Effect of concurrent beta-blocker use in patients receiving immune checkpoint inhibitors for advanced solid tumors

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Abstract

Purpose:

Stress-induced adrenergic signaling can suppress the immune system. In animal models, pharmacological beta-blockade stimulates CD8+ T-cell activity and improves clinical activity of immune checkpoint blockade (ICB) in inhibiting tumor growth. Herein, we investigated the effect of BB on clinical outcomes of patients receiving ICB in advanced solid tumors.

Methods:

We retrospectively evaluated patients with solid tumors treated with ICB at our institution from January 1, 2011 to April 28, 2017. The primary clinical outcome was disease control. Secondary clinical outcomes were overall survival (OS), and duration of therapy (DoT). The primary predictor was use of BB. Association between disease control status and BB use was assessed in univariable and multivariable logistic regression. OS was calculated using hazard ratios of BB-recipient patients versus BB non-recipient patients via Cox proportional hazards regression models. All tests were two-sided at a significance level of 0.05.

Results

Of 339 identified patients receiving ICB, 109 (32%) also received BB. In covariate-adjusted analysis, odds of disease control were significantly higher among BB recipients compared to BB-non-recipients (2.79; [1.54-5.03]; p=0.001). While we did not observe significant association of OS with the use of BB overall, significant association with better OS was observed for the urothelial carcinoma cohort (HR: 0.24; [0.09, 0.62]; P=0.0031).

Conclusions:

Concurrent use of BB may enhance the clinical activity of ICB and influence overall survival, particularly in patients with urothelial carcinoma. Our findings warrant further investigation to understand the interaction of beta adrenergic signaling and antitumor immune activity and explore a combination strategy.

Background

Since the initial approval of immune checkpoint inhibitors in 2011, there are now over 60 indications for immune checkpoint blockade (ICB) for various malignancies. Although the responses for some patients are dramatic and durable, the majority of the patients succumb to the disease. Thus, ideal predictive biomarkers of response and logical combination therapeutic strategies are urgently needed. Recent work has uncovered several possible mechanisms for the variation among responders and non-responders. Specifically, antitumor immunity is reliant on an overpopulation of CD8 + T-cell infiltrates in the tumor microenvironment (TME), a phenomenon more common in patients with increased immunogenic

neoantigens and a higher tumor mutational burden (Becht, Giraldo et al. 2016). Additionally, the TME houses immunosuppressive elements such as myeloid-derived suppressor cells, B- and T-regulatory cells and stromal components that inhibit T-cell infiltration and T-cell mediated killing of tumor cells (Becht, Giraldo et al. 2016). These examples are two of the many explanations for how underlying differences can lead to variations in tumor response to ICB.

One of the emerging mechanisms that plays a key role in regulating anti-tumor immune response is adrenergic signaling. The sympathetic nervous system, specifically β-adrenergic (βAR) receptors, function in lymphoid organs and are present on various immune cells (Qiao, Chen et al. 2018). Recent pre-clinical studies demonstrated that stress-driven β-adrenergic signaling was immunosuppressive and increased the number and activity of immunosuppressive cells, reduced the production of T cell growth-promoting cytokines, and inhibited T-cell cytotoxicity (Kokolus, Capitano et al. 2013, Slota, Shi et al. 2015). In animal models, beta blockers (BB) have been used to reduce βAR signaling (Bucsek, Qiao et al. 2017). Commonly used for hypertension, cardiovascular disease, symptoms of hyperthyroidism and anxiety, BBs can target both β1 and β2 receptors (non-selective BB) or select for β1 receptors (selective BB). Blocking βAR signaling in animal models promoted the recruitment of effector CD8 + T cells, increased the effector CD8 + T-cell to CD4 + regulatory T-cell ratio, and decreased expression of inhibitory PD-1 on effector CD8 + T cells (Bucsek, Qiao et al. 2017). Furthermore, PD-1 blockade used with BB slowed tumor growth in these models when compared to PD-1 blockade alone (Bucsek, Qiao et al. 2017).

In retrospective analyses of patients with metastatic melanoma and non-small cell lung cancer receiving ICB, patients on BB had improved survival compared to those who did not receive BB (Kokolus, Zhang et al. 2018, Oh, Guzner et al. 2020). Furthermore, inhibition of βAR in a preclinical model of melanoma improved antitumor efficacy of immune-based therapies (Kokolus, Zhang et al. 2018). Our work aimed to validate these findings and further explore this effect in other cancer subtypes. To this end, we performed a retrospective analysis of patients receiving ICB for advanced solid tumors with and without concurrent β-blockade.

