



Universiteit
Leiden
The Netherlands

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

Borgers, J.S.W.; Burgers, F.H.; Schina, A.; Not, O.J. van; Eertwegh, A.J.M. van den; Blank, C.U.; ... ; Haanen, J.B.A.G.

Citation

Borgers, J. S. W., Burgers, F. H., Schina, A., Not, O. J. van, Eertwegh, A. J. M. van den, Blank, C. U., ... Haanen, J. B. A. G. (2023). Seasonal variation of anti-PD-1 outcome in melanoma-Results from a Dutch patient cohort. *Pigment Cell & Melanoma Research*, 37(1), 15-20. doi:10.1111/pcmr.13117

Version: Publisher's Version
License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)
Downloaded from: <https://hdl.handle.net/1887/3753835>

Note: To cite this publication please use the final published version (if applicable).

The official journal of

INTERNATIONAL FEDERATION OF PIGMENT CELL SOCIETIES · SOCIETY FOR MELANOMA RESEARCH

PIGMENT CELL & MELANOMA Research

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

J. S. W. Borgers | F. H. Burgers | A. Schina | O. J. Van Not |
A. J. M. van den Eertwegh | C. U. Blank | M. J. B. Aarts |
F. W. P. J. van den Berkmortel | J. W. B. de Groot | G. A. P. Hospers |
E. Kapiteijn | D. Piersma | R. S. van Rijn | A. M. Stevense-den Boer |
A. A. M. van der Veldt | G. Vreugdenhil | M. J. Boers-Sonderen |
M. W. J. M. Wouters | K. P. M. Suijkerbuijk | J. V. van Thienen |
J. B. A. G. Haanen

DOI: [10.1111/pcmr.13117](https://doi.org/10.1111/pcmr.13117)

Volume 37, Issue 1, Pages 15-20

If you wish to order reprints of this article,
please see the guidelines [here](#)

Supporting Information for this article is freely available [here](#)

EMAIL ALERTS

Receive free email alerts and stay up-to-date on what is published
in Pigment Cell & Melanoma Research – [click here](#)

Submit your next paper to PCMR online at <http://mc.manuscriptcentral.com/pcmr>

Subscribe to PCMR and stay up-to-date with the only journal committed to publishing
basic research in melanoma and pigment cell biology

As a member of the IFPCS or the SMR you automatically get online access to PCMR. Sign up as
a member today at www.ifpcs.org or at www.societymelanomaresearch.org



To take out a personal subscription, please [click here](#)

More information about Pigment Cell & Melanoma Research at www.pigment.org

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. 2.2h 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, Ministry 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 composition (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.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Pigment Cell & Melanoma Research* published by John Wiley & Sons Ltd.

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.

Characteristic	BRAF-inhibitor cohort				Anti-PD-1 cohort			
	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	

^aMedian (IQR); n (%).

^b* $p < .05$; ** $p < .01$; *** $p < .001$.

