Association Between Time of Day of Combination Immune Checkpoint Inhibitor Administration and Overall Survival in Advanced Melanoma Patients

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Abstract

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Background: Immune checkpoint inhibitor (ICI) therapy has significantly improved the median overall survival of melanoma patients; however, many patients do not have clinical benefit from ICI therapy. The prognostic role of modifiable factors, such as the time of ICI administration, in immunotherapy treatment outcomes has not been well examined. Recent studies suggest that administration of ICIs earlier in the day may be associated with improved survival outcomes among cancer patients. In this study, we examined the association of treatment timing of the first dose of combination ICI (nivolumab + ipilimumab) with overall survival (OS) in patients with unresectable or metastatic melanoma without prior systemic therapy.

Methods: We conducted a retrospective cohort study of electric health record data of patients with unresectable or metastatic melanoma at the Fred Hutchinson Cancer Center (N = 74).

Patients assigned to the “early group” were administered the first dose of combination ICI therapy before 13:00h and the “late group” if administration was after 14:00h. The Kaplan-Meier method was used to estimate OS of the early and late groups. Additionally, Cox proportional hazard regression models were used to estimate the association between OS and time of ICI administration.

Results: There was a statistically significant difference in the 1-year and 3-year OS estimates of the early and late infusion groups ($p<0.05$). Differences were also observed at 5 years but were not statistically significant. The estimated hazard of death during follow-up among patients who received the first dose of their combination ICI therapy after 14:00h was 2.76 (95% CI: 0.79, 9.69) times as great as that among patients who had their first dose before 13:00h. Although not statistically significant, the magnitude and direction of the hazard ratio is consistent with more favorable survival among those who receive their initial ICI infusion earlier in the day.

Conclusion: This study found longer OS among unresectable and metastatic melanoma patients who were administered their first dose of combination ICI therapy earlier in the day compared to later in the day. Modulating the timing of initial ICI exposure could potentially improve outcomes in patients treated with ICIs.

Introduction

Since the approval of combination immune checkpoint inhibitor (ICI) therapy with nivolumab and ipilimumab by the FDA for unresectable or metastatic melanoma in 2015, the median overall survival of patients with metastatic melanoma has increased substantially (to more than 60.0 months).[1] Despite advances in treatment options, there are many patients who do not respond to ICI therapy. Prior studies have examined tumor markers (e.g., PD-L1 markers)[2] and clinical characteristics (e.g., lactate dehydrogenase levels at baseline)[3] as predictors of outcomes after treatment with ICIs. However, the prognostic role of modifiable factors has not been well examined.

ICIs work by blocking inhibitory immune regulatory signals (checkpoints), resulting in T cell activation and enhanced anticancer immune targeting. Given the circadian rhythmicity of the immune system (including predictable daily fluctuations in T cell levels),[4,5] an association between the time of day of ICI administration and response to ICI therapy may exist. Recent studies have assessed the potential association between timing of ICI administration and subsequent treatment response in a variety of treatment settings and disease types. The findings of these studies have suggested that patients who received proportionally more of their ICI infusions earlier in the day have longer overall survival compared to those with a lower proportion of infusions earlier in the day.[6–19] A pooled meta-analysis of 13 studies affirmed these findings, revealing statistically significant associations with overall survival as well as progression-free survival with earlier timing of treatment administration.[20]

This study aims to investigate the association of ICI treatment timing with overall survival among patients with unresectable or metastatic melanoma without prior systemic therapy. Reflecting the relatively long half-life of the ICI regimen used in this setting (i.e., 27

days for nivolumab,[21] 15.4 days for ipilimumab),[22] we focused this investigation on the timing of the first administered dose of combination ICI therapy as data suggests there is high receptor occupancy for PD-1 antibodies for many weeks after initial administration.[23]

Methods

Study Design & Participants

In this retrospective cohort study, we analyzed data collected from electronic health records (EHR) of the Fred Hutchinson Cancer Center, a quaternary referral center in Seattle, Washington. Patients aged 18 years or older diagnosed with unresectable or metastatic melanoma who received their first infusion of nivolumab and ipilimumab combination ICI therapy for their melanoma at the Fred Hutchinson Cancer Center between January 1, 2016, and December 31, 2022, were included in the analysis. Patients were excluded if they had received any prior systemic therapy for their melanoma (including but not limited to BRAF/MEK inhibitors or other ICI therapy in the adjuvant setting or metastatic setting).

