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Seasonal variation of anti-PD-1 outcome in melanoma—Results from a Dutch patient cohort

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LETTER TO THE EDITOR

WILEY

Seasonal variation of anti-PD-1 outcome in melanoma—Results from a Dutch patient cohort

Abstract

Despite the improved survival rates of patients with advanced stage melanoma since the introduction of ICIs, many patients do not have (long-term) benefit from these treatments. There is evidence that the exposome, an accumulation of host-extrinsic factors including environmental influences, could impact ICI response. Recently, a survival benefit was observed in patients with *BRAF* wild-type melanoma living in Denmark who initiated immunotherapy in summer as compared to winter. As the Netherlands lies in close geographical proximity to Denmark and has comparable seasonal differences, a Dutch validation cohort was established using data from our nationwide melanoma registry. In this study, we did not observe a similar seasonal difference in overall survival and are therefore unable to confirm the Danish findings. Validation of either the Dutch or Danish findings in (combined) patient cohorts from other countries would be necessary to determine whether this host-extrinsic factor influences the response to ICI-treatment.

To the Editor,

The introduction of immune checkpoint inhibitors (ICI) has significantly improved the survival rates of patients with advanced stage melanoma (Moreira et al., 2021). However, the majority of patients do not have a tumor response or eventually have progressive disease, and many attempts are ongoing to elucidate which mechanisms are involved in ICI resistance. These mechanisms can be divided into host-intrinsic, such as the patient's systemic immune response and the tumor microenvironment, and host-extrinsic factors, including lifestyle and environmental exposure (Morad et al., 2021). These factors external to the host, also called the exposome, are the accumulation of environmental influences and associated biological responses throughout life, which could impact response to ICI (Miller & Jones, 2014; Morad et al., 2021).

Recently, a Danish study investigated the impact of seasonal variation, a host-extrinsic factor, on overall survival (OS) among patients with advanced melanoma who were treated with PD-1 inhibitors (Ellebaek et al., 2022). When controlling for known factors associated with ICI treatment response in melanoma (including performance score, presence of brain metastases, baseline lactate dehydrogenase (LDH), and treatment line), the authors showed that initiation of anti-PD-1 immunotherapy in the summer half-year (April–September) was associated with prolonged OS in patients with *BRAF* wild-type (WT) melanoma living in Denmark (Ellebaek et al., 2022). The authors presented three potential factors contributing to their findings: (1) the sun hours vary between summer and winter; (2) the temperatures differ; (3) in wintertime the diversity of local fruits and vegetables is reduced and more food is imported, potentially leading to either a reduced intake of nutrients or different diet, which in turn can result in an altered gut microbiome (Ellebaek et al., 2022). Of note, the seasonal variation in OS was not observed for *BRAF*-mutated patients treated with anti-PD-1, or patients treated with BRAF inhibitor-based therapies.

As the Netherlands lies in close geographical proximity to Denmark, we aimed to validate these findings in a Dutch patient cohort. The Netherlands has a similar climate (Cfb [temperate oceanic climate] according to the Köppen classification, compared to Dfb [warm-summer humid continental climate]/Cfb in Denmark), with an average of 7.0 and 2.4 sun hours per day in the summer versus winter (9.2 vs. 2.2 h in Denmark), and average temperatures in summertime of 17.3 degrees Celsius and 3.9 in wintertime (16.9 vs. 1.5 degrees Celsius in Denmark) (Danmark, n.d.; Royal Netherlands Meteorological Institute, Ministery of Infrastructure and Water Management, n.d.). Furthermore, a comparable decrease in dietary diversity in the winter months is observed in the Netherlands, which has been associated with changes in the gut microbiome compositon (Davenport et al., 2014; Koliada et al., 2020). Using data from the Dutch Melanoma Treatment Registry (DMTR), a nationwide

JB and FH should be considered joint first author.

registry of all Stage III and IV melanoma patients established in 2013 (Jochems et al., 2017), a Dutch validation cohort was established.

We retrieved DMTR data from melanoma patients with irresectable or metastatic melanoma who received first-line treatment with anti-PD-1 (including combination therapy with ipilimumab) or a BRAF-based therapy. This included data on sex, *BRAF*-mutation status, performance status, baseline serum LDH, disease stage (American Joint Committee on Cancer 8th edition), presence of brain metastases, date of treatment initiation, age at time of treatment initiation, and response to treatment. Patients who initiated treatment after November 1, 2021 were excluded for our analyses. Progression-free survival (PFS) and OS were calculated from the day of treatment initiation. Progression included both radiological disease progression or death from any cause. Statistical analysis was performed using the same statistical methods and scripts as used for the Danish analyses (see the paper by Ellebaek et al. for full description) (Ellebaek et al., 2022). Of note, because of the complexity of obtaining data sharing agreements necessary to directly compare both cohorts from their nationwide registries, this analysis could not be performed.