Methods

Data Collection

The Mount Sinai Institutional Review Board approved our protocol for retrospective analysis of patient data. Due to the retrospective nature of patient data collection, this study was deemed exempt from requiring patient consent. We queried our cancer center immunotherapy database to retrospectively identify all patients aged 18 or older with recurrent/metastatic solid tumors who received at least two doses of immune checkpoint blockade between January 1, 2011 and April 28, 2017. ICB included were pembrolizumab, nivolumab, ipilimumab, atezolizumab, avelumab, durvalumab, and tremilimumab. Data was subsequently collected for this cohort using manual clinician electronic medical record (EMR) review. The following data was collected: Demographic information (age, gender, race/ethnicity), medical history (comorbidities, smoking history, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG)

performance status), use of β1-selective or non-selective BB (Atenolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Nadolol, Nebivolol, Propranolol, Sotalol) at the time of ICB initiation, tumor type, type of ICB, line of therapy, ICB initiation date, ICB discontinuation date, best radiographic response (stable/improved vs. progression of disease), date of last follow up, and date of death. Patients were defined as taking a BB based on the presence of an active prescription recorded in their EMR at the time of ICB initiation. Radiographic response was ascertained via radiology reports and data of death through EMR review. BMI was categorized as normal or underweight (BMI < = 24.9), Overweight (BMI = 25–29.9), and Obese (BMI > = 30.0).

Clinical Outcomes

The primary outcome was disease control. Disease control was assessed using the first imaging scan closest to 12 weeks following the initiation of ICB therapy. We defined disease control as stable, partial, or complete response on imaging at 12 weeks. The disease control rate (DCR) was defined as the number of patients with disease control at 12 weeks over the total number of evaluable patients. Our secondary outcomes were overall survival (OS) and duration of ICB therapy (DoT). OS was calculated as the time from treatment initiation to death for any reason, censor date, or date at last follow up (provided the patient was lost to follow up). DoT was calculated as the time between treatment initiation and discontinuation date.

Statistical Analysis

The characteristics of patients, including demographic, disease- and treatment-related variables, were summarized as median (first and third quartile) for continuous variables and as frequency (percentage) for categorical variables, stratified by the primary predictor (received beta-blocker or not). The distributions of these characteristic variables among those who used beta-blockers and those who did not use beta-blocker were compared by the Mann-Whitney U test for the continuous variable (e.g., age) and Chi-squared test for the categorical variables (e.g., gender).

Logistic regression was used for estimating odds ratios (ORs) for dichotomous outcome (disease control). Models were adjusted for the following covariates: beta blocker treatment status, age group, ECOG performance status, body mass index. Adjusted and unadjusted results were similar; adjusted models are presented here for simplicity. For overall survival, we initially estimated the survival probabilities for those receiving BB and those not receiving BB separately using Kaplan-Meier log rank test. Subsequently, we calculated the hazard ratios of BB-recipient patients versus BB non-recipient patients by using Cox proportional hazards regression model. We first checked the proportional hazards assumption by the Kaplan-Meier curve, and then tested the relationship between Schoenfeld residuals versus time, if necessary. We considered age (≥ 70 versus < 70 years), ECOG (≥ 2 versus < 2), BMI (obesity versus overweight versus underweight/normal), and first-line therapy (yes versus no) as covariates. All these models were constructed as follows: we first built a series of bivariable models between a particular outcome and each predictor. Then we created a multivariable model between an outcome and BB use status adjusted for all covariates identified to be significant in bivariate models at p-

value < 0.2 including age, BMI, performance status, line of therapy and comorbid factors (1) cardiovascular disease and (2) diabetes and hyperlipidemia. We also evaluated the association between BB and DoT, by ANOVA (Analysis of Variance).

We further explored the relationship between BB use-status and overall survival for each of the four most frequent cancer types – hepatocellular carcinoma, melanoma, non-small cell lung cancer, and urothelial carcinoma. We subsequently repeated the same analyses for patients with first line therapy only. Due to small sample size within each cancer type, the subtype analyses were not adjusted for any covariate. The unadjusted HR with 95% confidence interval and P-value were reported. The analysis was conducted by SAS software (SAS Institute, Cary, NC) and the visualization was completed by R version 3.6.1 (R Foundation, Vienna, Austria). All statistical tests were two-sided at the significance level of 0.05.

Results

Baseline Characteristics

Clinical data on 339 patients were included in the final analysis. A summary of baseline characteristics is provided in Table 1. In this patient cohort, 109 patients (32%) received BB and 230 patients (68%) did not receive BB. Of those receiving BB, 84 (77%) were on β1-selective BB and 25 (23%) were on non-selective BB. The median age was higher in the BB group, compared to the non-BB group (BB 69 (Q1-Q3: 57–74) vs. 64 (56–73), P < 0.001). In the BB group the proportion of patients with diabetes/hyperlipidemia (BB 61% vs. 42% P = .002), cardio-/cerebrovascular disease (BB 86% vs. 42% P < 0.001), and chronic kidney disease (BB 16% vs. 5% P = .003) was higher when compared to the non-BB group. The BB cohort had a higher proportion of active and former smokers (74% vs. 60%, P = 0.032). The median BMI was higher in the BB group (27 vs. 24, P = 0.0013) compared to the non-BB group. In both the BB and non-BB cohorts, the most common types of advanced solid tumors were non-small cell lung cancer (NSCLC; N_{BB} = 23, N_{non-BB} = 58), melanoma (N_{BB} = 21, N_{non-BB} = 52), hepatocellular carcinoma (HCC; N_{BB} = 18, N_{non-BB} = 33), and urothelial carcinoma (UC; N_{BB} = 22, N_{non-BB} = 29). The other tumor types comprised 23% and 25% of cases in the BB and non-BB cohorts, respectively. A detailed breakdown of all tumor types is listed in *supplementary table S1 and S2*. The distribution of gender (P = 0.963) and race (P = 0.317) was similar across those receiving BB and those not receiving BB. The proportion of patients receiving ICB as first-line therapy was similar between the two groups (BB 40.4% vs. 46%, P = 0.43). The median follow-up time for patients receiving BB was 25.0 (95% CI: 21.4–36.5) months compared to 23.6 (95% CI: 12.2–32.6) months for those not receiving BB.