This study was approved and granted a waiver of informed consent and HIPAA authorization by the University of Washington Institutional Review Board based on a determination of minimal risk to study participants.

Exposure

The start time and date of the first administration of combination ICI therapy was extracted from EHR. Patients were dichotomized into an early infusion or late infusion group based on the start time of the first drug administered. The clinic is open for patient infusions from 07:00h to 22:00h, with the latest combination ICI infusions scheduled at 18:30h. Although appointments may be scheduled as early as 07:00h, infusions typically begin one hour after

scheduled times to accommodate drug verification and preparation. Those who had their first infusion before 13:00h were assigned to the "early" infusion group. Those who received their first infusion after 14:00h were assigned to the "late" infusion group. Individuals who received their first infusion between 13:00h and 13:59h (N=15) were excluded in order to increase study sensitivity by increasing the timing discrimination between comparison groups.

Sensitivity analyses were also conducted to align with prior studies that used dichotomizations using cut points based on the median time of ICI administration, and a time threshold of 16:30h. In two such analyses, patients were assigned to the early group if they received their first infusion either before 14:00h (median time of ICI administration) or before 16:30h. Those who received their infusion at or after 14:00h or 16:30h were assigned to the late group.

Outcome

The outcome of interest was overall survival (OS). OS was defined as the time from initiation of combination ICI therapy to death due to any cause. Information regarding vital status and date of death (as applicable) was obtained from the EHR.

Covariates

Sociodemographic and clinical characteristics were also ascertained from the EHR. Sociodemographic characteristics included age at time of combination ICI therapy initiation, sex, race, ethnicity, and zip code. Zip code was used to estimate the distance between patient residence and the cancer center. Distance from the clinic was dichotomized as ≤50 miles and >50 miles. Information was also abstracted regarding several clinical characteristics that are established as prognostic factors in the setting of advanced melanoma, including: cancer stage at

time of ICI initiation, presence of liver metastases at time of ICI initiation, presence of brain metastases at time of ICI initiation, and baseline lactate dehydrogenase (LDH) levels. Baseline LDH level was dichotomized as elevated (≥210 U/L) or not elevated (<210 U/L).

Statistical Analysis

Descriptive statistics were used to summarize the study population, including patient demographics, and clinical characteristics. Patient characteristics of the two infusion groups were compared using χ^2 tests.

The Kaplan-Meier method was used to calculate OS and 95% confidence intervals in the early and late infusion groups. Additionally, Cox proportional hazard regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association between OS and time of ICI administration. Potential confounding factors were assessed by examining the distribution of the covariates across the two groups. The covariates associated with both the exposure and outcome were considered confounders, and those associated with the outcome only were considered precision variables in multivariate regression models. A p-value <0.05 was considered statistically significant. Statistical analyses were conducted using R.

Results

Between January 1, 2016, and December 31, 2022, 118 advanced melanoma patients initiated first line treatment with combination ICI therapy of nivolumab and ipilimumab (**Figure 1**). Out of the 118 patients, 29 were excluded for a diagnosis of non-cutaneous melanoma or resectable disease treated in a neoadjuvant setting. From this population, 15 additional patients whose infusions were between 13:00h and 13:59h were excluded to facilitate a 1-hour “washout” period between the two infusion timing groups. The final study population included 74 patients

with unresectable or metastatic cutaneous melanoma, consisting of 28 patients who received their first combination ICI infusion before 13:00h ("early group") and 46 patients received their first infusion after 14:00h ("late group"). The median time of ICI administration in our population was 14:07h (range: 08:13h, 19:30h). Among all eligible patients, infusion times peaked during midday (13:00h-13:59h) and tapered in the early morning and late evening (**Figure 2**). Characteristics of the study population are summarized in **Table 1**. Median follow-up was 40.2 months (range: 1.5, 90.7) in the early group and 35.8 months (range: 0.2, 93.1) in the late group. A majority of patients were non-Hispanic white (91.3%), male (n=33; 71.7%) and lived within 50 miles of the clinic (n=52; 70.3%). The median age at ICI initiation was 60.5 years (range: 22.0, 83.0). Nearly all patients were treated in a metastatic setting (n=72; 97.3%), 54.1% did not have brain metastases (n=40), 55.4% did not have liver metastases (n=41), and 64.9% had normal (<210 U/L) LDH concentrations (n=48) at time of combination ICI initiation. Overall, there were no statistically significant differences in baseline characteristics between the early and late groups.

