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Abstract
Melanoma is a highly immunogenic cancer, and circannual rhythms influence the activity of the immune system. We retrospectively collected information on all cases with metastatic melanoma (ocular melanoma excluded) that initiated treatment with BRAF-inhibitor-based therapy (BRAFi) or anti-PD-1 monotherapy (PD-1). Cases were divided in two groups based on treatment initiation in the summer half-year (April to September) or winter half-year (October to March). We collected a total of 1054 (BRAFi) and 1205 (PD-1) patient cases. Median follow-up was 39.7 (BRAFi) and 47.5 (PD-1) months. We did not observe differences in outcomes across patients who were treated in summer versus winter in the BRAFi cohort. Furthermore, we did not observe significant differences in ORR, CRR, and PFS in the PD-1 cohort. However, in patients with BRAF wild-type disease of the PD-1 cohort, treatment initiation in summer was associated with an improved OS (mOS 39.7 months [summer] versus 21.3 months [winter]; HR 0.70, 95% CI 0.57–0.86, p = .0007). This result remained robust to multivariable proportional hazards adjustment (HR 0.70, 95% CI 0.57–0.87, p = .001). Initiation of immunotherapy in summer is associated with prolonged survival in patients with BRAF wild-type melanoma living in Denmark.

Keywords
anti-PD-1, environment, immunotherapy, melanoma, season

1 | BACKGROUND
An increasing body of evidence highlights the role of host-extrinsic factors to influence the outcome of immunotherapies (Morad et al., 2021). Fueled by findings attributing a primary role to the gut microbiota in regulating anticancer immune responses, studies investigating dietary composition (Spencer et al., 2021) and the circadian rhythm (Qian et al., 2021) document a primary role of the exposome to impact cancer immunobiology and response to immunotherapies.

Perhaps the largest environmental variations with implications in ecological dynamics of a territory, influencing cyclically all natural systems including human life, depend on periodic seasonal changes. In regions with temperate and continental climates, cycles with cold and dark winters, alternated to hot and light summers, seasonal changes arguably influence essentially multiple aspects of human activities, including but not limited to diet, sun exposure, pathogen exposure, and indoor-outdoor stays. It is therefore not surprising that circannual rhythms influence periodically human immunobiology, with a prominent pro-inflammatory profile during temperate
and continental winters (Dopico et al., 2015; Wyse et al., 2021). Within human pathology, it is well established that circannual rhythms influence infectious diseases (Martinez, 2018), cardiovascular (Stewart et al., 2017), autoimmune (Watan et al., 2017), and psychiatric (Zhang et al., 2021) conditions. Yet, it is still largely unclear how seasonality influence disease activities, as the influence of seasonal changes on human diseases have been understudied (White & Hastings, 2020). For infectious diseases, Dowell hypothesized in 2001 the existence of an endogenous circannual rhythmicity in host immunity that generates cycles of enhancement and suppression of immune function, leading to windows of vulnerability to certain infections (Dowell, 2001).

To investigate associations between seasonality and outcome of treatments activating the immune system, we conducted a retrospective study on a nationwide cohort (Frank, 2000) of patients with advanced melanoma living in a geographical area with large winter-summer seasonal changes, who received anti-PD-1 over a span of almost a decade.

2 | METHODS

2.1 | Patient selection

The Danish Metastatic Melanoma Database (DAMMED) is a nationwide registry with an estimated coverage of >95% of the resident population in Denmark diagnosed with advanced melanoma, described extensively elsewhere (Ellebaek et al., 2021). We retrieved from DAMMED all cases with unresectable or metastatic melanoma (patients with resected metastatic melanoma receiving adjuvant immunotherapy or ocular melanoma were excluded) that received an anti-PD-1 monotherapy regimen (referred to as anti-PD-1), or a BRAF inhibitor with or without a MEK inhibitor (referred to as BRAFi).