Table 1
Descriptive statistics of demographic, disease-related and treatment-related variables

	Overall (N = 339)	BB (N = 109 [32%])	No BB (N = 230 [68%])	P-value
Age				< 0.001
Mean (SD)	65.2 (12.8)	69.6 (11.1)	63.2 (13.0)	
Median [Q1, Q3]	66.0 [57.0–74.0]	69.0 [57.0–74.0]	64.0 [56.0–73.0]	
Gender				1.0
Female n (%)	125 (36.9%)	85 (37.0%)	40 (36.7%)	
Race/Ethnicity				0.317
White	182 (53.7%)	66 (60.6%)	116 (50.4%)	
Black	38 (11.2%)	10 (9.2%)	28 (12.2%)	
Hispanic	36 (10.6%)	10 (9.2%)	26 (11.3%)	
Other	35 (10.3%)	7 (6.4%)	28 (12.2%)	
Unknown	48 (14.2%)	16 (14.7%)	32 (13.9%)	
Body mass index				0.008
Normal or Underweight	171 (50.4%)	43 (39.4%)	128 (55.7%)	
Obese	72 (21.2%)	25 (22.9%)	47 (20.4%)	
Overweight	94 (27.7%)	41 (37.6%)	53 (23.0%)	
Missing	2 (0.6%)	0 (0%)	2 (0.9%)	
ECOG status				0.102
0–1	274 (80.8%)	81 (74.3%)	193 (83.9%)	
2+	40 (11.8%)	18 (16.5%)	22 (9.6%)	
Missing	25 (7.4%)	10 (9.2%)	15 (6.5%)	
Relevant Comorbidities:				
Diabetes/hyperlipidemia	162 (47.8%)	66 (60.6%)	96 (41.7%)	0.002
Cardio-/cerebrovascular disease	191 (56.3%)	94 (86.2%)	97 (42.2%)	< 0.001
Chronic kidney disease	29 (8.6%)	17 (15.6%)	12 (5.2%)	0.003
First Line of Therapy	149 (44.0%)	44 (40.4%)	105 (45.7%)	0.425

	Overall (N = 339)	BB (N = 109 [32%])	No BB (N = 230 [68%])	P-value
Tumor type				0.390
Hepatocellular Cancer	51 (15.0%)	18 (16.5%)	33 (14.3%)	
Melanoma	73 (21.5%)	21 (19.3%)	52 (22.6%)	
NSCLC	81 (23.9%)	23 (21.1%)	58 (25.2%)	
Urothelial Cancer	51 (15.0%)	22 (20.2%)	29 (12.6%)	
Other Cancers	83 (24.5%)	25 (22.9%)	58 (25.2%)	

Clinical Outcomes

Disease Control:

Patients who received BB had a higher rate of disease control compared to those who did not receive BB (BB 62% vs. 39%) (Table 2). Similarly, the unadjusted odds ratio also revealed a statistically significant higher likelihood of disease control (2.52 [1.53, 4.20]; P < 0.001) for patients with BB. When adjusted for BB treatment status, age group, ECOG, line of therapy, cardio-/cerebro-vascular disease, and diabetes/hyperlipidemia, odds ratio indicated that the use of BB led to a statistically higher likelihood of disease control (2.79 [1.54, 5.03]; P < 0.001). Among the most common cancer types for all lines and first line of therapy (Table S4), we observed that the melanoma cohort showed significantly higher odds of disease control among BB-recipient patients (5.63 [95% CI: 1.41, 27.05]; P = 0.014), as compared to BB non-recipients.

Table 2
Unadjusted and adjusted logistic regression analysis of disease control. Potential explanatory variables included: beta blocker treatment status, age group, ECOG performance status, body mass index, first line therapy and common comorbidities. The results are summarized as odds ratios (with 95% confidence interval).