Median OS was not reached in our patient population (**Figure 3**). The 1-year, 3-year, and 5-year OS proportions for patients who received their first combination ICI infusion before 13:00h were 96.4% (95% CI: 77.2, 99.5), 91.4% (95% CI: 68.9, 97.8), and 79.9% (95% CI: 43.9, 94.1), respectively. The 1-year, 3-year, and 5-year OS proportions for patients who received their first combination ICI infusion after 14:00h were 82.6% (95% CI: 68.2, 90.0), 71.6% (95% CI: 55.1, 82.9), and 67.7% (95% CI: 50.0, 80.2), respectively. There were statistically significant differences between the OS estimates at 1-year and 3-year between the two infusion timing groups ($p<0.05$); differences persisted at 5 years, but were not statistically significant (**Table 2**).

A univariate Cox proportional hazards model indicated that patients who received the first dose of their combination ICI therapy after 14:00h had a hazard of death during follow-up that was 2.76 (95% CI: 0.79, 9.69) times as great as that among patients who had their first dose before 13:00h (**Table 3**). Although not statistically significant, the magnitude and direction of the HR is consistent with a more favorable survival among those who receive their initial ICI infusion earlier in the day.

While our initial comparisons of the study groups revealed no significant differences in demographic or clinical factors at baseline, we also examined a multivariate Cox model adjusting for age at time of combination ICI therapy initiation, sex, race and ethnicity, distance from clinic, presence of liver metastases at time of ICI initiation, presence of brain metastases at time of ICI initiation, and baseline LDH. This model estimated a HR of 2.22 (95% CI: 0.56, 8.70). Another multivariate Cox model adjusting exclusively for distance from clinic and baseline LDH concentration as precision variables estimated an HR of 2.39 (95% CI: 0.67, 8.56). Although attenuated towards the null, the multivariate hazard estimates are consistent with the findings from the univariate model.

We conducted sensitivity analyses examining the association without implementing a "washout" period from 13:00h to 13:59h. A number of prior studies utilized a time threshold based on the median ICI administration time. In our first sensitivity analysis, we chose a cut point of 14:00h which was closely aligned with median infusion start-time of our population (14:07h). The early and late infusion groups were well-balanced, with 43 and 46 patients in each group, respectively. A univariate model estimated an HR of 2.48 (95% CI: 0.89, 6.97; $p = 0.08$) comparing the late and expanded early treatment groups. To align with other prior studies, we also examined the association using a cutoff of 16:30h. There were 67 patients in this modified

early group and 22 in the truncated late group, yielding an HR of 0.78 (95% CI: 0.26, 2.36; p = 0.66) in a univariate model.

Discussion

This study found favorable OS among unresectable and metastatic melanoma patients who were administered their first dose of combination ICI therapy earlier in the day compared to later in the day. Univariate analysis revealed a hazard of death nearly three times greater among patients who received infusions later in the day. Multivariate analyses confirmed that our findings persist despite controlling for other factors that could be associated with OS in this population. Both multivariate models that adjusted for all study variables and a simplified model adjusting only for distance from clinic and baseline LDH concentration yielded hazards of death over two times greater among patients who received infusions later in the day. Although slightly attenuated towards the null, the multivariate hazard estimates indicate that the observed finding from the univariate model is not greatly impacted by other measured study variables. The timing of combination ICI administration is likely to be an independent modifiable factor for patient survival. As such, our results suggest that modulating ICI timing has the potential to improve outcomes in patients treated with ICIs.