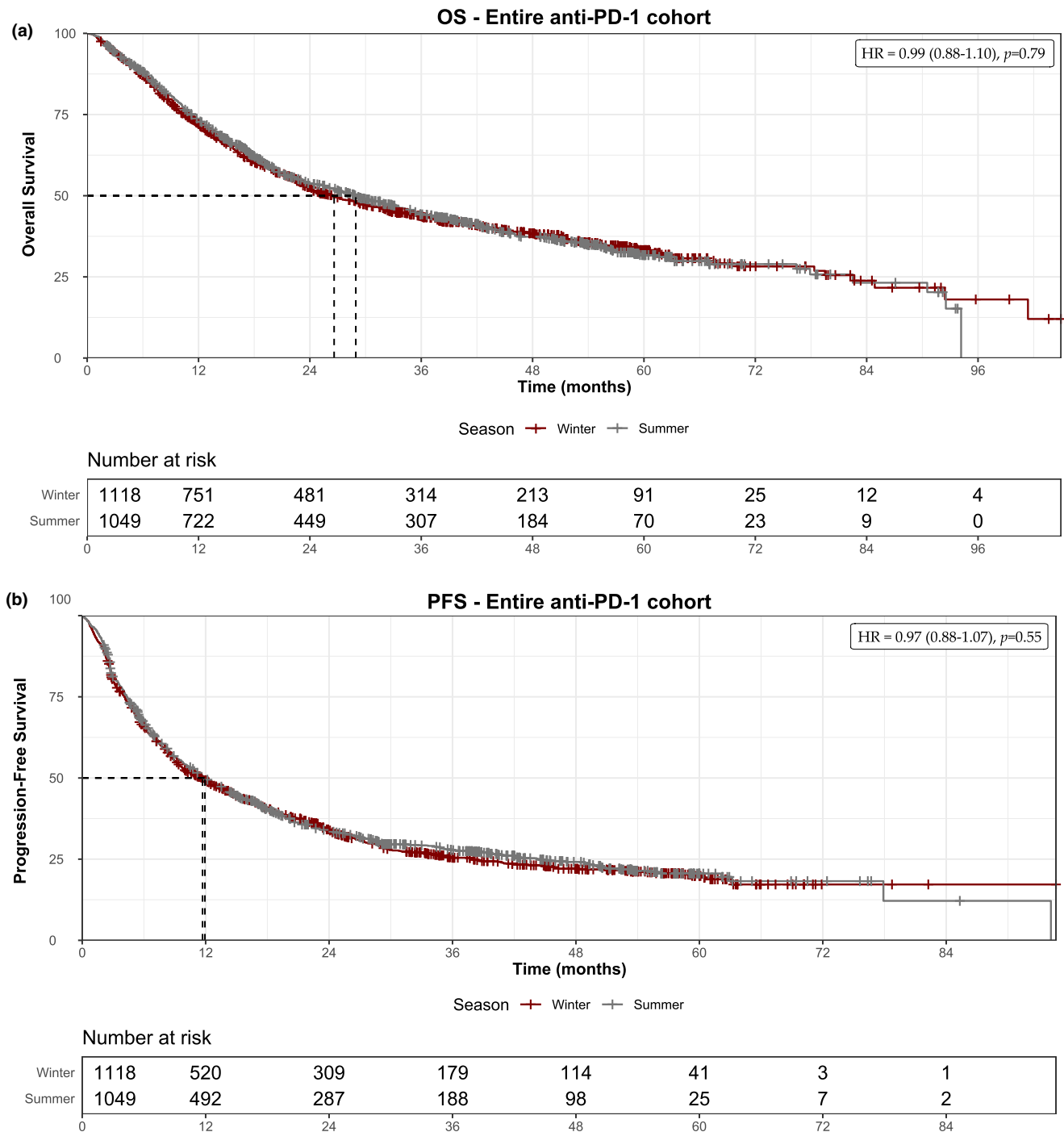


FIGURE 1 (Continued)