		Disease control status		OR (univariable)	OR (multivariable)
		No	**Yes**		
Beta blocker use	Not received	120 (60.6)	78 (39.4)	-	-
	Received	36 (37.9)	59 (62.1)	2.52 (1.53–4.20, p < 0.001)	2.79 (1.54–5.03, p = 0.001)
Age group	< 70	100 (56.5)	77 (43.5)	-	-
	>=70	56 (48.3)	60 (51.7)	1.39 (0.87–2.23, p = 0.168)	1.30 (0.77–2.17, p = 0.326)
ECOG performance score	<=1	123 (50.2)	122 (49.8)	-	-
	>=2	25 (78.1)	7 (21.9)	0.28 (0.11–0.64, p = 0.005)	0.24 (0.09–0.61, p = 0.003)
	Missing	8 (50.0)	8 (50.0)	1.01 (0.36–2.82, p = 0.987)	1.01 (0.35–2.94, p = 0.988)
BMI group	Normal/underweight	81 (54.7)	67 (45.3)	-	-
	Overweight	45 (54.9)	37 (45.1)	0.99 (0.58–1.71, p = 0.983)	-
	Obese	30 (47.6)	33 (52.4)	1.33 (0.74–2.41, p = 0.344)	-
First line therapy	No	100 (59.9)	67 (40.1)	-	-
	Yes	56 (44.4)	70 (55.6)	1.87 (1.17–2.99, p = 0.009)	1.92 (1.17–3.17, p = 0.010)
Cardio-/cerebro-vascular disease	No	77 (59.2)	53 (40.8)	-	-
	Yes	79 (48.5)	84 (51.5)	1.54 (0.97–2.47, p =	0.98 (0.55–1.75, p =

				0.067)	0.948)
Chronic kidney disease	No	144 (54.1)	122 (45.9)	-	-
	Yes	12 (44.4)	15 (55.6)	1.48 (0.67–3.33, p = 0.339)	-
Diabetes and/or hyperlipidemia	No	92 (59.7)	62 (40.3)	-	-
	Yes	64 (46.0)	75 (54.0)	1.74 (1.10–2.77, p = 0.019)	1.47 (0.87–2.47, p = 0.150)

Overall Survival:

There was no difference in OS seen between the BB and non-BB cohorts (HR 0.83, 95% CI 0.60–1.15, P = 0.27) (Fig. 1A). When adjusted for age, ECOG performance status, BMI, and line of therapy, the use of BB also did not influence OS compared to no BB use (HR 0.77, 95% CI 0.54–1.08, P = 0.13) (Fig. 1A). Patients on selective BB had improved OS, compared to those that were on non-selective BB or not on BB (HR 0.68, 95% CI 0.46-1.00, P = 0.05) (Fig. 1B). Among the four most common cancer types (Figs. 3 and 4), BB had a significant association with overall survival for the urothelial carcinoma cohort (HR: 0.24 (0.09, 0.62; P = 0.003). Overall survival did not differ significantly with BB use in the hepatocellular carcinoma cohort (HR: 1.03 (0.48, 2.24; P = 0.94), melanoma cohort (HR: .89 (0.41, 1.96; P = 0.77), or non-small cell lung cancer cohort (HR: 0.82 (0.40, 1.65; P = 0.5724). For those patients receiving first-line therapy, BB use trended towards association with improved overall survival (HR: 0.30 (0.08, 1.14; P = 0.08) for patients with urothelial carcinoma. However, BB use was not associated with overall survival for patients with hepatocellular carcinoma (HR: 0.50 [0.14, 1.80]; P = 0.29), melanoma (HR: 0.97 [0.39, 2.41]; P = 0.95). The minimum number of events was not met to calculate the hazard ratio for the non-small cell lung cancer for first line therapy.

Duration of Therapy:

Among all lines of therapy, patients who received BB had a significantly longer DoT unadjusted compared to those who did not receive BB (mean [range]: 10 [6–30] vs. BB 21 [9–69]; P < 0.001) (Table S3). Moreover, DoT was significantly longer for patients receiving BB for the melanoma cohort (mean [range]: 10 [8–21] vs. 19 [10–51]; P = 0.015), non-small cell lung cancer cohort (mean [range]: 11 [6–29] vs. 24 (12–60); P = 0.036), and the urothelial carcinoma cohort respectively (mean [range]: 7 [4–22] vs. 24 [6–77]; P < 0.037). For first line therapy only, DoT was significantly longer for the BB cohort (mean [range]: 10 [6–24] vs. 19 [9–70]; P = 0.024) overall. For first line therapy only among tumor types, DoT for the melanoma cohort (mean [range]: 9 [8–18] vs. 18 [10–53]; P = 0.016) was significantly longer for patients receiving BB.

Discussion

We investigated the impact of concurrent use of BB and ICB strategies on clinical outcomes for patients with advanced solid tumors. Although we did not detect a difference in OS between the non-BB and BB groups, we observed that in comparison with the non-BB group, patients in the BB group had improved disease control and longer median duration of therapy. After adjusting for clinically relevant covariates including age group, ECOG performance status, first line therapy and common comorbidities, the use of BB remained significantly associated with improved disease control. Our findings represent the first study to show the association of disease control with concomitant use of BB and ICB in a cohort of advanced solid tumors.

