Immunotherapy in advanced melanoma: crossing borders

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CHAPTER
7.2

Failure to validate existing clinical prediction scale for response to PD-1 monotherapy in advanced melanoma in national cohort study

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Introduction

Treatment with targeted therapy and immune checkpoint inhibitors has significantly improved survival of patients with advanced melanoma. Unfortunately, a large proportion of patients are either primary non-responders or will eventually develop secondary resistance.

In 2017, Nosrati and colleagues published a prediction scale in the British Journal of Cancer, which included five clinical parameters that were associated with lower response to anti-PD-1 treatment; female sex (1 point), age <65 years (1 point), history of ipilimumab (anti-CTLA-4) treatment (2 points), elevated lactate dehydrogenase (LDH) (1 point), and the presence of liver metastasis (2 points)[1]. This study used a derivation cohort of 228 patients treated in California, and a validation cohort of 87 patients treated in Switzerland. The primary outcome measure was best tumor response to treatment evaluated using computed tomography at 12 and 16 weeks after the first administration of anti-PD-1 monotherapy, and every 12 weeks thereafter.

The aim of this correspondence is to validate the prediction scale, published by Nosrati and colleagues.

Patients and methods

Registry

Since 2013, all patients with advanced melanoma in the Netherlands are referred to one of 14 expert hospitals and data are prospectively registered in the Dutch Melanoma Treatment Registry (DMTR).

Data are collected from patient files by trained data managers and approved by the treating physicians. In compliance with Dutch regulations, the DMTR was approved by a medical ethical committee (METC Leiden University Medical Center, 2013) and is not considered subject to the Medical Research Involving Human Subjects Act.

Patients and data

We extracted data for all patients registered between July 2013 and July 2018. Patients without response evaluation scans ≥10 weeks after start of treatment (n=284), with missing data on the clinical parameters included in the prediction scale (n=134), or with uveal melanoma (n=17) were excluded. Baseline characteristics at the start of anti-PD-1 monotherapy were collected, including serum LDH, age, sex, previous treatments

and the presence of liver metastasis. Response was defined as complete response (CR) or partial response (PR), based on clinical judgement of the medical team.

Results

Between July 2013 and July 2018, 1292 patients started anti-PD-1 treatment and met inclusion criteria. Baseline characteristics are summarized in Table 1A, including differences between the derivation cohort of Nosrati et al. and our national cohort. Patients' sex was more equally distributed in our cohort. Furthermore, our cohort contained more patients with WHO performance score >0, fewer patients with elevated LDH levels, fewer BRAF wild type melanoma, and fewer patients who were previously treated with ipilimumab or targeted therapy.

Table 1B presents all clinical parameters that were found to be significantly associated with response to anti-PD-1 monotherapy in the univariate analysis by Nosrati et al. Both prior ipilimumab treatment (OR=0.73 95%CI; 0.56-0.96, *P*=0.02) and the presence of liver metastases (OR=0.70 (95% CI 0.54-0.90), *P*=0.006) were also found to be significantly correlated with lack of response to treatment in our cohort.

Figure 1 shows the predictive value of the clinical prediction scale of 0-7 points of Nosrati et al. With an AUC of 0.55 (*p*=0.001) this scale did not predict response to anti-PD-1 monotherapy in our cohort.