2.2 | Data retrieved

We retrieved data on gender, BRAF mutation status, type of therapy, treatment line, best overall response; relative to treatment initiation: month of the year, age, disease stage (according to American Joint Committee on Cancer 8th edition), Eastern Oncology Cooperative Group performance status (PS), serum lactate dehydrogenase (LDH), presence of brain metastases, progression-free survival (PFS), and overall survival (OS). PFS and OS were calculated from the day of treatment initiation. For disease stage, stage III unresectable disease was recorded as stage IV M1a. Only patients who initiated treatment before 30 September 2021 were included, and the date for database lock was 18 February 2022.

2.3 | Statistical analysis

Patient characteristics were summarized using descriptive statistics for continuous, categorical, and dichotomous variables. For continuous variables, groups were compared with the non-parametric Wilcoxon rank-sum test, while for categorical variables groups were compared using either Pearson's Chi-squared test or Fisher's exact test. Median follow-up was calculated with the reverse Kaplan–Meier method. Non-parametric survival analyses were performed using the Kaplan–Meier method for PFS and OS. Hazard ratio with 95% confidence intervals calculated using Mantel–Haenszel is displayed along with the associated log-rank (Mantel–Cox) \( p \)-values. Multivariable cox proportional hazards regression analysis was performed to further explore the prognostic effect of the variables included in the study and their inter-dependence. Statistical analyses were carried out using GraphPad Prism 9.3.1 (GraphPad Software) and R studio 2021.09.1 + 372 (Rstudio Public-Benefit Corporation) using the survivalAnalysis (Wiesweg, 2021) and gtsmsyary (Sjoberg et al., 2021) packages. Values of \( p < .05 \) were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics and treatments

We retrieved a total of 1054 patients treated with BRAFi (n = 192 with vemurafenib [+/- cobimetinib], n = 580 with dabrafenib [+/- trametinib] and n = 282 with encorafenib [+/- binimetinib]) and 1205 patients treated with anti-PD-1 (n = 32 with nivolumab and n = 1173 with pembrolizumab). To understand whether the time of the year for treatment initiation influenced patient characteristics and outcomes, we divided patients treated with BRAFi or anti-PD-1 into two groups who started treatment between 1 October and 31 March (winter) or 1 April and 31 September (summer). In the BRAFi cohort, the total amount of patients was 522 in winter and 532 in summer; in the anti-PD-1 cohort, 640 patients initiated treatment in winter and 565 in summer. Baseline and treatment characteristics are depicted in Table 1. No major differences were observed across seasons, except in the anti-PD-1 cohort where a larger proportion of patients who initiated treatment in winter had BRAF wild-type disease (62% versus 55%, \( p = .025 \)). In the BRAFi cohort, a large proportion of patients had poor baseline prognostic factors, reflecting the national treatment strategy with the use of this drug class in patients with more aggressive disease features. The BRAFi cohort only reports clinical results on BRAF mutant patients.
3.2 | Clinical outcomes based on time of the year for treatment initiation in the BRAFi and anti-PD-1 cohorts

We investigated differences among patients who initiated treatment in winter and summer. Median follow-up was 39.7 and 47.5 months for patients in the BRAFi cohort and in the anti-PD-1 cohort, respectively. Overall response rates (ORR) and complete response rates (CRR) were similar across seasons in both cohorts. In the BRAFi cohort, a 61.0% ORR and 9.6% CRR were reported in summer, with a 60.0% ORR and 8.1% CRR in winter (\( p = .80 \) for ORR and \( p = .44 \) for CRR). In the anti-PD-1 cohort, a 46.5% ORR and 20.4% CRR were reported in summer, with a 47.5% ORR and 23.1% CRR in winter (\( p = .73 \) for ORR and \( p = .29 \) for CRR).

Also, PFS were comparable across seasons in the BRAFi cohort, with a median PFS of 5.9 months in summer versus 5.5 months in winter (HR 0.95, 95% CI 0.83–1.08, \( p = .43 \); Figure 1a); similar results were observed for OS, with a median OS of 9.6 months in summer versus 9.4 months in winter (HR 0.96, 95% CI 0.84–1.10, \( p = .53 \); Figure 1b). Multivariable analyses confirmed known prognostic factors being predictive of PFS and OS in the BRAFi cohort (Figure S1).