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

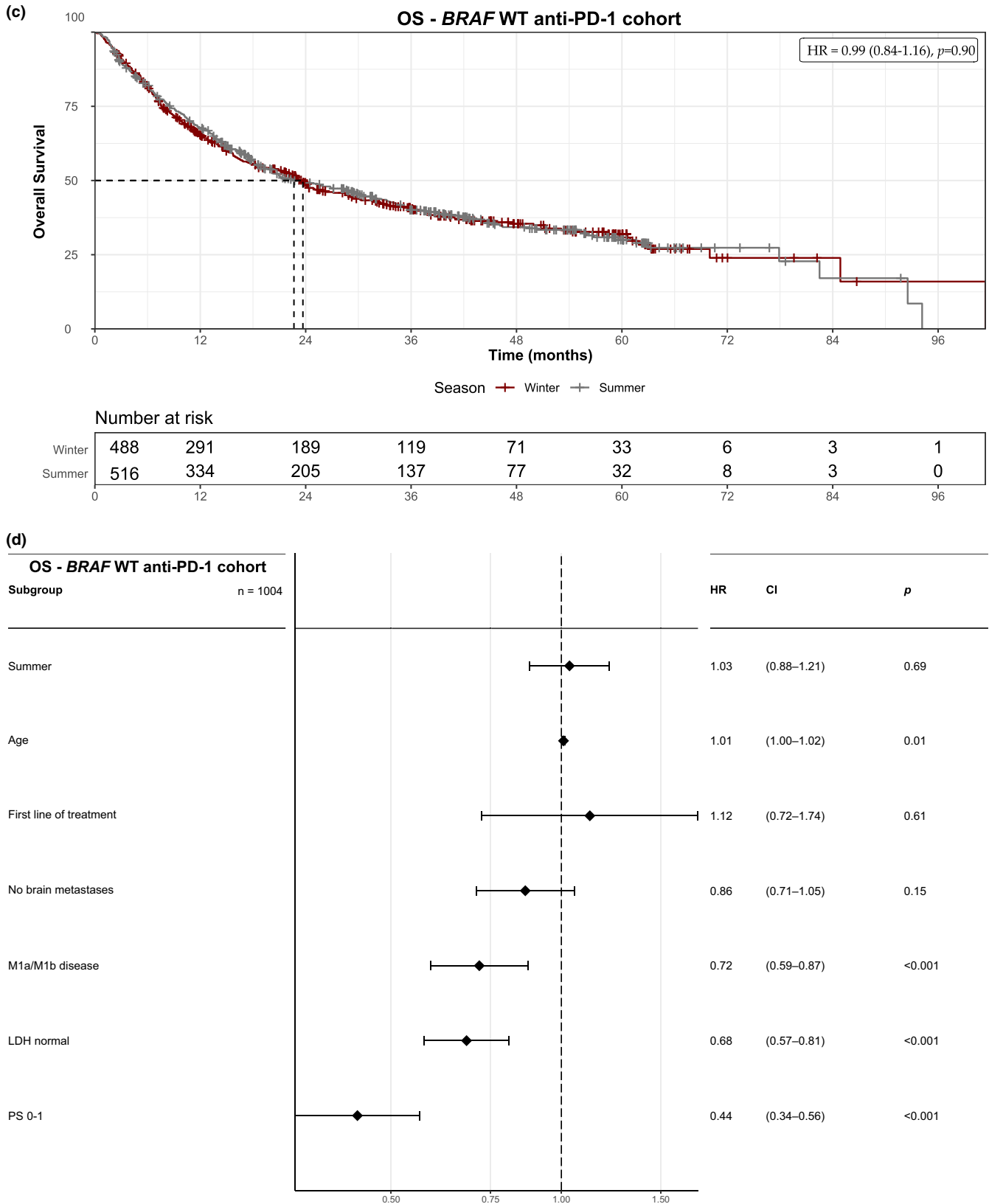


FIGURE 1 Seasonal survival outcomes anti-PD-1 cohort. Median overall (a) and progression-free survival (b) survival for all patients who initiated treatment with anti-PD-1 in summer (gray) or winter (red). Overall survival subgroup analysis of BRAF wild type patients (c). Hazard ratio, 95% confidence 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.

FUNDING INFORMATION

No funding was obtained for this manuscript. The Dutch Institute for Clinical Auditing (DICA) foundation received a start-up grant for the Dutch Melanoma Treatment Registry (DMTR) from The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002). The DMTR is structurally funded by Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis, and Roche Pharma. Roche Pharma ended their funding in 2019, and Pierre Fabre started funding the DMTR in 2019.

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.

ACKNOWLEDGMENTS

We would like to thank all the patients who are part of the DMTR dataset, the physicians and data managers who registered the patients in the DMTR, and Marco Donia, Eva Ellebaek, and Inge Marie Svane for the invitation to write this letter and the interesting discussions about our data.