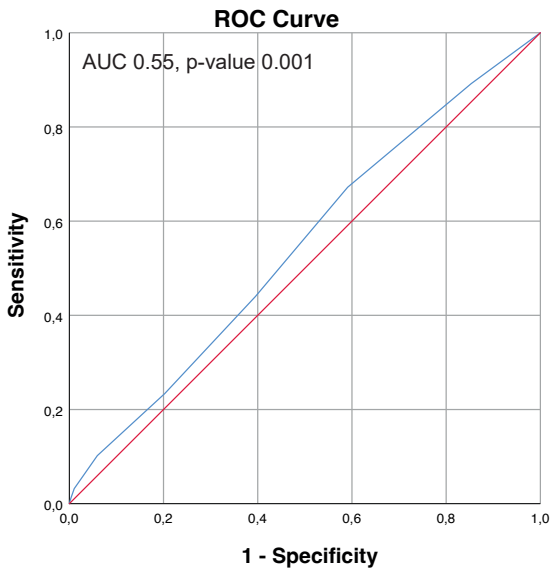

FIGURE 1 Receiver operation characteristics curve of the clinical prediction scale of 0-7 points of Nosrati et al. to predict response to anti-PD-1 monotherapy in our cohort.

TABLE 1 Baseline characteristics and performance of prediction scale. (**A**) Comparison of baseline characteristics between validation cohort of Nosrati and colleagues and our cohort, using descriptive statistics. (**B**) Significance of predictive clinical parameters of Nosrati's univariate analysis in our cohort, calculated using logistic regression.

Variable	Nosrati Number (%)	van der Kooij Number (%)
Age, years		
Mean +/- SD	62.5 +/- 13.1	63.3 +/- 12.9
Age <65 years	126 (55.3)	627 (48.5)
Sex		
Male	148 (64.9)	771 (59.7)
Female	80 (35.1)	521 (40.3)
Primary site		
Cutaneous	200 (87.7)	1032 (79.9)
Mucosal	13 (5.7)	43 (3.3)
Acral		32 (2.5)
Eye		
Unknown	15 (6.6)	185 (14.3)
ECOG		
0	157 (68.9)	725 (56.1)
1	65 (28.5)	419 (32.4)
2	5 (2.2)	58 (4.5)
3	1 (0.4)	6 (0.5)
Unknown		84 (6.5)
LDH		
Normal	150 (65.8)	939 (72.7)
Elevated	78 (34.2)	353 (27.3)
BRAF mutation		
Negative	162 (72.0)	619 (47.9)
Positive	63 (28.0)	626 (48.5)
Unknown	3 (1.3)	47 (3.6)
Liver metastasis		
No	160 (70.2)	968 (74.9)
Yes	68 (29.8)	324 (25.1)
Lung metastasis		
No	94 (42.1)	595 (46.1)
Yes	132 (57.9)	678 (52.5)
Unknown		19 (1.4)
Brain metastasis		
No	178 (78.1)	961 (74.4)
Yes	50 (21.9)	294 (22.8)
Unknown		37 (2.8)
Prior ipilimumab		
No	**81 (35.5)**	**1021 (79.0)**
Yes	147 (64.5)	271 (21.0)
Prior targeted therapy		
No	**174 (76.3)**	**1144 (88.5)**
Yes	54 (23.7)	148 (11.5)

	ORR (%)	OR (95% CI)	*P* value
Total cohort	49.8	NA	NA
Age ≥65 years	49.7	Ref.	Ref.
Age <65 years	50.3	1.03 (0.82-1.28)	0.82
Normal LDH	51.6	Ref.	Ref.
Elevated LDH	45.7	0.79 (0.62-1.01)	0.06
Male sex	50.5	Ref.	Ref.
Female sex	49.3	0.96 (0.77-1.19)	0.69
No prior ipilimumab	51.6	Ref.	Ref.
Prior ipilimumab	43.9	0.73 (0.56-0.96)	0.02
No liver metastasis	52.2	Ref.	Ref.
Liver metastasis	43.3	0.70 (0.54-0.90)	0.006

Discussion

We could not confirm the predictive value of the clinical prediction scale of 0-7 points for response to anti-PD-1 monotherapy as published by Nosrati et al. A possible explanation could be the significantly higher ORR in the derivation (63.3%) cohort from Nosrati et al. compared to our cohort (49.8%), which could have led to an initial overestimation of the predictive value of their prediction scale. Additionally, our cohort differed from the group treated by Nosrati et al. when comparing the pre-treatment. More patients received prior targeted therapy in our cohort, while more patients received prior ipilimumab treatment in the group from Nosrati et al. Therefore, our cohort more closely resembles the current clinical setting where ipilimumab is less frequently given as a first line monotherapy for patients with advanced melanoma.