In the anti-PD-1 cohort, median PFS was 8.6 months in summer versus 8.2 months in winter (HR 0.90, 95% CI 0.79–1.04, \( p = .15 \); Figure 1c), and median OS was 32.5 in summer versus 24.3 months in winter (HR 0.80, 95% CI 0.69–0.94, \( p = .0056 \); Figure 1d). Multivariable analyses confirmed that the time of the year for treatment initiation was independently predicting improved OS, but not PFS, alongside other known prognostic features (Figure S1). In conclusion, treatment initiation with anti-PD-1 in summer was associated with improved OS in the overall population.

3.3 | Clinical outcomes based on time of the year for treatment initiation in the anti-PD-1 cohort, according to BRAF status

Next, we investigated whether the OS differences observed above were driven by defined patient subgroups. BRAFi are only

---

**TABLE 1** Baseline and treatment characteristics of the BRAFi-treated patient cohort and of the anti-PD-1-treated patient cohort, grouped by time of the year for treatment initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRAFi inhibitor-treated patient cohort</th>
<th>Anti-PD-1 treated patient cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall, ( N = 1053^a )</td>
<td>Overall, ( N = 1205^a )</td>
</tr>
<tr>
<td></td>
<td>Winter, ( N = 522^a )</td>
<td>Winter, ( N = 640^a )</td>
</tr>
<tr>
<td></td>
<td>Summer, ( N = 531^a )</td>
<td>Summer, ( N = 565^a )</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>Median (IQR); ( n ) (%)</td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td><strong>BRAF status</strong></td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>BRAF mutant</td>
<td>1053 (100%)</td>
<td>698 (59%)</td>
</tr>
<tr>
<td><strong>BRAF wild type</strong></td>
<td>0 (0%)</td>
<td>489 (41%)</td>
</tr>
<tr>
<td><strong>BRAF missing</strong></td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td><strong>Brain metastases</strong></td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>Present</td>
<td>398 (38%)</td>
<td>193 (16%)</td>
</tr>
<tr>
<td><strong>Absent/unknown</strong></td>
<td>655 (62%)</td>
<td>1012 (84%)</td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>M1a/M1b</td>
<td>173 (16%)</td>
<td>492 (41%)</td>
</tr>
<tr>
<td>M1c/M1d</td>
<td>880 (84%)</td>
<td>713 (59%)</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>Normal</td>
<td>393 (39%)</td>
<td>377 (67%)</td>
</tr>
<tr>
<td>Elevated</td>
<td>611 (61%)</td>
<td>388 (33%)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>49</td>
<td>45</td>
</tr>
<tr>
<td><strong>PS</strong></td>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>PS 0–1</td>
<td>718 (68%)</td>
<td>1055 (88%)</td>
</tr>
<tr>
<td><strong>PS ≥2</strong></td>
<td>334 (32%)</td>
<td>150 (12%)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\)Median (IQR); \( n \) (%). 
\(^b\)\(*\ p < .05; **\( p < .01; ***\( p < .001.\)
administered to patients with BRAF mutant melanoma, highlighting an intrinsic difference between the two cohorts analyzed in this study. To investigate whether BRAF mutational status could identify patients with distinct outcomes when initiating immunotherapy at different times of the year, we segregated patients in the anti-PD-1 cohort by the detection of BRAF mutations. Baseline and treatment characteristics, according to BRAF status, are displayed in Table 2. Patients with BRAF wild-type disease were older in average (mean...
73 versus 66 years, \( p < .001 \)), and a larger proportion was treated with anti-PD-1 in first-line (mean 79% versus 62%, \( p < .001 \)) and had a PS \( \geq 2 \) (mean 15% versus 8.6%, \( p < .001 \)). Overall, patients with BRAF wild-type disease receiving anti-PD-1 had superior PFS but not OS compared to patients with BRAF mutant disease (Figure S2a,b).