The interplay between adrenergic signaling and immune cells is well-described in animal model models. Specifically, BBs have been shown to prevent βAR-related immunosuppression, leading to the recruitment of effector CD8 + T-cells, an increased effector CD8 + to CD4 + regulatory T-Cell ratio, and a decreased expression of PD-1 (Bucsek, Qiao et al. 2017). Furthermore, in melanoma, a combination of anti-PD-1 and BB was associated with significantly more decrease in tumor volume, compared to the anti-PD-1 therapy alone. In this clinical context, two retrospective datasets for melanoma and NSCLC have each confirmed that the addition of BB was associated with improved OS (Kokolus, Zhang et al. 2018, Cortellini, Tucci et al. 2020, Wang, McQuade et al. 2020, Gandhi, Pandey et al. 2021, Oh, Guzner et al. 2021). In contrast, our study did not find an association between BB use and OS. The heterogeneity in tumor types within our cohort maybe accounting for the discrepancy, when compared to evidence in animal model systems and prior retrospective datasets in melanoma and NSCLC.

We also aimed to determine whether there was a difference in association between BB use and clinical outcomes by specific tumor type. We analyzed the four most common tumor types in our dataset: melanoma, NSCLC, HCC, and UC. We found that the addition of BB improved OS, compared to non-BB, only in the UC patients. However, when evaluating patients receiving ICB as first-line therapy for UC, the addition of BB was not associated with change in OS. Similarly, prior retrospective and prospective studies (Kokolus, Zhang et al. 2018, Gandhi, Pandey et al. 2021) suggesting enhanced activity of ICB when combined with BB in melanoma, our dataset demonstrated improved rates of disease control among melanoma patients receiving beta blockade. The mechanism for why BB use in melanoma was associated with increased disease control remains unknown. Prior research has detected increased βAR expression in biopsies of melanoma (Yang, Kim et al. 2009). Moreover, CTLA-4 monoclonal antibodies have more extensively been used in melanoma compared with other solid tumor types and might have unique synergy with beta blockade (Rotte 2019). Further research should explore how BB affects tumor response based on the distinct molecular mechanisms of ICB.

The final question we aimed to answer was the importance of beta-blockade selectivity in influencing clinical outcomes in patients receiving ICB. In previous studies of melanoma and NSCLC, patients with non-selective BB had improved clinical outcomes, compared to those on β1-selective blockers and those not on BB (Kokolus, Zhang et al. 2018, Oh, Guzner et al. 2021). Animal model systems substantiated that β2-adrenergic signaling may be driving the immune modulation through T-cell induced cytokine secretion and (Bucsek, Qiao et al. 2017, Kokolus, Zhang et al. 2018). In contrast, our study indicates that β1-

selective BB improved clinical outcomes when compared to non-selective BB and no BB. The reason for this remains unclear – it is important to note that a substantial proportion of patients on BB were receiving β1-selective BB, thus potentially underpowering the non-selective BB group.

` Our study has several limitations. First, by including multiple cancer types we had significant tumor heterogeneity across our cohorts. Such heterogeneity can limit the ultimate application of our findings. Second, each individual tumor cohort was limited in its sample size and potentially underpowered. Finally, because we did not control for the use of chemotherapy with immunotherapy, we do not know how their interaction may have positively or negatively affected our final results. Despite these limitations, the external validity of our study is improved due the multitude of tumor types, similarity of demographics and gender between groups, and the inclusion distinct patient populations.

Ultimately, we provide evidence, consistent with prior studies, that BB may play a role in influencing the immune activity of ICB. BB are safe, low-cost, and widely available agents for serving as an adjunct to ICB therapy. The initial data from phase I study of propranolol and pembrolizumab provides an important safety signal to proceed with larger, prospective studies for validation (Gandhi, Pandey et al. 2021). This work also serves as a pioneering study to perform prospective studies in other tumor types such as UC. Additional research should incorporate detailed immune profiling and genomic analysis to identify predictors of response and to explore the underlying mechanism of this combinatorial approach.

Declarations

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Patient consent for publication:

Exempt.

Ethics Approval:

This study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board as a minimal risk study.

Author's Contributions:

Study conception and design: V.G.P and C.-K.T. Data collection and management. V.G.P., G.M., Q.Q., B. W., P.A., P.G., A.L., A.B.P. Data analysis and interpretation: V.G.P., G.M., X.Z., H.P., C.-K.T. Manuscript preparation and review: All authors.

