25P: Impact of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma (the MEMOIR study): a propensity score-matched analysis David C. Qian, MD, PhD^{1,} Troy Kleber, MSCR¹, Brianna Brammer, BS², Karen M. Xu, MD¹, Jeffrey M. Switchenko, PhD, MS³, James R. Janopaul-Naylor, MD¹, Jim Zhong, MD¹, Melinda L. Yushak, MD, MPH⁴,

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Conclusions

Receiving more evening infusions of immune checkpoint inhibitors was independently associated with shorter overall survival among patients with advanced melanoma. This time-of-day effect was more pronounced among women, patients with brain metastases, and patients who received dual immune checkpoint inhibitors (ipilimumab + nivolumab). Patients with more evening infusions were also far more likely to have received at least one of the initial two infusions in the evening.

These findings are in line with a growing body of evidence that the adaptive immune response may be less robust when stimulated later in the day. While prospective studies of immunotherapy time-of-day infusions are warranted, effort toward scheduling infusions before mid-afternoon may be considered in the multidisciplinary management of advanced melanoma.



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Background

Circadian rhythm dependence of the adaptive immune system is an emerging field of study with potential therapeutic implications. Specific time-of-day patterns of immune checkpoint inhibitor (ICI) infusion may alter the efficacy of melanoma treatment through differential synchronization with T cell circadian cycles.

Methods

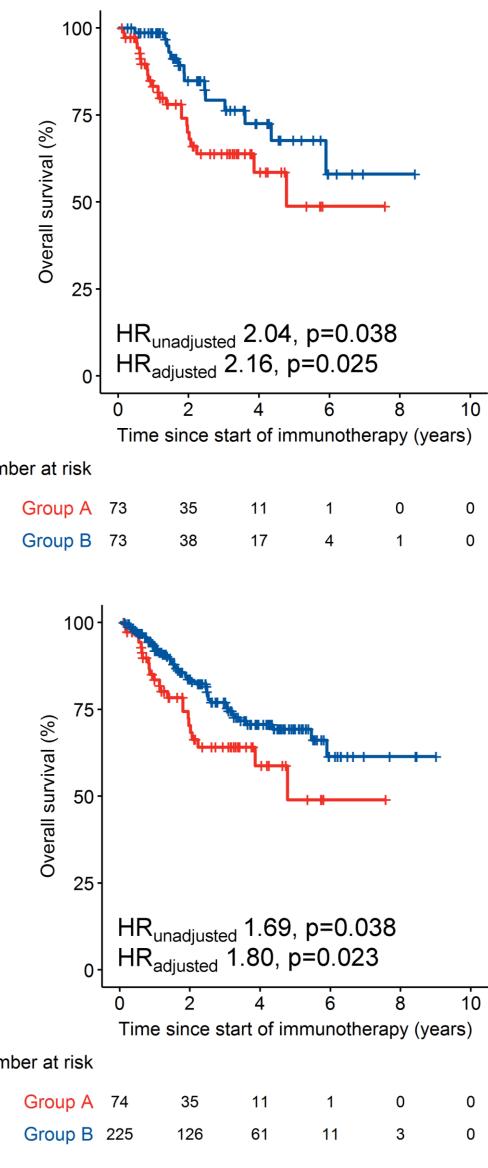
<u>MElanoMa</u> Outcomes following ImmunotheRapy (MEMOIR) is a longitudinal study of all patients with melanoma who received ipilimumab, nivolumab, and/or pembrolizumab at a single tertiary cancer centre. The association between overall survival (OS) and having an abundance of ICI infusions after 16:30, a composite time cutoff derived from seminal studies of the immune-circadian rhythm to represent onset of evening, was computed using multivariable Cox proportional hazards regression and propensity score-matched analysis