A total of 2772 patients treated with anti-PD-1, and 2763 patients treated with BRAF-inhibitors were included in our analyses (Table 1). Of the patients treated with anti-PD-1, 1421 (51%) initiated treatment in winter (defined as treatment initiation between October 1 and March 31), and 1351 (49%) in summer (defined as treatment initiation between April 1 and September 30th); in the BRAF-inhibitor group this was 1399 (51%) and 1364 (49%), respectively. An overview of all patient characteristics can be found in Table 1.

When looking at the entire anti-PD-1 cohort, OS was comparable across seasons with a median OS of 29 months in summer versus 27 months in winter (Figure 1a; HR 0.99, 95% CI 0.88–1.10, $p = .79$). Likewise, the median PFS did not show differences between summer and winter (12 months in both) (Figure 1b; HR 0.97, 95% CI 0.88–1.07, $p = .55$). In Denmark a survival benefit was found in *BRAF* WT patients who initiated treatment with anti-PD-1 in the summer months. Therefore, we performed a similar subgroup analysis and, with a median OS of 23 months in summer and 24 in winter (Figure 1c,d; HR 0.99, 95% CI 0.84–1.16, $p = .90$), we were not able to confirm the

TABLE 1 Patient characteristics per treatment arm.

	BRAF-inhibitor cohort				Anti-PD-1 cohort			
Characteristic	Overall, $N = 2{,}763$[a]	Winter, $N = 1{,}399$[a]	Summer, $N = 1{,}364$[a]	p-Value[b]	Overall, $N = 2{,}772$[a]	Winter, $N = 1{,}421$[a]	Summer, $N = 1{,}351$[a]	p-Value[b]
Age first treatment	62 (52, 70)	61 (51, 70)	62 (52, 71)	.022*	67 (56, 75)	66 (56, 74)	67 (56, 75)	.041*
BRAF status				>.999				.039*
BRAF mutant	2677 (98%)	1353 (98%)	1324 (98%)		1387 (52%)	733 (54%)	654 (50%)	
BRAF wild type	48 (1.8%)	24 (1.7%)	24 (1.8%)		1263 (48%)	616 (46%)	647 (50%)	
Missing	38	22	16		122	72	50	
Treatment line				.653				.236
First	2278 (82%)	1158 (83%)	1120 (82%)		2216 (80%)	1123 (79%)	1093 (81%)	
Other	485 (18%)	241 (17%)	244 (18%)		556 (20%)	298 (21%)	258 (19%)	
Brain metastasis				.358				.210
0	1468 (57%)	753 (58%)	715 (56%)		1846 (75%)	961 (76%)	885 (74%)	
1	1092 (43%)	540 (42%)	552 (44%)		621 (25%)	305 (24%)	316 (26%)	
Missing	203	106	97		305	155	150	
Stage				.950				.894
M1a/M1b	289 (11%)	147 (11%)	142 (11%)		704 (28%)	358 (28%)	346 (28%)	
M1c/M1d	2348 (89%)	1188 (89%)	1160 (89%)		1821 (72%)	932 (72%)	889 (72%)	
Missing	126	64	62		247	131	116	
LDH				.817				>.999
Normal	1302 (48%)	665 (49%)	637 (48%)		1955 (72%)	1002 (72%)	953 (72%)	
High	1390 (52%)	703 (51%)	687 (52%)		766 (28%)	392 (28%)	374 (28%)	
Missing	71	31	40		51	27	24	
PS				.224				.234
PS = 0–1	1815 (75%)	934 (76%)	881 (74%)		2397 (92%)	1249 (93%)	1148 (92%)	
PS>/=2	611 (25%)	297 (24%)	314 (26%)		196 (7.6%)	93 (6.9%)	103 (8.2%)	
Missing	337	168	169		179	79	100	

[a]Median (IQR); *n* (%).

[b]*$p < .05$; **$p < .01$; ***$p < .001$.

