25P: Impact of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma (the MEMOIR study): a propensity score-matched analysis

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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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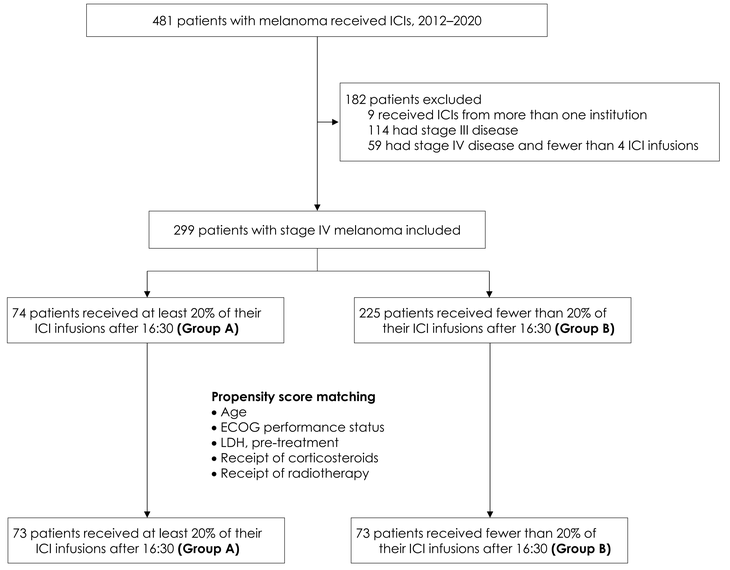
Background

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.

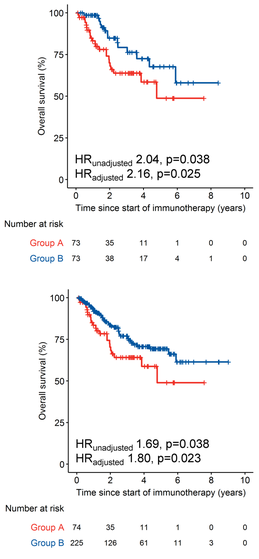
Methods

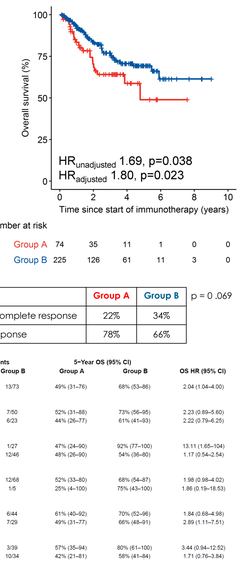
MElanoMa Outcomes following ImmunotheRapy (MEMOIR) is a longitudinal study of all patients with melanoma who received ipilimumab, nivolumab, and/or pembrolizumab at a single tertiary cancer centre. The association between overall survival (OS) and having an abundance of ICI infusions after 16:30, a composite 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.



Results

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





	Group A	Group B	p < 0.0001
Received FIRST and/or SECOND infusion in the evening	50%	14%	
Received NEITHER first nor second infusion in the evening	50%	86%	

	Group A	Group B	p = 0.069
Ever achieved complete response	22%	34%	
No complete response	78%	66%