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Figures

Figure 1(A)

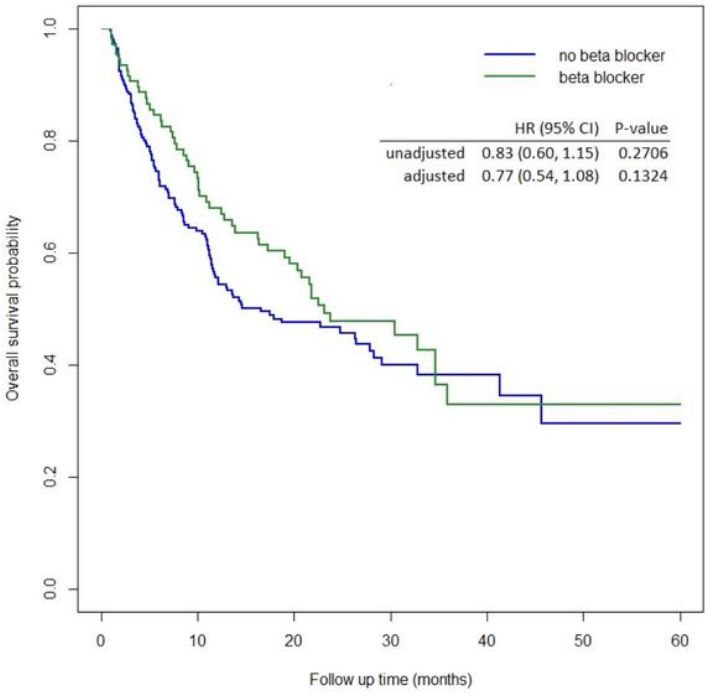

Figure 1(B)

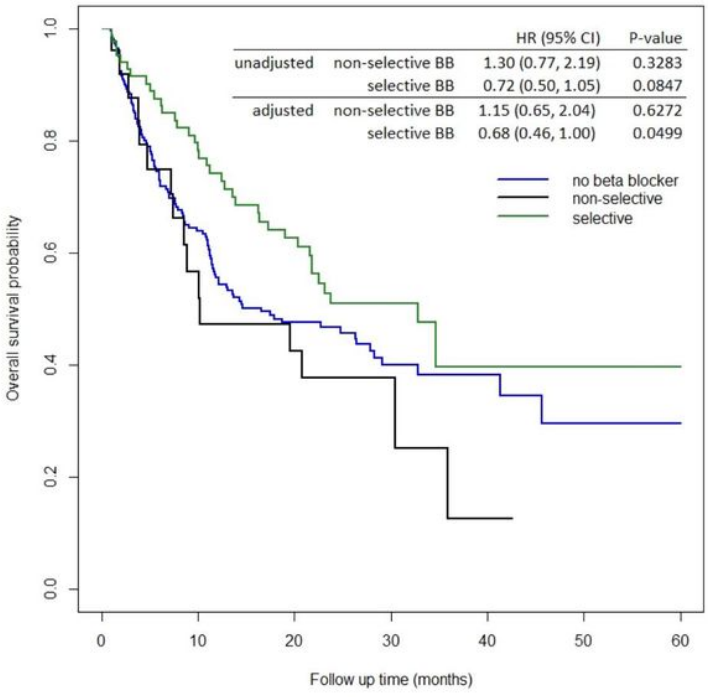

Figure 1

Overall survival of (A) Beta blocker vs. no beta blocker adjusted for age, ECOG performance status, BMI, and line of therapy (B) selective vs. non-selective vs. no beta blocker for overall patients age, ECOG performance status, BMI, and line of therapy, the use of BB (N=331)