Overall, our findings are aligned with other studies examining the relationship between ICI timing and survival among various cancer types and time thresholds (**Table 4**). These studies generally found that patients who received a greater proportion of ICI doses earlier in the day had more favorable OS when compared to those who received a greater proportion of ICI doses later in the day.[6–19] A number of these studies were limited to patients who completed at least four infusions of ICI therapy.[6,9,19] It is possible that the overall fraction of doses received early in the day is less important than the timing of the first dose or early doses. The response to early

doses of immunotherapy are known to be predictive of long-term outcomes in melanoma.[24] Furthermore, phase I studies demonstrate that PD-1 receptors on peripheral T cells are occupied for up to 100 days after one dose of nivolumab. The biologic impact of timing of subsequent doses is unclear given there is already high receptor occupancy at the time of second dose administration.[23]

Two studies have examined the timing of early doses of ICI therapy in advanced melanoma patients[13] and metastatic or recurrent esophageal squamous cell carcinoma.[12] Yeung et al reported a poorer OS for patients who received all initial four doses of ICI in the afternoon (after 13:00h) compared to those who had at least one infusion in the morning (before 13:00h).[13] Nomura et al also used a cutoff of 13:00h, but examined the first dose of nivolumab only. They similarly reported longer OS in patients in the early group compared to the late group.[12] Our study corroborates these findings and is further evidence to support the hypothesis that ICI administration earlier in the day may be more impactful on treatment outcomes. Additionally, our findings suggest that the time of ICI administration relative to the circadian rhythm is a modifiable factor that may serve a prognostic role in responses to ICI therapy.

A potential mechanism that supports an association between ICI administration time and clinical responses involves the circadian rhythmicity of the immune system. Aspects of the immune system, including T cell levels, fluctuate throughout the day, with oscillation patterns aligned to the circadian clock.[4,5] The circadian clock serves to regulate molecular and cellular processes at predictable intervals that are synced to environmental cues, such as daily light and dark cycles.[25] T cell levels have been shown to drop during active phases of the day (~14:00h) and peak during inactive phases of the day (~02:00h).[4] As such, administration of ICIs late in the day when T cell levels are lower may lead to decreased ICI efficacy.

Previous work has used heterogeneous and disparate time cutoffs that were often unaligned with T cell rhythms and assigned groups based on subjective thresholds (e.g., patients who received <20% of all infusions after 16:30h vs. those who received ≥20% of infusions after 16:30h). Our study implemented a cutoff at 13:00h with a 1-hour "washout" period between the early and late groups. A 13:00h time threshold is consistent with previous studies examining the timing of initial infusions[12,13] and also aligns with the behavior of T cell fluctuations throughout the day.[4] Notably, our sensitivity analyses implementing time thresholds that were used in other studies suggest that the time classification structure could have an important impact on findings. There was no remarkable change in the hazard estimates when we used a simple dichotomization without the 1-hour "washout" period and a cut point based on the median time of ICI administration. However, in our examination using a cut point of 16:30h, the hazard of death among patients with infusions late in the day is lower than those with infusions earlier in the day. This contradicts the findings from our primary analysis in addition to the findings of other studies. Due to the hours of operation at our clinic, few patients started their infusions after 16:30h which may have had an impact on our unexpected hazard estimate. Regardless, this highlights the need for further research to inform the choice of appropriate time thresholds that are biologically and mechanistically informed in order to determine the optimal timing of ICI administration.

A strength of our study is that we used institutional medical records to ascertain outcomes and time of ICI administration for the entire population of patients who received first line combination ICI therapy with nivolumab and ipilimumab for treatment of their unresectable or metastatic melanoma. The total population size is relatively small due to the stringent inclusion criteria as patients who received combination nivolumab and ipilimumab after adjuvant therapy

or as a later line of therapy were excluded from this analysis. Despite this, we still detected differences in survival at 1- and 3-years among the early and late groups, in addition to elevated hazard of death in the later infusion groups. A larger, multi-institutional study would be important to examine if these associations persist with larger sample sizes, longer follow-up periods, and individual-level characteristics (e.g., chronotype).

As an observational, retrospective study, we were constrained in this analysis based on what was available in the EHR. However, we did have access to long-term outcomes and detailed institutional records on time of administration, and clinical data to allow examination of other associated demographic and clinical factors. This study was also limited to one academic cancer center, which impacts generalizability of the results since health care access and utilization at academic medical centers may differ from community clinics. We were also unable to assess for differences in patient preference or other sociodemographic factors that may play a role in timing of ICI administration. For instance, wealthier patients may elect for earlier infusion times, and are expected to have better outcomes.[11] While we were limited in the sociodemographic factors we had access to and assessed for, among the factors that were available (e.g., age, sex, race and ethnicity, distance from clinic), we affirmed that these factors were not differentially associated with the exposure or outcome in our analysis. Lastly, we are unable to assess sleep patterns and chronotype of study patients, which inherently have a role in circadian cycles and therefore may impact ICI responses. Since our study examined the time of administration of the first dose only, the longitudinal impacts of patient preference and other factors is largely mitigated. Future examinations should account for these nuanced factors.