CONFLICT OF INTEREST STATEMENT

A.J.M. van den Eertwegh has received research study Grants not related to this paper from Sanofi, Roche, Bristol-Myers Squibb, TEVA, and Idera; received travel expenses from MSD Oncology, Roche, Pfizer, and Sanofi; and received speaker honoraria from Bristol-Myers Squibb and Novartis. C.U. Blank has received commercial research Grants from Novartis, BristolMyers Squibb, and NanoString; is a paid advisory board member for Bristol Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, GenMab, and Pierre Fabre; and holds ownership interest in Uniti Cars, Neon Therapeutics, and Forty Seven. M.J.B. Aarts has received advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, and Bayer, and research Grants from Merck-Pfizer, not related to the current work and paid to the institute. J.W.B. de Groot has consultancy/advisory relationships with Bristol


Myers Squibb, Pierre Fabre, Servier, MSD, and Novartis. G.A.P. Hospers has consultancy/advisory relationships with Amgen, Bristol Myers Squibb, Roche, MSD, Pfizer, Novartis, and Pierre Fabre, and has received research Grants not related to this paper from Bristol Myers Squibb and Seerave, all paid to the institution. E. Kapiteijn has consultancy/advisory relationships with Bristol Myers Squibb, Novartis, Merck, Lilly, and Pierre Fabre, all paid to institution, and has received research grants not related to this paper from Bristol Myers Squibb, Delcath, and Pierre Fabre. R.S. van Rijn has received advisory board/consultancy honoraria from Pfizer, and an expert meeting fee from Roche. A.A.M. van der Veldt has consultancy relationships with Bristol Myers Squibb, MSD, Sanofi, Merck, Pfizer, Ipsen, Eisai, Roche, Pierre Fabre, and Novartis, all paid to the institute. M.J. Boers-Sonderen has consultancy/advisory relationships with Pierre Fabre, MSD and Novartis, all paid to the institution. K.P.M. Suijkerbuijk has advisory relationships with Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, and Abbvie, and has received honoraria from Novartis, MSD, and Roche and research grants from Philips, TigeTx and BMS, all paid to the institution. J.B.A.G. Haanen has advisory relationships with Aim, Achilles Therapeutics, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, BioNTech, GSK, Immunocore, Ipsen, MSD, Merck Serono, Molecular Partners, Novartis, Neogene Therapeutics, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics, Third Rock Ventures, and Vaximm, and has received research Grants not related to this paper from Amgen, Bristol Myers Squibb, MSD, BioNTech, Neogene Therapeutics, and Novartis. All Grants were paid to the institutions. All remaining authors have declared no conflicts of interest.

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.

J. S. W. Borgers¹ 

F. H. Burgers¹

A. Schina²

O. J. Van Not^{3,4}

A. J. M. van den Eertwegh⁵

C. U. Blank¹

M. J. B. Aarts⁶

F. W. P. J. van den Berkmortel⁷

J. W. B. de Groot⁸

G. A. P. Hospers⁹

E. Kapiteijn¹⁰

D. Piersma¹¹
 R. S. van Rijn¹²
 A. M. Stevense-den Boer¹³
 A. A. M. van der Veldt¹⁴
 G. Vreugdenhil¹⁵
 M. J. Boers-Sonderen¹⁶
 M. W. J. M. Wouters^{3,17,18}
 K. P. M. Suijkerbuijk⁴
 J. V. van Thienen¹
 J. B. A. G. Haanen¹

¹⁸Department of Surgical Oncology, Antoni van Leeuwenhoek-
 The Netherlands Cancer Institute, Amsterdam, The Netherlands

Correspondence

J.B.A.G. Haanen, The Netherlands Cancer Institute-Antoni
 van Leeuwenhoek, Department of Medical Oncology,
 Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
 Email: j.haanen@nki.nl