Baseline and treatment characteristics, according to time of the year for initiation of anti-PD-1 therapy for BRAF wild-type and BRAF mutant patients, respectively, are displayed in Supplementary material, Table 1. No major differences across seasons were observed. In patients with BRAF wild-type disease (\( n = 698 \)), median PFS was 10.7 months in summer versus 8.1 months in winter (HR 0.84, 95% CI 0.70–1.01, \( p = .07 \); Figure 2a); median OS was 39.7 months in summer versus 21.3 months in winter (HR 0.70, 95% CI 0.57–0.86, \( p = .0007 \); Figure 2b). In contrast, in patients with BRAF mutant disease (\( n = 489 \)), median PFS was 6.3 months in summer versus 8.0 months in winter (HR 0.98, 95% CI 0.80–1.21, \( p = .88 \); Figure 2c); median OS was 30.3 months in summer versus 31.8 months in winter (HR 0.99, 95% CI 0.78–1.25, \( p = .91 \); Figure 2d). Multivariable analyses confirmed that the time of the year for treatment initiation was independently predicting improved OS, but not PFS, alongside other known prognostic features in patients with BRAF wild-type disease (Figure 3a,b).

Overall, the superior OS outcomes when anti-PD-1 is initiated in summer were largely driven by patients with BRAF wild-type disease.

### 4 | DISCUSSION

While the access to anti-PD-1 immunotherapy for patients with melanoma have increased globally, and with longer follow-up of treatments within large real-world patient cohorts, we are starting to appreciate how host-extrinsic factors influence clinical outcomes of patients treated with immune checkpoint inhibitors.

Denmark was one of the first countries in the world where anti-PD-1 was made universally available to patients with unresectable or metastatic melanoma, with widespread adoption since July 2014 through an early-access program and since September 2015 as standard of care. In addition, Denmark is a prototype for all-country real-world cohort studies (Frank, 2000) and the DAMMED (Ellebaek et al., 2021) allows such investigations in melanoma. With predominantly humid continental and partly oceanic climate (Dfb and Cfb, according to the Köppen classification; Beck et al., 2018), Denmark has cold dark winters and pleasant moderately sunny summers with mean temperatures of 1.5 and 16.9°C, and a mean of 2.15 and 12.26 h of sunshine in January and June–July (Klima Danmark, n.d.; Klimanormaler Danmark, n.d.), respectively. The diversity of local fruits and vegetables for human consumption is also reduced during winter months (Frugt og grønt, n.d.), leading to a potentially reduced intake of healthier nutrients, or different diet due to imported vegetables in winter months and thereby potentially an altered gut microbiota.

The data presented in this manuscript report superior OS outcomes in BRAF wild-type patients with metastatic melanoma, who initiated treatment with anti-PD-1 monotherapy in the summer-half of the year. In contrast, no major differences were observed in patients treated with BRAF inhibitor-based therapies or in the BRAF mutant population of patients treated with anti-PD-1. While confirming the prognostic value of known patient (e.g., PS), disease (e.g., brain metastases or LDH level), and treatment (e.g., first-line treatment) characteristics, multivariable analyses indicated the independence of the time of the year for

**FIGURE 2** Survival outcomes based on time of the year for treatment initiation among patients with BRAF mutant or BRAF wild-type metastatic melanoma, treated with anti-PD-1 monotherapy in Denmark. (a) Progression-free survival and (b) overall survival with BRAF wild-type disease in the anti-PD-1 cohort; (c) Progression-free survival and (d) overall survival with BRAF Mutant disease in the anti-PD-1 cohort. Survival analysis was performed using the Kaplan–Meier method. Hazard ratio (HR) with 95% confidence intervals (CI) calculated using Mantel–Haenszel is displayed along with the associated log-rank (Mantel-Cox) \( p \)-values.
treatment initiation as a predictor of longer OS in patients with BRAF wild-type disease treated with anti-PD-1. The time of the year for treatment initiation did not influence rates of tumor regression; in addition, as shown in previous immunotherapy studies (e.g., Borghaei et al., 2015), the absence of statistically significant differences in PFS did not preclude improved survival in patients with BRAF wild-type disease initiating treatment in the summer-half of the year.