The results of our study suggest that the timing of the very first dose of combination ICI therapy could have an impact on OS. If confirmed in larger studies and preferably in a

prospective clinical trial, this work suggests that preferential scheduling could be implemented for the first cycle of nivolumab and ipilimumab combination therapy to begin in the morning where resources allow. The complexities of clinic schedules, fixed operating hours, and limited capacity hinders the ability to schedule all patient infusions earlier in the day. Scheduling first doses preferentially in the morning, however, is more feasible to implement at scale.

Combination ICI therapy has improved the survival of patients; however, many patients do not respond to treatment. Our cohort study found that patients who received their first dose of combination ICI therapy early in the day had more favorable survival outcomes compared to those treated later in the day. This suggests that adjusting clinical practice to preferentially schedule first doses of combination ICIs earlier in the day may improve patient outcomes.

Tables & Figures

Figure 1. Study profile.

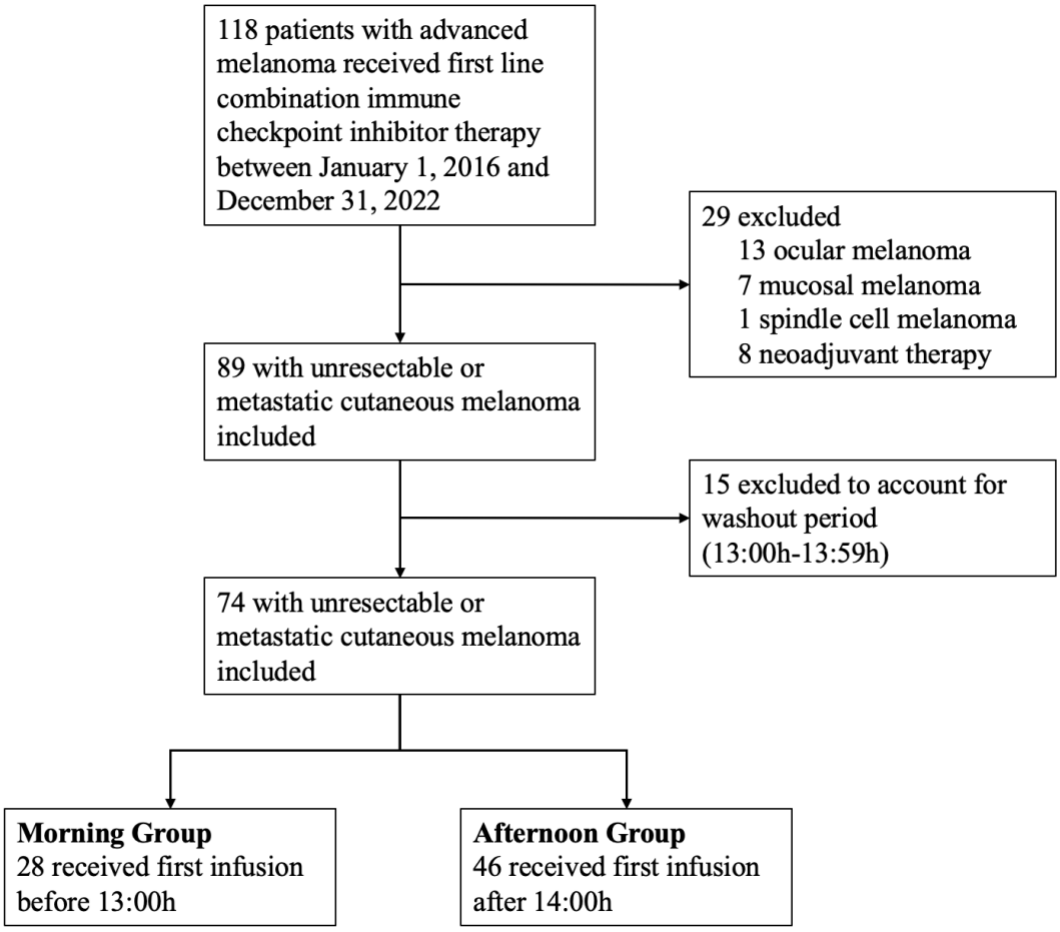

Figure 2. Distribution of infusion start times.