Although the prediction scale could not be validated in our cohort, we did show that prior ipilimumab treatment and the presence of liver metastases was associated with a smaller response chance. This lack of response in the group of patients that has been pre-treated with ipilimumab could be due to the fact that patients who already progressed on prior immune checkpoint inhibition have a primary or acquired resistance to this type of treatment[2]. And therefore might also be less susceptible to a second line of immunotherapy.

In recent years, multiple meta-analyses have been published investigating the sex-dependent magnitude of benefit following treatment with immune checkpoint inhibition. The first study showed that men have more benefit from immune checkpoint inhibition, including anti-PD-1[3], whereas the latter three showed no difference in efficacy and overall survival[4-6]. Our study supports the findings that sex on itself is not a predictor for response to anti-PD-1 treatment.

Failure to validate the prediction scale by Nosrati et al. indicates that response to anti-PD-1 monotherapy cannot only be predicted by clinical parameters, but is influenced by other factors. Examples currently being studied include tumor-intrinsic factors, immune cells and cytokines both in tumor tissue and blood[7,8] and include more readily available blood parameters, such as LDH, S100B, absolute leukocyte, lymphocyte, neutrophil counts and their ratios[9-11]. While further research on predictive models is encouraged, validation of these models in sufficiently large independent cohorts is of even more importance to test robustness and clinical applicability.

Additional information

Authors' contributions

Conceptualization, M.K.v.d.K., O.M.D. and E.K.; Data curation, M.K.v.d.K.; Formal analysis, M.K.v.d.K.; Methodology, M.K.v.d.K., O.M.D. and E.K.; Resources, F.W.P.J.v.d.B., M.J.B.-S., J.W.B.d.G., G.A.P.H., D.P., R.S.v.R., K.P.M.S., H.M.W., A.A.M.v.d.V., G.V., C.U.B., M.W.J.M.W., J.B.A.G.H., A.J.M.v.d.E. and E.K.; Software, M.J.B.A.; Supervision, O.M.D. and E.K.; Visualization, M.K.v.d.K.; Writing—original draft, M.K.v.d.K.; Writing—review & editing, O.M.D., M.J.B.A., F.W.P.J.v.d.B., M.J.B.-S., J.W.B.d.G., G.A.P.H., D.P., R.S.v.R., K.P.M.S., H.M.W., A.A.M.v.d.V., G.V., C.U.B., M.W.J.M.W., J.B.A.G.H., A.J.M.v.d.E. and E.K. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The DMTR was approved by a medical ethical committee (METC Leiden University Medical Center, 2013) and is not considered subject to the Medical Research Involving Human Subjects Act.

Patient consent was waived due to the fact that the DMTR was not considered to be subject to the Medical Research Involving Human Subjects Act.

Conflict of Interest

M.J.B.S. has served as an advisory board member for Bristol-Myers Squibb, Novartis, Merck and Pierre Fabre. A.J.M.v.d.E. has served as a speaker for Bristol-Myers Squibb and Novartis and an advisory board member for Bristol Myers Squibb, MSD oncology, Amgen, Roche, Novartis, Sanofi, Pfizer, Ipsen, Merck, Pierre Fabre and has received research grants not related to this paper from Sanofi, Roche, Bristol Myers Squibb, TEVA and Idera. C.U.B. has served as ab advisory board member for Bristol-Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, GenMab, and Pierre Fabre, and reports to have ownership interests in Uniti Cars, Neon Therapeutics, and Forty Seven, and received commercial grants from Novartis, Bristol-Myers Squibb, and NanoString. J.W.B.d.G. is a paid consultant for Bristol Myers Squibb, MSD, Pierre Fabre, and Servier. G.A.P.H. is an unpaid consultant/advisory board member for Bristol Myers Squibb, MSD, Roche, and Novartis. D.P. has served as an advisory board member for Amgen, Bristol Myers Squibb and Pierre Fabre. A.A.M.v.d.V. is a paid consultant for Bristol Myers Squibb, MSD, Novartis, Roche, Pfizer, Eisai, Ipsen, Pierre Fabre, Sanofi, and Bayer. J.H. is a paid consultant for AIMM, Neon Therapeutics, Immunocore, Vaximm, and Neogene Therapeutics, and reports receiving commercial research grants from Bristol Myers Squibb, MSD, Novartis, and Neon Therapeutics. K.P.M.S.