ORCID

J. S. W. Borgers  <https://orcid.org/0000-0002-6478-7821>

REFERENCES

- ¹Department of Medical Oncology, Antoni van Leeuwenhoek-
 The Netherlands Cancer Institute, Amsterdam, The Netherlands
- ²National Center for Cancer Immune Therapy, Department of
 Oncology, Copenhagen University Hospital, Herlev, Denmark
- ³Dutch Institute for Clinical Auditing, Leiden, The Netherlands
- ⁴Department of Medical Oncology, University Medical Center
 Utrecht, Utrecht, The Netherlands
- ⁵Department of Medical Oncology, Amsterdam UMC, VU
 University Medical Center, Cancer Center Amsterdam,
 Amsterdam, The Netherlands
- ⁶Department of Medical Oncology, GROW School for Oncology
 and Developmental Biology, Maastricht University Medical
 Centre+, Maastricht, The Netherlands
- ⁷Department of Medical Oncology, Zuyderland Medical Centre,
 Sittard, The Netherlands
- ⁸Isala Oncology Center, Zwolle, The Netherlands
- ⁹Department of Medical Oncology, University Medical Centre
 Groningen, University of Groningen, Groningen, The Netherlands
- ¹⁰Department of Medical Oncology, Leiden University Medical
 Centre, Leiden, The Netherlands
- ¹¹Department of Internal Medicine, Medisch Spectrum Twente,
 Enschede, The Netherlands
- ¹²Department of Internal Medicine, Medical Centre Leeuwarden,
 Leeuwarden, The Netherlands
- ¹³Department of Internal Medicine, Amphia Hospital, Breda,
 The Netherlands
- ¹⁴Department of Medical Oncology and Radiology & Nuclear
 Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands
- ¹⁵Department of Internal Medicine, Maxima Medical Center,
 Veldhoven, The Netherlands
- ¹⁶Department of Medical Oncology, Radboud University
 Medical Centre, Nijmegen, The Netherlands
- ¹⁷Department of Biomedical Data Sciences, Leiden University
 Medical Centre, Leiden, The Netherlands
- Danmark, K. (n.d.). Temperaturer, Hydrotermfigur, Klima borde til
 Danmark. [Climate-Data.org](https://climate-data.org). (Assessed on 02/nov/2022)
- Davenport, E. R., Mizrahi-Man, O., Michelini, K., Barreiro, L. B., Ober,
 C., & Gilad, Y. (2014). Seasonal variation in human gut microbiome
 composition. *PLoS One*, 9, e90731.
- Ellebaek, E., Schina, A., Schmidt, H., Haslund, C. A., Bastholt, L., Svane,
 I. M., & Donia, M. (2022). Seasonal variation in effect of anti-PD-1
 initiation on overall survival among patients with advanced mela-
 noma. *Pigment Cell & Melanoma Research*, 36, 224–231.
- Jochems, A., Schouwenburg, M. G., Leeneman, B., Franken, M. G., van
 den Eertwegh, A. J. M., Haanen, J. B. A. G., Gelderblom, H., Uyl-de
 Groot, C. A., Aarts, M. J. B., van den Berkmoortel, F. W. P. J., Blokk,
 W. A. M., Cardous-Ubbink, M. C., Groenewegen, G., de Groot, J.
 W. B., Hospers, G. A. P., Kapiteijn, E., Koornstra, R. H., Kruit, W. H.,
 Louwman, M. W., ... van der Hoeven, J. J. M. (2017). Dutch mela-
 noma treatment registry: Quality assurance in the care of patients
 with metastatic melanoma in The Netherlands. *European Journal of
 Cancer*, 72, 156–165.
- Koliada, A., Moseiko, V., Romanenko, M., Piven, L., Lushchak, O.,
 Kryzhanovska, N., Guryanov, V., & Vaiserman, A. (2020). Seasonal
 variation in gut microbiota composition: Cross-sectional evidence
 from Ukrainian population. *BMC Microbiology*, 20, 100.
- Miller, G. W., & Jones, D. P. (2014). The nature of nurture: Refining the
 definition of the exposome. *Toxicological Sciences*, 137, 1–2.
- Morad, G., Helmink, B. A., Sharma, P., & Wargo, J. A. (2021). Hallmarks of
 response, resistance, and toxicity to immune checkpoint blockade.
Cell, 184, 5309–5337.
- Moreira, A., Heinzlering, L., Bhardwaj, N., & Friedlander, P. (2021).
 Current melanoma treatments: Where do we stand? *Cancers*, 13,
 221.
- Royal Netherlands Meteorological Institute, Ministry of Infrastructure
 and Water Management. (n.d.). Klimatologie – Metingen en waar-
 nemingen. (Assessed on 02/nov/2022).

SUPPORTING INFORMATION

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