Dermatology Practical & Conceptual

Comparison of the Efficacy and Safety between Adjuvant and Palliative Anti-PD-1 Treatment of Stage 4 Oligometastatic Melanoma

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Introduction

For patients with oligometastatic stage 4 melanoma, two treatment options may be considered: i) resection of metastases followed by anti-PD-1 adjuvant therapy; ii) direct anti-PD-1 initiation without resection [1,2]. However, it still remains unclear which of these approaches is superior. We therefore performed a retrospective single-center observational study focusing on oligometastatic (one or two metastases in one organ system) stage 4 melanoma patients treated with anti-PD-1 in palliative or adjuvant setting at the Department of Dermatology and Venereology, Královské Vinohrady University Hospital between January 2016 and January 2024. The objective of the study was to compare 24-month relapse-free survival (RFS) and progression-free survival (PFS) between these groups. Two hundred and three patients with stage 4 melanoma treated with anti-PD-1 were identified, of whom 39 met the oligometastatic definition: 18 in the palliative indication and 21 in the adjuvant indication. Sixteen of the 18 palliative patients had a minimum follow-up of two years, three of the adjuvant patients developed progression before or shortly after resection of metastases, and two patients did not have a minimum follow-up of 24 months and were

therefore excluded. In the end, 16 patients were enrolled in the palliative arm and 16 in the adjuvant arm. Basic characteristics of the study population are summarized in Table 1.

Findings

The 6-, 12-, 18- and 24-month RFS/PFS were 81%, 63%, 50%, and 50%, respectively, in the adjuvant group compared to 69%, 69%, 69% and 63%, respectively, in the palliative group. Kaplan-Meier curves for RFS/PFS in both groups are shown in Figure 1. The median RFS/PFS was 21.0 (3.0-NR) months in the adjuvant group and was not reached in the palliative group (3.0-NR). The median overall survival (OS) was not reached in either group. Immune-mediated adverse events (imAE) were significantly more common in the palliative group compared to the adjuvant group (56 % vs 25% of patients). No new unexpected imAE occurred during follow-up.