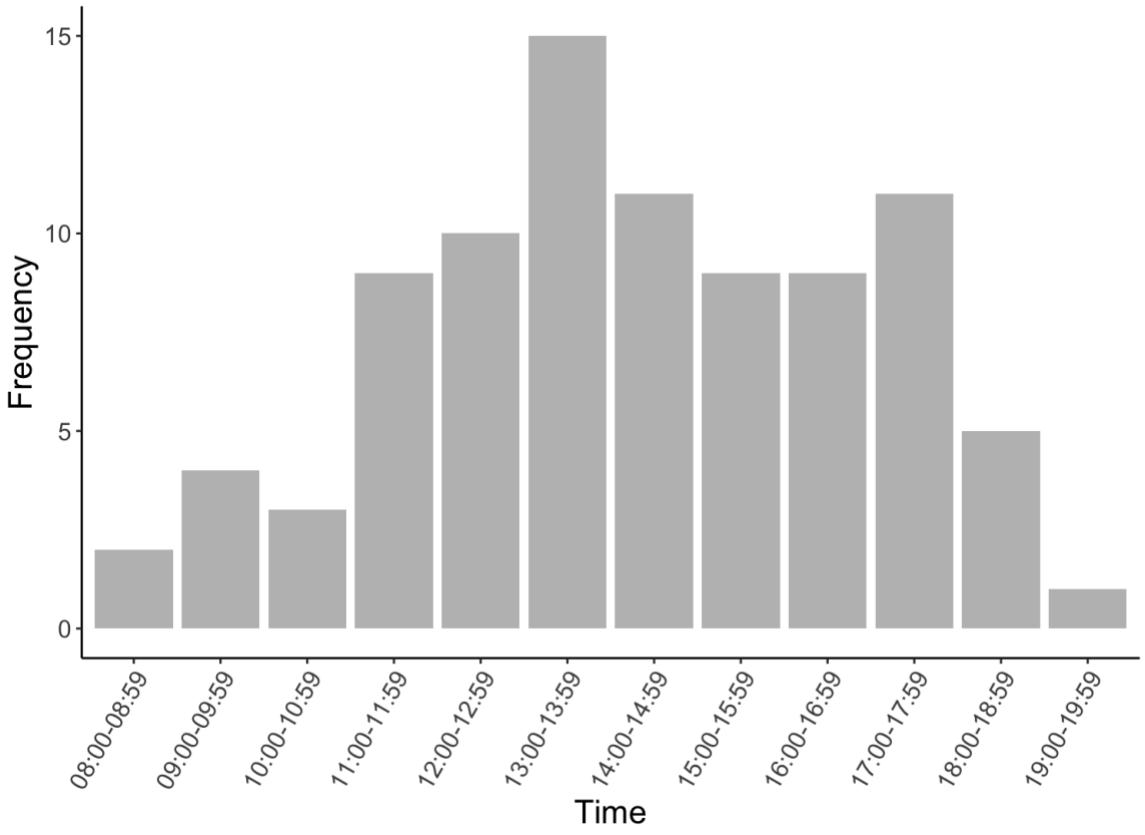

Table 1. Patient characteristics at baseline by time-of-day of ICI infusion.