Importantly, while the group with BRAF mutant disease within the anti-PD-1 cohort may be too small to detect small survival differences, we detected no major differences in this subgroup of patients depending on the season for treatment initiation, in sharp contrast to patients with BRAF wild-type disease treated with anti-PD-1. Our study cannot rule out a specific biology of BRAF wild-type disease when metastatic disease is diagnosed in the summer half-year. Additionally, specific characteristics of BRAF wild-type disease leading to a better prognosis when any given treatment is initiated in summer cannot be ruled out and should be investigated in future studies. However, BRAFi are available only for patients with BRAF mutant disease; therefore, an intrinsic difference between BRAF wild type and BRAF mutant patients in all immunotherapy-treated cohorts is due to physician’s choice. In Denmark, this will typically lead to initiation of treatment with BRAFi in patients with poor prognosis (Keilholz et al., 2020). This is also indicated by poor prognostic features of patients with BRAF wild-type disease treated with anti-PD-1 in our cohort. In Checkmate-067, patients treated with first-line nivolumab had a median PFS of 5.6 months (CI 95% 2.8–9.5) if BRAF mutant and 8.2 months (CI 95% 5.1–19.6) if BRAF wild type (Wolchok et al., 2022). Even though Checkmate-067 was not powered to detect differences across these subgroups, the numerical PFS advantage suggests that patients with BRAF wild-type disease may obtain increased benefits from anti-PD-1 monotherapy; these results may translate to our findings, making the “seasonal” effect more evident in the BRAF wild-type subgroup.

The original hypothesis of this study was to investigate a potential booster effect of influenza vaccinations on immunotherapy. Campaigns of influenza vaccination in Denmark typically start in October and cover a significant fraction of patients with melanoma (internal observation). To our surprise, results on survival analyses were opposite to our expectations; nonetheless, large differences in vaccination rates between summer and winter seasons in the pre- and presumably post-COVID 19 era may add one additional variable to immune-influencing activities associated with periodic seasonal changes. A plethora of other factors including and certainly not limited to psychological, dietary, hormonal, and infectious variables potentially influencing both cancer and the immune response to cancer, are subject to periodic seasonal changes. It is unclear how—and which—of these factors are important to improve survival following treatment with anti-PD-1 immunotherapy in melanoma.

This is a study conducted within a single homogeneous country of relatively small size (5.8 million residents) and with specific periodic seasonal changes; it is important to clarify whether results obtained in Denmark can be generalized to other countries with similar climate characteristics, and whether distinct climates can associate to different outcomes. It is not surprising that a seasonal difference in OS outcomes was not identified in previous randomized phase III trials, as these studies were typically conducted in multi-geographical settings, and the number of patients in each geographical area was unlikely to be sufficiently powered to detect OS differences.

In conclusion, our study adds another piece to the puzzle of host-extrinsic factors influencing the clinical outcomes of patients with cancer treated with immune-based therapies. Additional efforts to validate these results in other geographical areas with both similar and different periodic seasonal changes should be undertaken. Future identification of specific factors associated with periodic seasonal changes, influencing clinical outcomes of patients with melanoma, may lead to further improvement of current treatment strategies.

**AUTHOR CONTRIBUTIONS**

EE: conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; writing-original draft; writing-review and editing. AS: methodology, formal analysis, data curation, writing-review and editing. HS: conceptualization; data curation; formal analysis; investigation; writing-original draft. LB: funding acquisition; project administration; resources; supervision; writing-review and editing. IMS: funding acquisition; project administration; resources; supervision; writing-review and editing. MD: conceptualization; data

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**FIGURE 3** Multivariable analyses on BRAF wild-type patients in the anti-PD-1 cohort. Multivariable analyses using a cox proportional regression analyses on progression-free survival (a) and overall survival (b) for patients with BRAF wild-type disease in the anti-PD-1 cohort.
curation; formal analysis; investigation; methodology; supervision; validation; visualization; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST
EE received honoraria from BMS, Pierre Fabre, Novartis for consultations and lectures, and travel/conference expenses from MSD. MD has received honoraria for lectures from Roche (past 2 years) and received access to research data from Bristol Myers Squibb and from Genentech. Within the last 2 years, IMS has received honoraria for consultancies and lectures from IO Biotech, Novartis, MSD, Pierre Fabre, BMS, Novo Nordisk, TILT Bio; research grants from IO Biotech, BMS, Lytx, Adaptimmune, TILT Bio. All other authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study can be made available via application to the Danish Metastatic Melanoma Database steering committee. Further details are available from the corresponding author upon request.

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