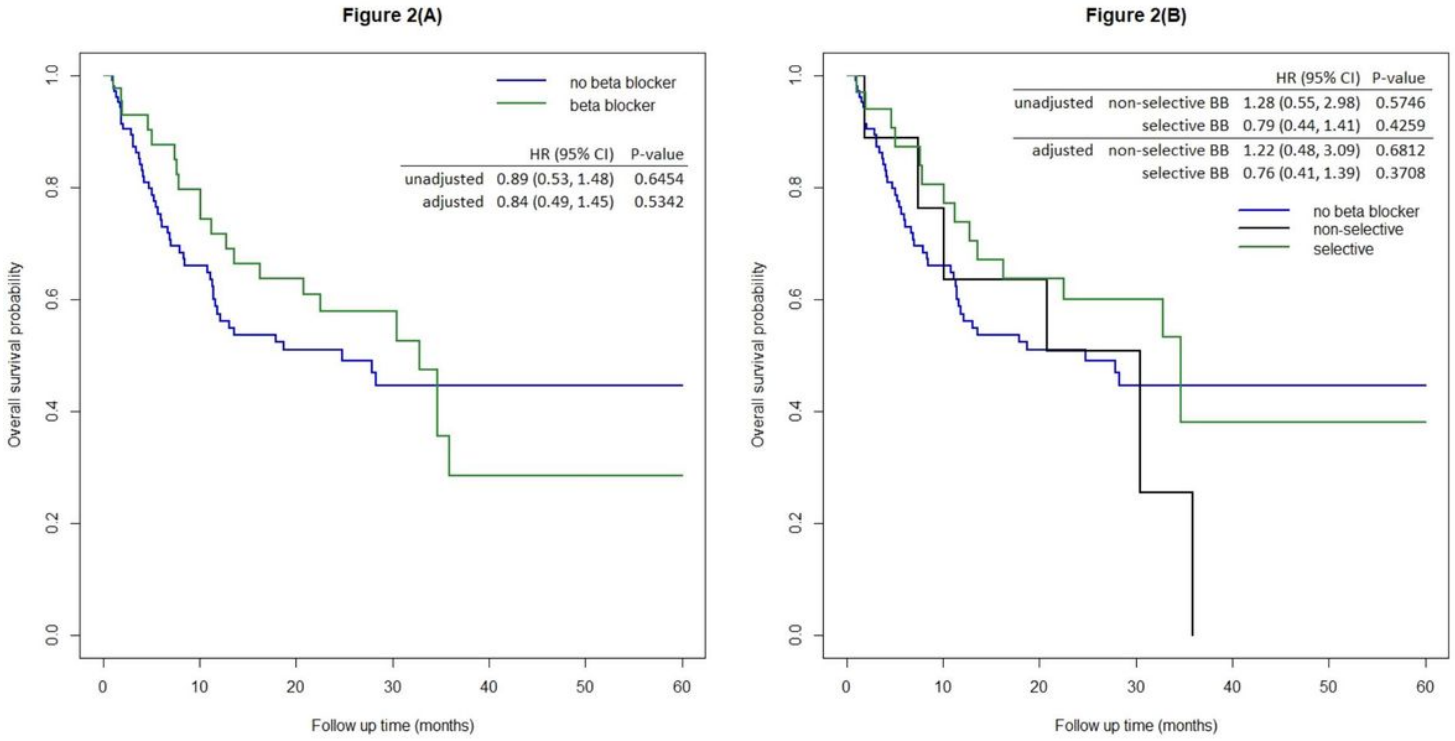

Figure 2

Overall survival of (A) Beta blocker vs. no beta blocker (adjusted for age, ECOG performance status, BMI) (B) selective vs. non-selective vs. no beta blocker for patients received first line therapy (adjusted for age, ECOG performance status, BMI(N=149)