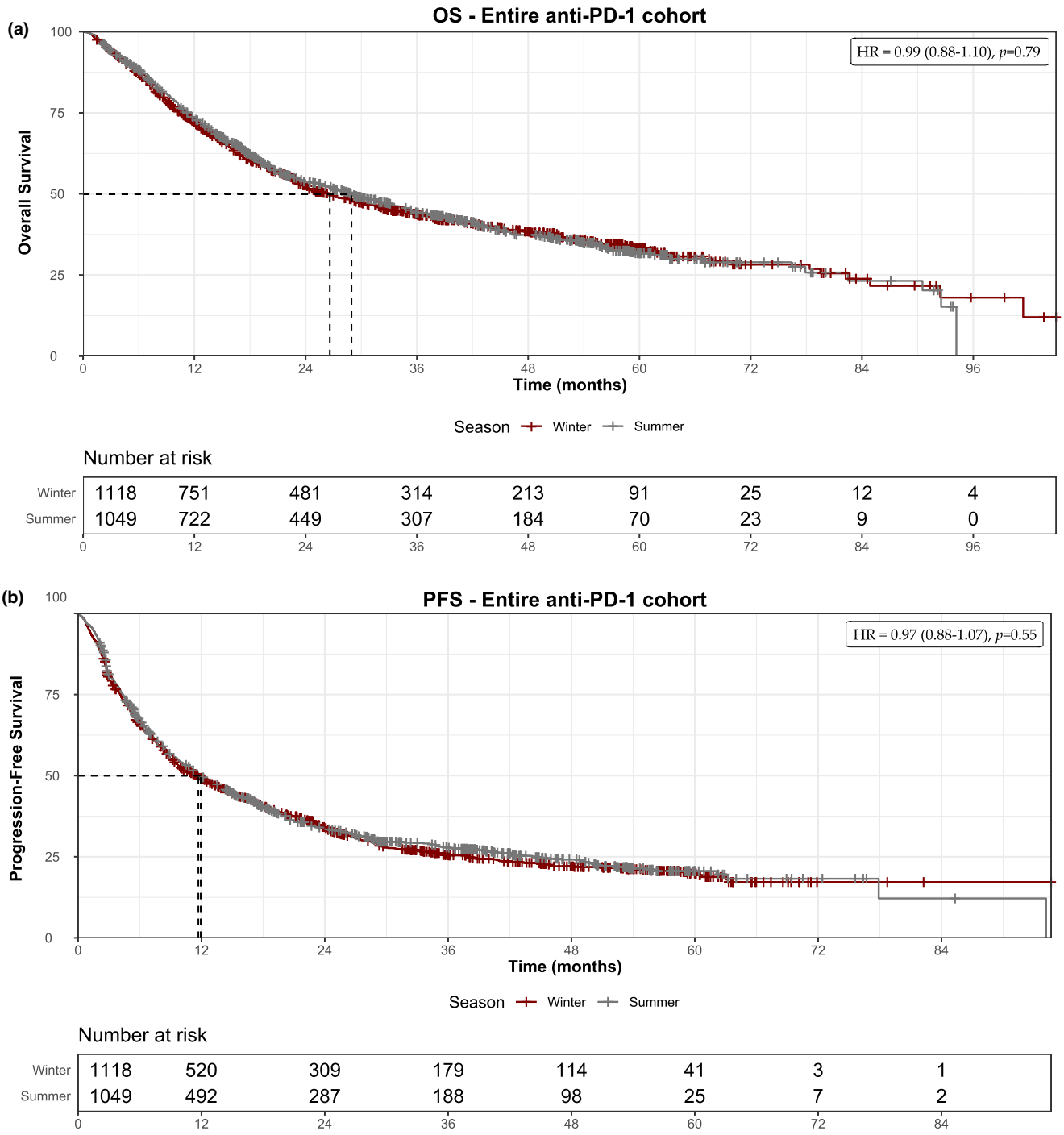
