0-1		≥2		≤2		>2		≤18.5		18.5-25		25-30		≥30			P value	Mean (SD)
Calcium antagonist																			
(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)	F(11 006)=7.01; p=0.008						
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*																			
(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)	F(1937)=9.96; p=0.008						
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																			
(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)	F(11 006)=0.37; p=0.542						
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																			
(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)	F(11 006)=4.42; p=0.036						
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)							
Opioidst																			
(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)	F(1915)=8.26; p=0.004						
Yes	51 (75.0)	17 (25.0)		22 (82.4)	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+Tcell 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 through 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 from 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 immunomodulating 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.

Author affiliations

¹Department of Biotechnology and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

²Medical Oncology, St. Salvatore Hospital, L'Aquila, Italy

³Medical Oncology Unit, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy

⁴National Cancer Research Center, Tumori Institute IRCCS Giovanni Paolo II, Bari, Italy

⁵Medical Oncology, Department of Human Pathology, A.O. Papardo, University of Messina, Messina, Italy

⁶IRCCS Ospedale Policlinico San Martino, Genova, Italy

⁷Medical Oncology, ASUR District Area 4 Fermo, Fermo, Italy

⁸Medical Oncology, Campus Bio-Medico University, Rome, Italy

⁹Medical Oncology Unit, Sant'Andrea Hospital of Rome, Rome, Italy

- ¹⁰Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy
- ¹¹Medical Oncology Unit B, Policlinico Umberto I, Sapienza University of Rome, Roma, Italy
- ¹²Medical Oncology, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
- ¹³Medical Oncology, University Hospital Modena, Modena, Italy
- ¹⁴UOC Oncologia Padova Sud, Azienda ULSS 6 Euganea, Padova, Italy
- ¹⁵Medical Oncology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore di Milano Policlinico, Milano, Italy
- ¹⁶Medical Oncology, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy
- ¹⁷Department of Medical, Oral and Biotechnological Sciences, Gabriele d'Annunzio University of Chieti and Pescara, Chieti, Italy
- ¹⁸Department of Psychological, Health and Territorial Sciences, University G. D'Annunzio of Chieti and Pescara, Chieti, Italy
- ¹⁹Division of Medical Oncology for Melanoma, Sarcoma and Rare Tumors, IEO European Institute of Oncology IRCCS, Milan, Italy
- ²⁰Medical Oncology, Azienda Ospedaliera S. Maria, Terni, Italy
- ²¹Oncology Unit, IRCCS Ospedale Sacro Cuore Don Calabria, Negrar, Italy
- ²²Medical Oncology, Santa Maria Goretti Hospital, Latina, Italy
- ²³Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale", Napoli, Italy
- ²⁴Division of Cancer, Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital, London, UK

Twitter Alessandro Russo @Al3ssandroRusso

Contributors 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.

Funding This work was supported by the Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO). DP is supported by grant funding from the Wellcome Trust Strategic Fund (PS3416) and from the NIHR Imperial Biomedical Research Center (BRC) ITMAT Push for Impact Scheme 2019 and acknowledges infrastructural support by the Cancer Research UK Imperial Center and the Imperial Experimental Cancer Medicine Center (ECMC).

Competing interests AC received speaker fees and grant consultancies from Roche, MSD, BMS, AstraZeneca, Novartis, Astellas. RG received speaker fees and grant consultancies from AstraZeneca and Roche. MG received speaker fees, grant consultancies and travel support from BMS, Ipsen, Novartis, Pfizer, Astellas, Jansen and Pierre-Fabre. AR received grant consultancies from AstraZeneca and MSD. RM received grant consultancies from Pierre-Fabre, MSD, Incyte, BMS, and Roche. FS received speaker fees and grant consultancies from Roche, Novartis, BMS, MSD, Pierre-Fabre, Sanofi, Merck and Sunpharma. DP received lecture fees from ViiV Healthcare, Bayer Healthcare and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, Eisai, Roche, AstraZeneca; received research funding (to institution) from MSD, BMS. PAA 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.

Patient consent for publication Not required.

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).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets used during the present study are available from the corresponding author on reasonable request.