	Overall (N=74)	Early Group (N=28)	Late Group (N=46)	p-value
Age (years)[a]				0.61
Mean (SD)	58.4 (14.2)	59.5 (14.0)	57.8 (14.5)	
Median [Min, Max]	60.5 [22.0, 86.0]	60.5 [34.0, 86.0]	60.5 [22.0, 83.0]	
Sex				0.97
Female	20 (27.0%)	7 (25.0%)	13 (28.3%)	
Male	54 (73.0%)	21 (75.0%)	33 (71.7%)	
Race and Ethnicity				0.73
Asian/Pacific Islander, non-Hispanic	1 (1.4%)	0 (0%)	1 (2.2%)	
White, non-Hispanic	68 (91.9%)	26 (92.9%)	42 (91.3%)	
Hispanic or Latino	3 (4.1%)	1 (3.6%)	2 (4.3%)	
Missing	2 (2.7%)	1 (3.6%)	1 (2.2%)	
Distance from Clinic (miles)				1.00
Less than 50 miles	52 (70.3%)	20 (71.4%)	32 (69.6%)	
More than 50 miles	22 (29.7%)	8 (28.6%)	14 (30.4%)	
Cancer Stage[a]				0.70
Unresectable	2 (2.7%)	0 (0%)	2 (4.3%)	
Metastatic	72 (97.3%)	28 (100%)	44 (95.7%)	
Brain Metastases[a]				0.83
Present	27 (36.5%)	11 (39.3%)	16 (34.8%)	
Not Present	40 (54.1%)	14 (50.0%)	26 (56.5%)	
Missing	7 (9.5%)	3 (10.7%)	4 (8.7%)	
Liver Metastases[a]				0.59
Present	30 (40.5%)	13 (46.4%)	17 (37.0%)	
Not Present	41 (55.4%)	14 (50.0%)	27 (58.7%)	
Missing	3 (4.1%)	1 (3.6%)	2 (4.3%)	
Lactase Dehydrogenase Concentration (U/L)[a]				0.24
<210 U/L	48 (64.9%)	21 (75.0%)	27 (58.7%)	
>210 U/L	26 (35.1%)	7 (25.0%)	19 (41.3%)	
Median Follow Up (months)				0.92
Mean (SD)	40.8 (26.9)	41.2 (24.6)	40.6 (28.5)	
Median [Min, Max]	36.6 [0.2, 93.1]	40.2 [1.5, 90.7]	35.8 [0.2, 93.1]	

[a]at time of ICI initiation

Figure 3. Kaplan-Meier survival curve of overall survival by time-of-day of ICI infusion.