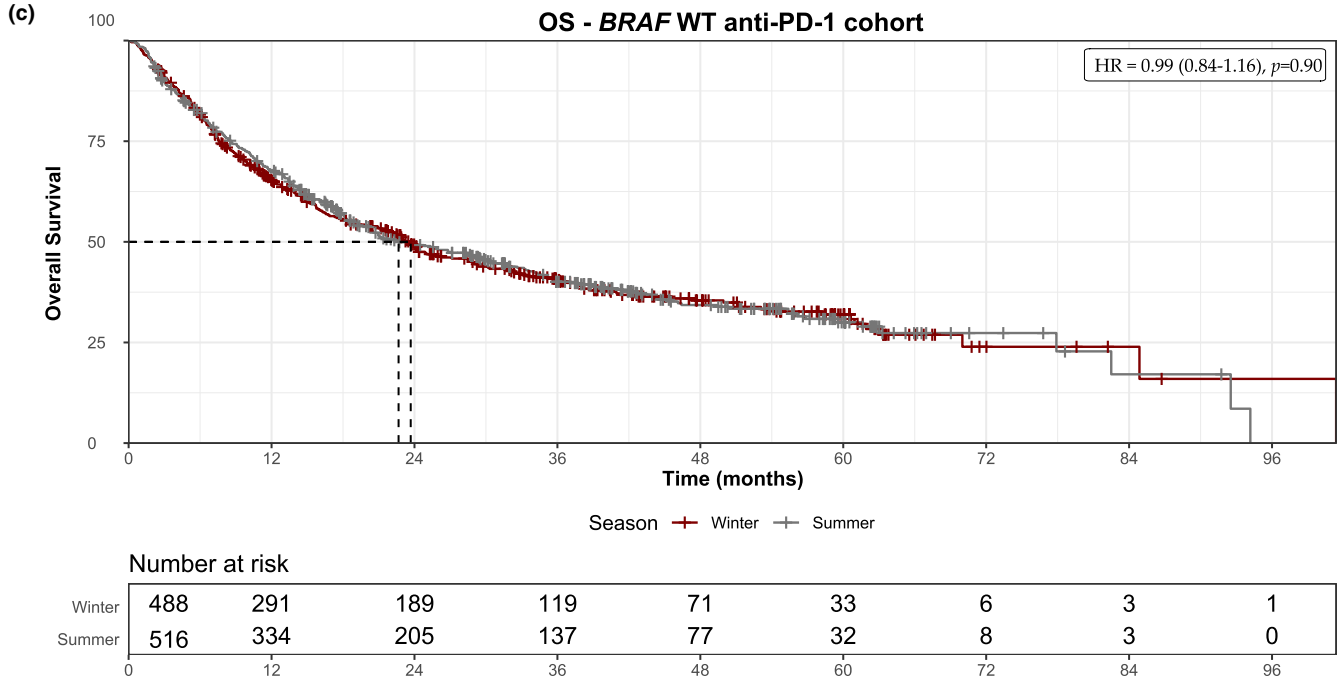