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are

not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Alessio Cortellini <http://orcid.org/0000-0002-1209-5735>
David James Pinato <http://orcid.org/0000-0002-3529-0103>
Paolo Antonio Ascierto <http://orcid.org/0000-0002-8322-475X>

REFERENCES

- Scripture CD, Figg WD. Drug interactions in cancer therapy. *Nat Rev Cancer* 2006;6:546–58.10.1038/nrc1887 [published correction appears in *Nat Rev Cancer*. 2006 Sep;6(9):741]
- Hussain N, Naeem M, Pinato DJ. Concomitant medications and immune checkpoint inhibitor therapy for cancer: causation or association? *Hum Vaccin Immunother* 2020:1–7.
- Gopalakrishnan V, Helmink BA, Spencer CN, *et al*. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. *Cancer Cell* 2018;33:570–80.
- Malmberg K-J. Effective immunotherapy against cancer: a question of overcoming immune suppression and immune escape? *Cancer Immunol Immunother* 2004;53:879–92.
- Arbour KC, Mezquita L, Long N, *et al*. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed Death-Ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol* 2018;36:2872–8.
- Ricciuti B, Dahlberg SE, Adeni A, *et al*. Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus Nonpalliative indications. *J Clin Oncol* 2019;37:1927–34.
- Petrelli F, Signorelli D, Ghidini M, *et al*. Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancers* 2020;12:546.
- 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;29:1437–44.
- Chalabi M, Cardona A, Nagarkar DR, *et al*. Efficacy of chemotherapy and atezolizumab in patients with non-small-cell lung cancer receiving antibiotics and proton pump inhibitors: pooled post hoc analyses of the oak and poplar trials. *Ann Oncol* 2020;31:525–31.
- Pinato DJ, Howlett S, Ottaviani D, *et al*. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. *JAMA Oncol* 2019;5:1774–8.
- Homiczko K, Richtig G, Tuchmann F, *et al*. Proton pump inhibitors negatively impact survival of PD-1 inhibitor based therapies in metastatic melanoma patients. *Ann Oncol* 2018;29:x40.
- Wang DY, McQuade JL, Rai RR, *et al*. The impact of nonsteroidal anti-inflammatory drugs, beta blockers, and metformin on the efficacy of anti-PD-1 therapy in advanced melanoma. *Oncologist* 2020;25:e602–5.
- Gandhi S, Pandey M, Ammannagari N, *et al*. Impact of concomitant medication use and immune-related adverse events on response to immune checkpoint inhibitors. *Immunotherapy* 2020;12:141–9.
- Hakozaki T, Hosomi Y, Shimizu A, *et al*. Polypharmacy as a prognostic factor in older patients with advanced non-small-cell lung cancer treated with anti-PD-1/PD-L1 antibody-based immunotherapy. *J Cancer Res Clin Oncol* 2020;146:2659–68.
- Cortellini A, Bersanelli M, Buti S, *et al*. A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable. *J Immunother Cancer* 2019;7:57.
- Cortellini A, Bersanelli M, Santini D, *et al*. Another side of the association between body mass index (BMI) and clinical outcomes of cancer patients receiving programmed cell death protein-1 (PD-1)/Programmed cell death-ligand 1 (PD-L1) checkpoint inhibitors: a