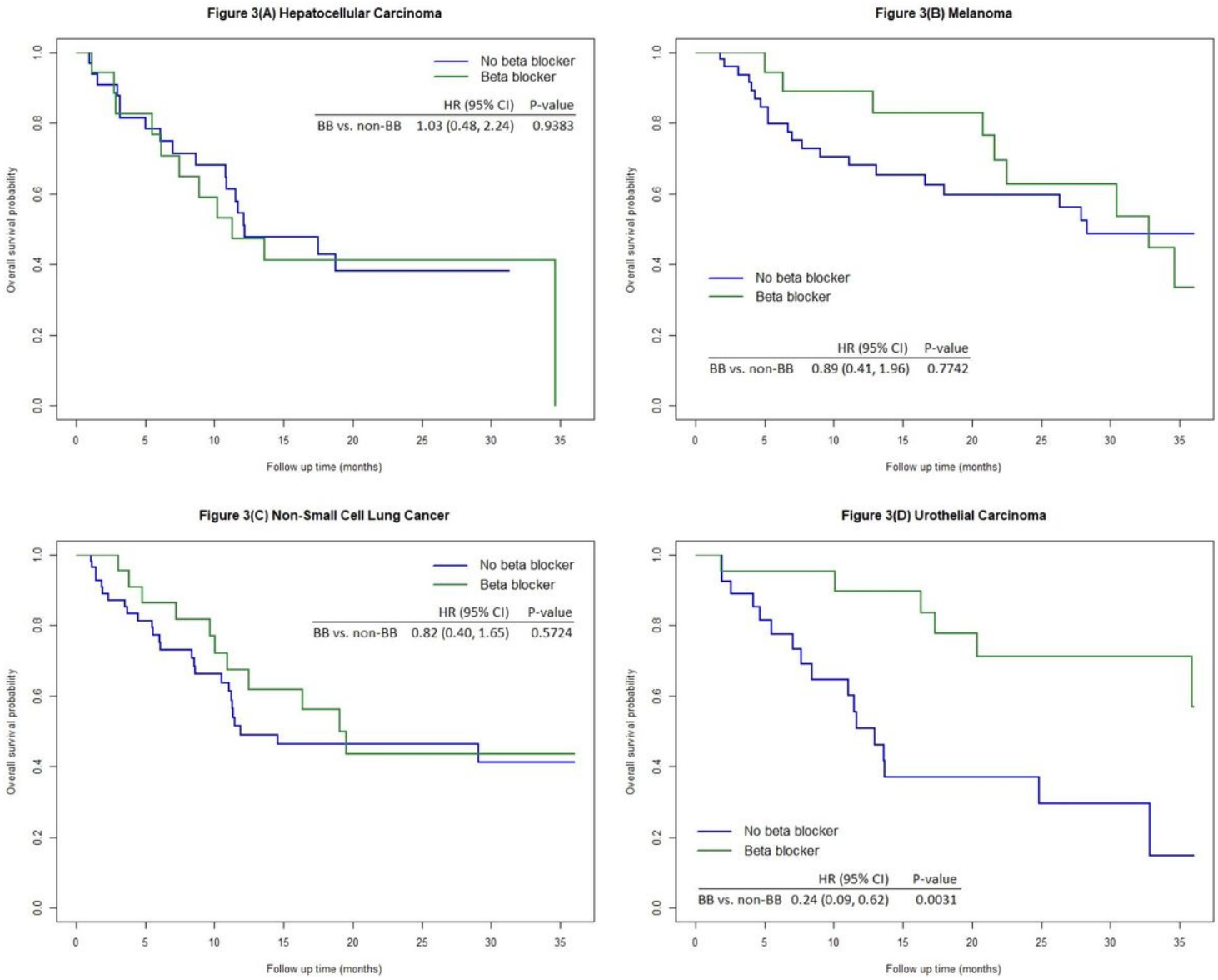

Figure 3

Overall survival of Beta blocker vs. no beta blocker (A) Hepatocellular Carcinoma (B) Melanoma (C) Non-small Cell Lung Cancer and (D) Urothelial Carcinoma

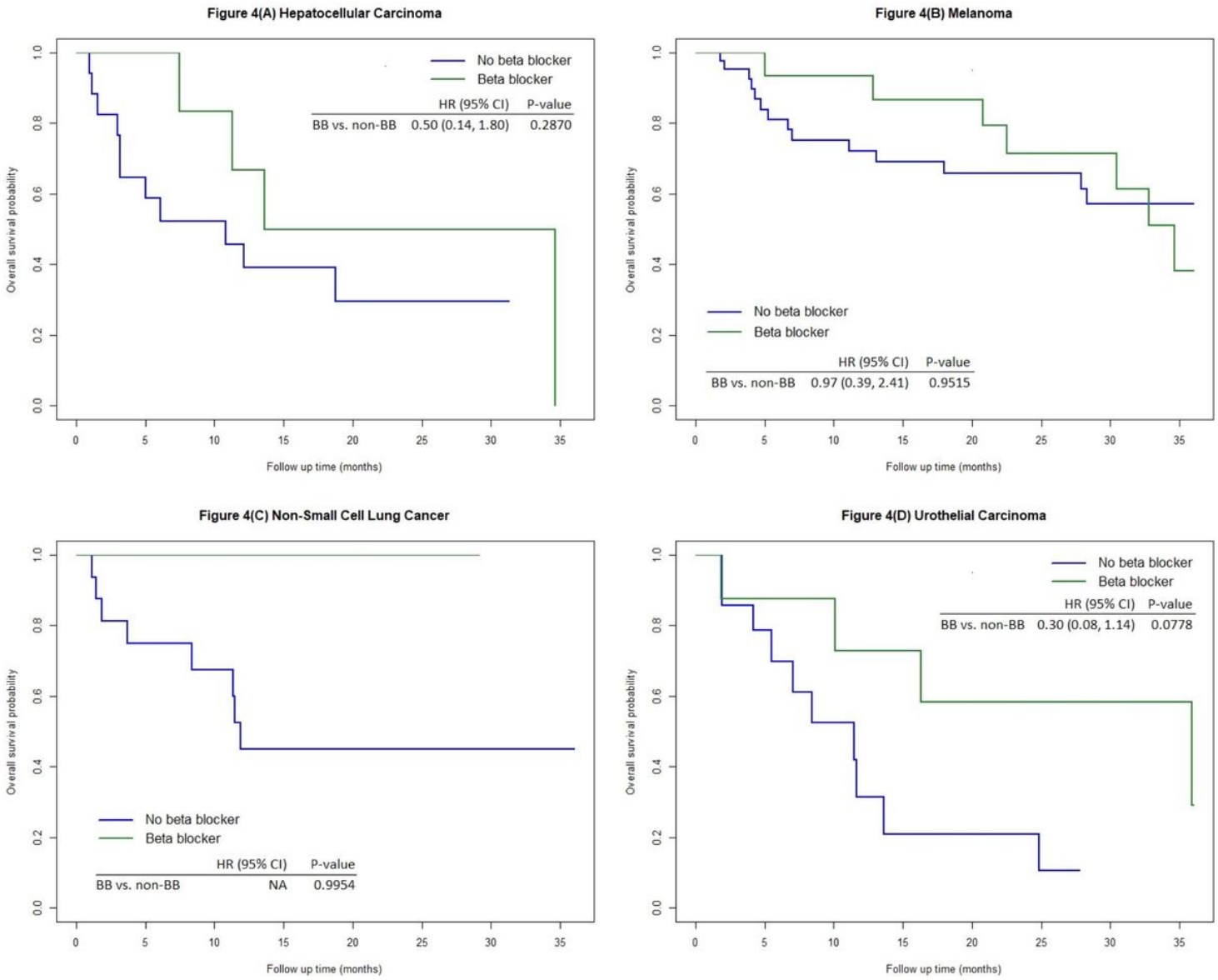

Figure 4

Overall survival of Beta blocker vs. no beta blocker (A) Hepatocellular Carcinoma (B) Melanoma (C) Non-small Cell Lung Cancer and (D) Urothelial Carcinoma for patients received first line therapy

Supplementary Files

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