FIGURE 1 (Continued)

Danish findings in our Dutch patient cohort. Furthermore, when looking at our BRAF-based therapy cohort, a median OS of 11 (Figure S1a; HR 0.98, 95% CI 0.89–1.08, $p = .72$) and a median PFS of 8 months (Figure S1b; HR 0.98, 95% CI 0.89–1.07, $p = .61$) was found across both seasons, respectively. Multivariable analysis confirmed that absence of brain metastases, M1a/M1b disease, normal baseline LDH and a performance score ≤1 were associated with a longer median OS and PFS for both patient cohorts (Figure S2a–d).

In summary, seasonal variation could be a host-extrinsic factor influencing the response to ICI-treatment. This hypothesis was illustrated by an important, recently published Danish study which showed that *BRAF* WT melanoma patients who initiated anti-PD-1 treatment in summer had a better overall survival compared to patients who started treatment in winter (Ellebaek et al., 2022). To confirm this novel finding in a comparable patient population, a larger Dutch validation cohort was established. In this study, we did not



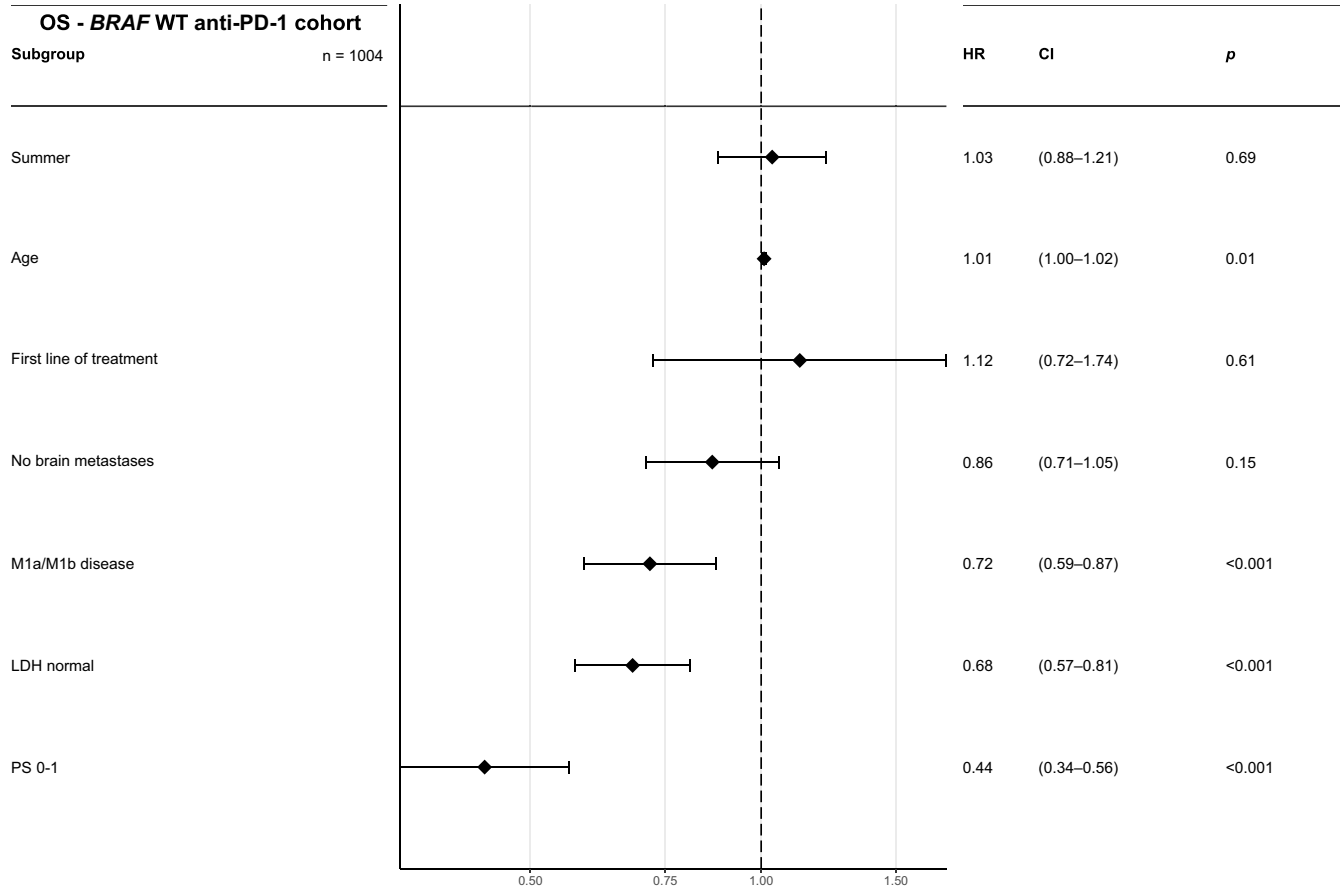


FIGURE 1 Seasonal survival outcomes anti-PD-1 cohort. Median overall (a) and progression-free survival (b) survival for all patients who initiated treatment with anti-PD-1 in summer (gray) or winter (red). Overall survival subgroup analysis of *BRAF* wild type patients (c). Hazard ratio, 95% confidence intervals, *p*-value and number at risk are depicted in each graph. Forest plot showing subgroup multivariable analyses on *BRAF* wild type patients treated with anti-PD-1 (d).

observe a similar seasonal variation in immunotherapy outcomes and we are thus unable to confirm the Danish findings. However, as we were unable to directly compare the Dutch and Danish patient cohorts, we were therefore unable to identify other underlying cohort-specific factors that may explain the difference in our findings. Validation of either the Dutch or Danish findings in (combined) patient cohorts from other countries would be a necessary first step before further attempts are made to identify specific factors associated with seasonal changes that may influence the outcomes for these patients.

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AUTHOR CONTRIBUTIONS

Conception and design: JB, FB, and JH. Collection of data: DMTR working group (OvN, AvdE, CB, MA, FvdB, JdG, GH, EK, DP, RvR, ASdB, AvdV, GV, MBS, MW, and KS). Data analysis and interpretation: JB, FB, AS, OvN, JvT, and JH. Manuscript writing: JB, FB, and HvT. All authors reviewed and approved the final manuscript before submission.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The Dutch Melanoma Treatment Registry (DMTR) patient data used for the study are not publicly available due to Dutch privacy regulations, but can be requested via the Dutch Institute for Clinical Auditing (https://dica.nl/dmtr/onderzoek).

ETHICS STATEMENT

In compliance with Dutch regulations, research using DMTR data were approved by a Medical Ethical Committee (METC, Leiden University Medical Center, 2013), and not considered subject to the Medical Research Involving Human Subjects Act.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.