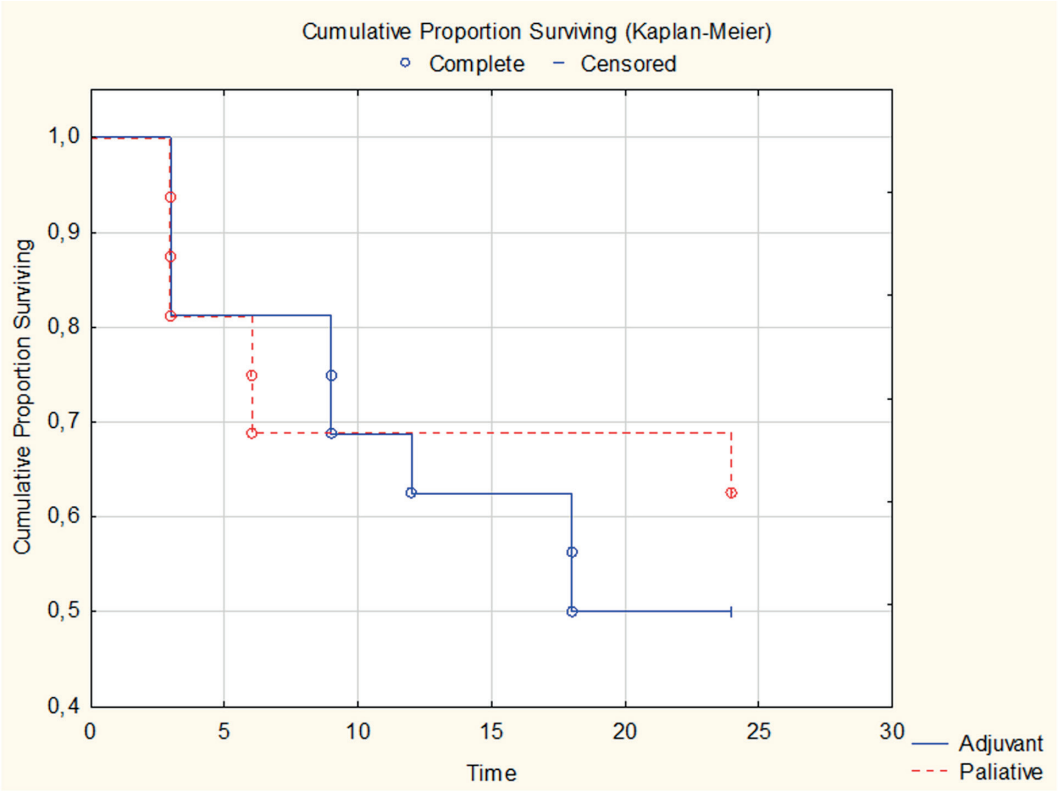
Conclusion

Although patients with oligometastatic melanoma treated with anti-PD-1 in the palliative setting were a prognostically less favorable group (31% vs 6% elevated LDH, 38% vs 25% in M1c stage), 24-month PFS reached up to 63% in this group of patients. Based on our data, it appears that starting anti-PD-1 directly in the palliative setting instead of resection of metastases followed by anti-PD-1 in the adjuvant setting is at least equivalent to or even a better option for oligometastatic stage 4 patients (P=0.558, long-rank test). Before recommending resection of metastases in oligometastatic melanoma, it is also important to remember that around 14% of patients (1/7 recommended) will develop disease progression before or shortly after resection.

Our results appear to be in line not only with the current ESMO recommendations for the management of melanoma, but also with the results of the prospective randomized phase 2/3 neoadjuvant clinical trials SWOG S1801 and NADINA

Table 1. Baseline characteristics of study population.

Population characteristics	Stage 4 (adjuvant, N=16)	Stage 4 (palliative, N=16)
Male sex	56 % (9)	56 % (9)
Median age, years	62 (40-79)	63 (38-71)
Median Breslow, mm	2.2 (1.6-15.0)	3.1 (1.0-24.0)
Subtype of melanoma		
Super. Spreading	12 % (2)	19 % (3)
Nodular	38 % (6)	44 % (7)
Unknown origin	44 % (7)	31 % (5)
Mucosal	6 % (1)	0 % (0)
Acrolentiginous	0 % (0)	6 % (1)
Stage of melanoma		
St. 4a	56 % (9)	62 % (10)
St. 4b	19 % (3)	0 % (0)
St. 4c	25 % (4)	38 % (6)
LDH above normal	6 % (1)	31 % (5)
BRAF wild-type	69 % (11)	81 % (13)
BRAF V600E/K	31 % (5)	19 % (3)
Nivolumab	100 % (16)	75 % (12)
Pembrolizumab	0 % (0)	25 % (4)
Adverse events during the first 12 months	25 % (4)	56 % (9)
Objective response rate	/	75 % (12/16)
Disease control rate	/	81 % (13/16)
Median duration of response (months)	/	NR (5.9-NR)
Another line of the treatment	38 % (6)	19 % (3)
Anti-PD-1 + anti-CTLA-4	50 % (3)	66 % (2)
Anti-PD-1 +/- other molecules	17 % (1)	34 % (1)
BRAFi + MEKi	33 % (2)	0 % (0)



Population	3 months RFS/PFS	6 months RFS/PFS	9 months RFS/PFS	12 months RFS/PFS	15 months RFS/PFS	18 months RFS/PFS	21 months RFS/PFS	24 months RFS/PFS
St. IV (adjuvant, n=16)	81 % (13/16)	81 % (13/16)	69 % (11/16)	63 % (10/16)	63 % (10/16)	50 % (8/16)	50 % (8/16)	50 % (8/16)
St. IV (palliative, n=16)	81 % (13/16)	69 % (11/16)	69 % (11/16)	69 % (11/16)	69 % (11/16)	69 % (11/16)	69 % (11/16)	63 % (10/16)

Figure 1. Kaplan-Meier estimates of relapse-free survival and progression-free survival in oligometastatic stage 4 melanoma treated by adjuvant or palliative anti-PD-1.

[3,4,5]. Both trials demonstrated the superiority of immediate anti-PD-1 (neoadjuvant) versus delayed anti-PD-1 (adjuvant) administration after resection of metastases (1- and 2-year event-free survival difference of 26% in NADINA and 23% in SWOG S1801) [4,5]. The very promising results described should be further confirmed in more robust prospective randomized trials.

Ethical Approval: This study was approved by the Ethics Committee of the Královské Vinohrady University Hospital.

Ethics Statement: The patients in this manuscript provided written informed consent to publication of their case details.

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