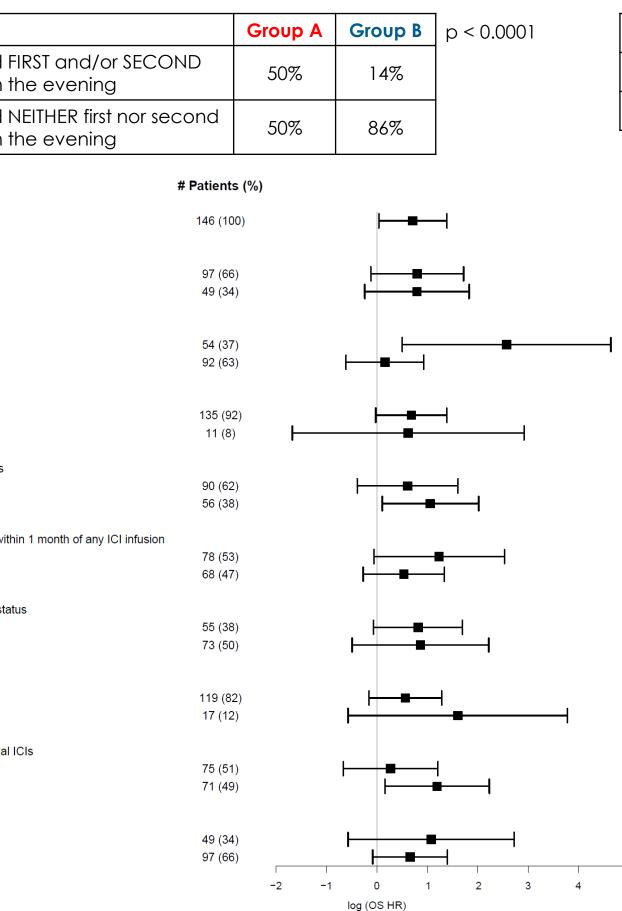
ICI y 515.			Winter (Janu Spring (April
481 patients with me	lanoma received ICls, 2012–2020		Summer (Jul Fall (Octobe Experienced No Yes
	182 patients excluded 9 received ICIs from more than one institution 114 had stage III disease 59 had stage IV disease and fewer than 4 ICI infusions		Experienced No Yes Radiotherapy None Definitive int Palliative int Received infusion in
299 patients with	stage IV melanoma included		Received infusion in Subgroup
			Overall Age < 65 ≥ 65
↓ 74 patients received at least 20% of their ICI infusions after 16:30 (Group A)	↓ 225 patients received fewer than 20% of their ICI infusions after 16:30 (Group B)		Sex Female Male ECOG ≤ 1 ≥ 2
			Brain metastases No Yes
Propensity score matching • Age • ECOG performance status • LDH, pre-treatment			Corticosteroids wit No Yes <i>BRAF</i> mutation sta Mutant Wild-type
	of corticosteroids of radiotherapy		LDH ≤ 280 > 280 Ever received dua No
↓ 73 patients received at least 20% of their ICI infusions after 16:30 (Group A)	▼ 73 patients received fewer than 20% of their ICI infusions after 16:30 (Group B)		Yes Radiotherapy No Yes