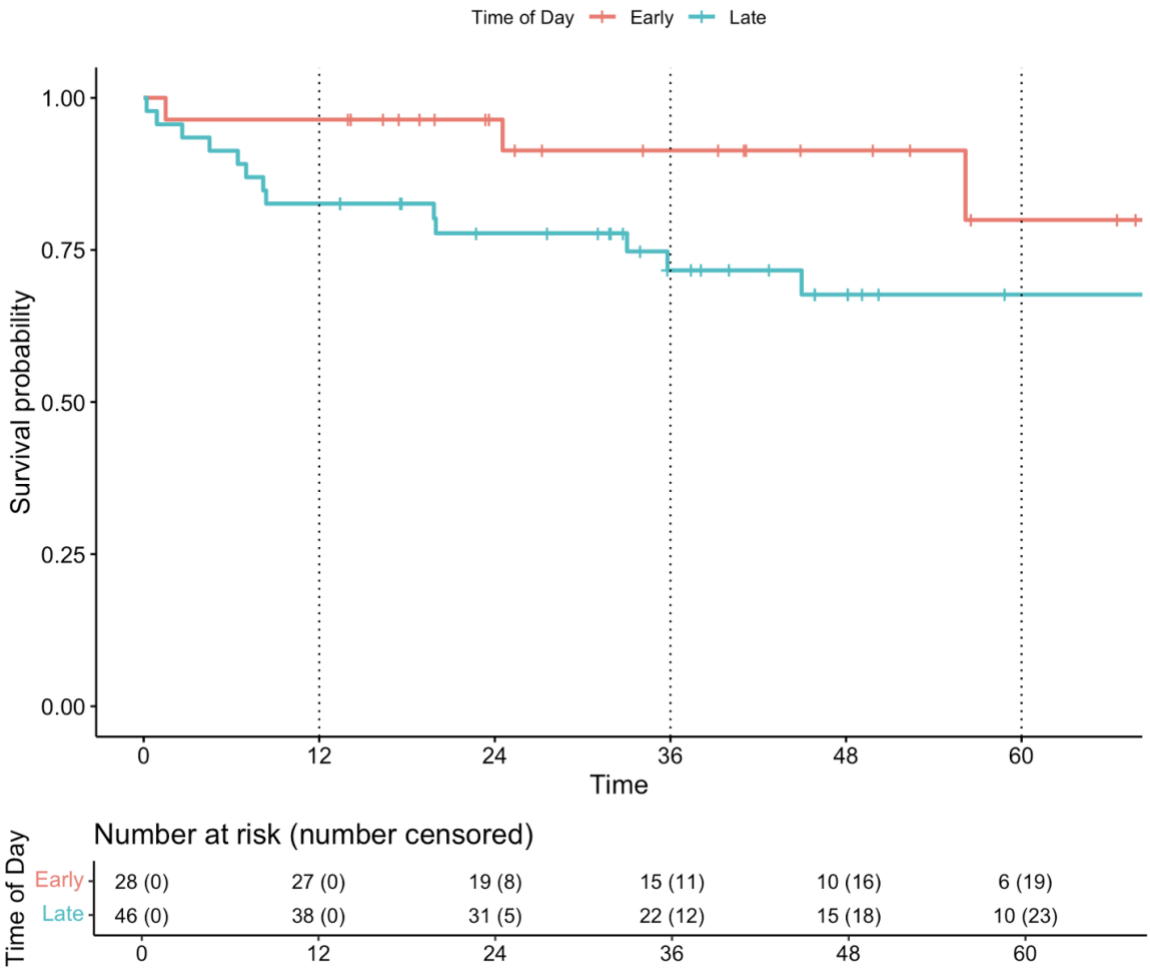

Table 2. Overall survival estimates at 1-year, 3-year, and 5-year post-ICI initiation.

	Early Group	**Late Group**	**p-value**
1-year	96.4% (77.2, 99.5)	82.6% (68.2, 90.0)	**0.04**
3-year	91.4% (68.9, 97.8)	71.6% (55.1, 82.9)	**0.03**
5-year	79.9% (43.9, 94.1)	67.7% (50.0, 80.2)	0.39

Table 3. Univariate Cox proportional hazards regression of overall survival in the early and late infusion groups.

	Overall Survival		
	Hazard Ratio (HR)	**95% CI**	**p-value**
Received First Combination ICI Infusion After 14:00h	2.76	0.79, 9.69	0.11

Table 4. Summary of characteristics of peer-reviewed studies.

Study	Year	Cancer Type	Treatment	Line of Therapy	ICI Time Threshold	Number of Patients (Early/Late)	Outcome Measure
Qian et al. United States 2012-2020	2021	Melanoma	4+ infusions of nivolumab, ipilimumab, pembrolizumab, or a combination	1+	20% infusions after 16:30h	146 (73/73)	OS PFS
Karaboue et al. France 2015-2020	2022	NSCLC	Single agent nivolumab	2+	Median infusion time (12:54h)	95 (48/47)	OS PFS
Cortellini et al. United States, United Kingdom, and Italy 2018-2022	2022	NSCLC	Pembrolizumab	1+	20% infusions after 16:30h	180 (136/44)	OS PFS
Rousseau et al. France 2016-2021	2023	NSCLC	4+ infusions of nivolumab, pembrolizumab, or atezolizumab	1+	20% infusions after 16:30h	180 (115/65)	OS PFS
Nomura et al. Japan 2017-2022	2023	SCC	Nivolumab	1+	13:00	62 (27/45)	OS PFS
Yeung et al. Canada 2015-2021	2023	Melanoma	1+ infusion of single-agent PD-1 or PD-L1 or dual ICI	1+	At least 1 of the first 4 ICI infusions prior to 13:00h	121 (98/23)	OS PFS
Goncalves et al. Portugal 2016-2022	2023	Melanoma	Pembrolizumab, nivolumab, or combination nivolumab + ipilimumab	1+	75% of infusions after 14:00h	73 (48/25)	OS
Dizman et al. United States 2018-2022	2023	RCC	2+ infusions of nivolumab or combination nivolumab + ipilimumab	1 or 2	20% infusions after 16:30h	135 (89/46)	OS
Patel et al. United States 2015-2021	2024	RCC	Pembrolizumab, nivolumab, or combination nivolumab + ipilimumab	1+	20% infusions after 12:00h	201 (101/100)	OS PFS
Hirata et al. Japan 2018-2022	2024	NSCLC	4+ infusions of durvalumab	1+	20% infusions after 15:00h	82 (70/12)	OS PFS
Ruiz-Torres et al. United States 2016-2023	2024	HNSCC	Pembrolizumab, nivolumab, ipilimumab, durvalumab, combination ICI, or chemo-immunotherapy	1+	20% infusions after 15:00h	113 (49/49)	OS PFS

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