- multicentre analysis of immune-related adverse events. *Eur J Cancer* 2020;128:17–26.
- 17 Cortellini A, Buti S, Bersanelli M, *et al.* Evaluating the role of family history of cancer and diagnosis of multiple neoplasms in cancer patients receiving PD-1/PD-L1 checkpoint inhibitors: the multicenter FAMI-L1 study. *Oncimmunology* 2020;9:1710389.
 - 18 Cortellini A, Vitale MG, De Galitiis F, *et al.* Early fatigue in cancer patients receiving PD-1/PD-L1 checkpoint inhibitors: an insight from clinical practice. *J Transl Med* 2019;17:376.
 - 19 Cortellini A, Buti S, Santini D, *et al.* Clinical outcomes of patients with advanced cancer and pre-existing autoimmune diseases treated with Anti-Programmed death-1 immunotherapy: a real-world transverse study. *Oncologist* 2019;24:e327–37.
 - 20 Cortellini A, Chiari R, Ricciuti B, *et al.* Correlations between the immune-related adverse events spectrum and efficacy of anti-PD1 immunotherapy in NSCLC patients. *Clin Lung Cancer* 2019;20:237–47.
 - 21 Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
 - 22 Woolley KK. How variables uncorrelated with the dependent variable can actually make excellent predictors: the important suppressor variable case. Southwest educational research association annual meeting proceedings, 1997. Available: <https://eric.ed.gov/?id=ED407420> [Accessed 10 Jun 2020].
 - 23 Thompson FT, Levine DU. Examples of easily Explainable suppressor variables in multiple regression research. *Multi Linear Regres Viewpoints* 1997;24:11–13.
 - 24 “Stopping stepwise: Why stepwise selection is bad and what you should use instead”. On [towardsdatascience.com](https://towardsdatascience.com/stopping-stepwise-why-stepwise-selection-is-bad-and-what-you-should-use-instead-90818b3f52df). Available: <https://towardsdatascience.com/stopping-stepwise-why-stepwise-selection-is-bad-and-what-you-should-use-instead-90818b3f52df> [Accessed 10 Jun 2020].
 - 25 Miñana B, Cózar JM, Palou J, *et al.* Bladder cancer in Spain 2011: population based study. *J Urol* 2014;191:323–8.
 - 26 Ciocan D, Barbe C, Aubin F, *et al.* Distinctive features of melanoma and its management in elderly patients: a population-based study in France. *JAMA Dermatol* 2013;149:1150–7.
 - 27 Gridelli C, Balducci L, Ciardiello F, *et al.* Treatment of elderly patients with non-small-cell lung cancer: results of an international expert panel meeting of the Italian association of thoracic oncology. *Clin Lung Cancer* 2015;16:325–33.
 - 28 Azawi NH, Joergensen SM, Jensen NV, *et al.* Trends in kidney cancer among the elderly in Denmark, 1980–2012. *Acta Oncol* 2016;55(Suppl 1):79–84.
 - 29 Wu T, Yang L, Jiang J, *et al.* Chronic glucocorticoid treatment induced circadian clock disorder leads to lipid metabolism and gut microbiota alterations in rats. *Life Sci* 2018;192:173–82.
 - 30 He Z, Kong X, Shao T, *et al.* Alterations of the gut microbiota associated with promoting efficacy of prednisone by Bromofuranone in MRL/lpr mice. *Front Microbiol* 2019;10:978.
 - 31 Li Z-Y, Fan M-B, Zhang S-L, *et al.* Intestinal Metrnl released into the gut lumen acts as a local regulator for gut antimicrobial peptides. *Acta Pharmacol Sin* 2016;37:1458–66.
 - 32 Hagan T, Cortese M, Roupheal N, *et al.* Antibiotics-Driven gut microbiome perturbation alters immunity to vaccines in humans. *Cell* 2019;178:1313–28. e13.
 - 33 Bruno G, Zaccari P, Rocco G, *et al.* Proton pump inhibitors and dysbiosis: current knowledge and aspects to be clarified. *World J Gastroenterol* 2019;25:2706–19.
 - 34 Jackson MA, Goodrich JK, Maxam M-E, *et al.* Proton pump inhibitors alter the composition of the gut microbiota. *Gut* 2016;65:749–56.
 - 35 Gao C, Major A, Rendon D, *et al.* Histamine H2 receptor-mediated suppression of intestinal inflammation by probiotic *Lactobacillus reuteri*. *mBio* 2015;6:e01358–15.
 - 36 Diebel LN, Liberati DM, Hall-Zimmerman L. H2 blockers decrease gut mucus production and lead to barrier dysfunction in vitro. *Surgery* 2011;150:736–43.