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2	20% of infusions after 16:30 (Group A, n=73)	<20% of infusions after 16:30 (Group B, n=73)	Р
Age, years ≤ 40	(Group A, n=73)	(Group B, n=73)	0.758
41-60 61-80 ≥ 81	30 (41) 32 (44) 1 (1)	32 (44) 30 (41) 0 (0)	
ex Female Male	27 (37) 46 (63)	27 (37) 46 (63)	1.000
ECOG 0–1 2	67 (92) 6 (8)	68 (93) 3 (4)	0.222
3 Brain metastases No	0 (0) 46 (63)	2 (3) 44 (60)	0.863
Yes BRAF mutation status Mutant Wild-type	27 (37) 29 (40) 36 (49)	29 (40) 26 (36) 37 (51)	0.819
Unknown DH, pre-treatment < 280 U/L > 280 U/L	8 (11) 57 (78) 10 (14)	10 (14) 62 (85) 7 (10)	0.566
Unknown Corticosteroids within 1 month of any IC No Yes	6 (8) I infusion 39 (53) 34 (47)	4 (5) 39 (53) 34 (47)	1.000
Number of ICI infusions 4–10 11–15 16–20 ≥ 21	46 (63) 13 (18) 7 (10) 7 (10)	33 (45) 15 (21) 11 (15) 14 (19)	0.139
Ever received Pembrolizumab Single agent ipilimumab Single agent nivolumab Dual ICIs	28 (38) 17 (23) 14 (19) 38 (52)	31 (42) 21 (29) 17 (23) 33 (45)	0.740 0.572 0.689 0.507
First infusion Pembrolizumab Single agent ipilimumab Single agent nivolumab Dual ICIs	23 (32) 11 (15) 12 (16) 27 (37)	20 (27) 16 (22) 13 (18) 24 (33)	0.717
Season of first infusion Winter (January–March) Spring (April–June) Summer (July–September) Fall (October–December)	13 (18) 18 (25) 18 (25) 24 (33)	13 (18) 13 (18) 27 (37) 20 (27)	0.396
Experienced toxicity that led to change No Yes	in ICI 60 (82) 13 (18)	57 (78) 16 (22)	0.680
Experienced toxicity that led to discontir No Yes	nuation of all ICIs 53 (73) 20 (27)	48 (66) 25 (34)	0.475
Radiotherapy None Definitive intent Palliative intent	22 (30) 45 (62) 21 (29)	27 (37) 39 (53) 26 (36)	0.502





			Group A	Group B	p = 0 .069	
Ever achieve	d complete	plete response 22% 34%		-		
No complete	response		78% 66%		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	
5−Year /	t Evonto	5-Vo	ar OS (95% CI)			
Group A	Group B	Group A	Grou	ир В С	OS HR (95% CI)	
23/73	13/73	49% (31–76)	68% (5	3–86)	2.04 (1.04–4.00)	
13/47	7/50	52% (31–88)	73% (5	6–95)	2.23 (0.89–5.60)	
10/26	6/23	44% (26–77)	61% (4	1–93)	2.22 (0.79–6.25)	
9/27	1/27	47% (24–90)	92% (77	7–100)	13.11 (1.65–104)	
14/46	12/46	48% (26–90)	54% (3	6–80)	1.17 (0.54–2.54)	
20/67	12/68	52% (33–80)	68% (5	4–87)	1.98 (0.98–4.02)	
3/6	1/5	25% (4–100)) 75% (43–100)		1.86 (0.19–18.53)	
11/46 12/27	6/44 7/29	61% (40–92) 49% (31–77)	70% (5 66% (4	,	1.84 (0.68–4.98) 2.89 (1.11–7.51)	
12/27	1129	49% (31-77)	00 % (4	0-91)	2.09 (1.11-7.51)	
10/39	3/39	57% (35–94)			3.44 (0.94–12.52)	
13/34	10/34	42% (21–81)	58% (4	1–84)	1.71 (0.76–3.84)	
13/29	8/26	28% (7–100)	, , ,		2.26 (0.94–5.48)	
7/36	3/37	69% (52–91)	82% (65	5–100)	2.37 (0.61–9.17)	
18/57	12/62	45% (24–85)			1.76 (0.86–3.64)	
5/10	1/7	48% (25–94)	75% (43	3–100) 4	4.98 (0.57–43.81)	
9/35	8/40	56% (33–93)) 73% (59–92)		1.31 (0.51–3.36)	
14/38	5/33	44% (23–83)	52% (26	6–100)	3.30 (1.17–9.29)	
5/22	2/27	74% (57–97)	72% (44	4–100) 2	2.93 (0.56–15.24)	
18/51	11/46	34% (14–83)	65% (5	0–85)	1.93 (0.92–4.04)	