has served as a consultant and/or advisory board member for Bristol Myers Squibb, Novartis, MSD, Pierre Fabre and AbbVie and received honoraria/research support not related to this manuscript from Novartis, Roche and MSD. All paid to institution. EK has served as a consultant and/or advisory board member for Bristol Myers Squibb, Novartis, Merck, Pierre Fabre and has received research grants not related to this paper from Bristol Myers Squibb. H.M.W. received travel expenses from Ipsen and honoraria from Astellas and Roche. No potential conflicts of interest were disclosed by the other authors. Role of the Funder: The funders had no role in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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References

1 Nosrati A, Tsai KK, Goldinger SM, Tumeh P, Grimes B, Loo K, et al. Evaluation of clinicopathological factors in PD-1 response: derivation and validation of a prediction scale for response to PD-1 monotherapy. Br J Cancer. 2017;116(9):1141-7.

2 Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017;168(4):707-23.

3 Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol. 2018;19(6):737-46.

4 Wallis CJD, Butaney M, Satkunasivam R, Freedland SJ, Patel SP, Hamid O, et al. Association of Patient Sex With Efficacy of Immune Checkpoint Inhibitors and Overall Survival in Advanced Cancers: A Systematic Review and Meta-analysis. JAMA Oncol. 2019;5(4):529-36.

5 Sun L, Zhang L, Yu J, Zhang Y, Pang X, Ma C, et al. Clinical efficacy and safety of anti-PD-1/PD-L1 inhibitors for the treatment of advanced or metastatic cancer: a systematic review and meta-analysis. Sci Rep. 2020;10(1):2083.

6 van der Kooij MK, Dekkers OM, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, de Groot JWB, et al. Sex-Based Differences in Treatment with Immune Checkpoint Inhibition and Targeted Therapy for Advanced Melanoma: A Nationwide Cohort Study. Cancers (Basel). 2021;13(18).

7 Melief SM, Visconti VV, Visser M, van Diepen M, Kapiteijn EH, van den Berg JH, et al. Long-term Survival and Clinical Benefit from Adoptive T cell Transfer in Stage IV Melanoma Patients Is Determined by a Four-Parameter Tumor Immune Signature. Cancer Immunol Res. 2017;5(2):170-9.

8 Krieg C, Nowicka M, Guglietta S, Schindler S, Hartmann FJ, Weber LM, et al. High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy. Nat Med. 2018;24(2):144-53.

9 Diehl A, Yarchoan M, Hopkins A, Jaffee E, Grossman SA. Relationships between lymphocyte counts and treatment-related toxicities and clinical responses in patients with solid tumors treated with PD-1 checkpoint inhibitors. Oncotarget. 2017;8(69):114268-80.

10 Capone M, Giannarelli D, Mallardo D, Madonna G, Festino L, Grimaldi AM, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. J Immunother Cancer. 2018;6(1):74.

11 Wagner NB, Forschner A, Leiter U, Garbe C, Eigentler TK. S100B and LDH as early prognostic markers for response and overall survival in melanoma patients treated with anti-PD-1 or combined anti-PD-1 plus anti-CTLA-4 antibodies. Br J Cancer. 2018;119(3):339-46.