 - 37 U.S. Food and Drug Administration. Questions and answers: NDMA impurities in ranitidine (commonly known as Zantac). Available: <https://www.fda.gov/drugs/drug-safety-and-availability/questions-and-answers-ndma-impurities-ranitidine-commonly-known-zantac> [Accessed 14 Jun 2020].
 - 38 European Medicines Agencies. EMA to review ranitidine medicines following detection of NDMA. Available: <https://www.ema.europa.eu/en/news/ema-review-ranitidine-medicines-following-detection-ndma> [Accessed 14 Jun 2020].
 - 39 Strobel L, Johswich KO. Anticoagulants impact on innate immune responses and bacterial survival in whole blood models of *Neisseria meningitidis* infection. *Sci Rep* 2018;8:10225.
 - 40 Taylor A. Revealing a brain-gut microbiome connection following chronic opioid treatment. *J Pain* 2018;19:S1.
 - 41 Acharya C, Betrapally NS, Gillevet PM, *et al.* Chronic opioid use is associated with altered gut microbiota and predicts readmissions in patients with cirrhosis. *Aliment Pharmacol Ther* 2017;45:319–31.
 - 42 Banerjee S, Sindberg G, Wang F, *et al.* Opioid-induced gut microbial disruption and bile dysregulation leads to gut barrier compromise and sustained systemic inflammation. *Mucosal Immunol* 2016;9:1418–28.
 - 43 Ren M, Lotfipour S. The role of the gut microbiome in opioid use. *Behav Pharmacol* 2020;31:113–21.
 - 44 Dai X, Yan J, Fu X, *et al.* Aspirin inhibits cancer metastasis and angiogenesis via targeting heparanase. *Clin Cancer Res* 2017;23:6267–78.
 - 45 Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol* 2012;13:518–27.
 - 46 Botti G, Fratangelo F, Cerrone M, *et al.* COX-2 expression positively correlates with PD-L1 expression in human melanoma cells. *J Transl Med* 2017;15:46.
 - 47 Zelenay S, van der Veen AG, Böttcher JP, *et al.* Cyclooxygenase-Dependent tumor growth through evasion of immunity. *Cell* 2015;162:1257–70.
 - 48 Ma X, Bi E, Lu Y, *et al.* Cholesterol Induces CD8⁺ T Cell Exhaustion in the Tumor Microenvironment. *Cell Metab* 2019;30:143–56. e5.
 - 49 Yang W, Bai Y, Xiong Y, *et al.* Potentiating the antitumour response of CD8(+) T cells by modulating cholesterol metabolism. *Nature* 2016;531:651–5.
 - 50 Mok EHK, Lee TKW. The pivotal role of the dysregulation of cholesterol homeostasis in cancer: implications for therapeutic targets. *Cancers* 2020;12:E1410.
 - 51 Perrone F, Minari R, Bersanelli M, *et al.* The prognostic role of high blood cholesterol in advanced cancer patients treated with immune checkpoint inhibitors. *J Immunother* 2020;43:196–203.
 - 52 De Giorgi V, Grazzini M, Benemei S, *et al.* Propranolol for off-label treatment of patients with melanoma: results from a cohort study. *JAMA Oncol* 2018;4:e172908.
 - 53 Kokolus KM, Zhang Y, Sivik JM, *et al.* Beta blocker use correlates with better overall survival in metastatic melanoma patients and improves the efficacy of immunotherapies in mice. *Oncimmunology* 2018;7:e1405205.
 - 54 Thiele M, Wiest R, Gluud LL, *et al.* Can non-selective beta-blockers prevent hepatocellular carcinoma in patients with cirrhosis? *Med Hypotheses* 2013;81:871–4.
 - 55 Kichenadasse G, Miners JO, Mangoni AA, *et al.* Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non-small cell lung cancer. *JAMA Oncol* 2020;6:e195241:512.
 - 56 Afzal MZ, Mercado RR, Shirai K. Efficacy of metformin in combination with immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) in metastatic malignant melanoma. *J Immunother Cancer* 2018;6:64.
 - 57 Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol* 2011;335:2–13.
 - 58 Luo Y, Zheng SG. Hall of fame among pro-inflammatory cytokines: interleukin-6 gene and its transcriptional regulation mechanisms. *Front Immunol* 2016;7:604.
 - 59 Giles AJ, Hutchinson M-KND, Sonnemann HM, *et al.* Dexamethasone-induced immunosuppression: mechanisms and implications for immunotherapy. *J Immunother Cancer* 2018;6:51.
 - 60 Biswas S, Benedict SH, Lynch SG, *et al.* Potential immunological consequences of pharmacological suppression of gastric acid production in patients with multiple sclerosis. *BMC Med* 2012;10:57.
 - 61 Hussain M, Javeed A, Ashraf M, *et al.* Aspirin and immune system. *Int Immunopharmacol* 2012;12:10–20.