Nature and management of melanoma recurrences following adjuvant anti-PD-1 (PD1) therapy

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Background

- Adjuvant anti-PD-1 therapy reduces the risk of recurrence by 40-50%.
- Despite this, up to 50% of patients still recur by 5 years[1].
- Data is lacking to define this population[2] and best management is unknown, including the role for retreatment with anti-PD-1.

Objectives

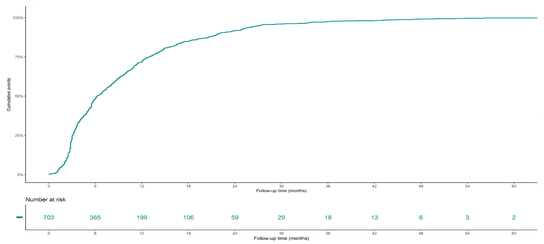
- To describe disease characteristics of patients recurring following adjuvant anti-PD-1 (PD1) therapy.
- To describe local and systemic management of recurrences, and the success of each as defined by survival endpoints of RFS, PFS, OS and tumor endpoints of ORR and DOR.
- To clarify the prognostic and predictive significance of recurrence intervals.

Methods

- Data from 17 sites of patients with resected stage II-IV melanoma who received at least one dose of adjuvant anti-PD-1 therapy before January 2022.
- Demographics, disease characteristics, treatment, toxicity, recurrence details and management were collected.
- Clinical outcomes were assessed independently for those with local recurrences and those with distant recurrences.
- Outcomes for those with local recurrences who underwent local therapy with second adjuvant therapy included relapse-free survival-2 (RFS2), distant metastasis-free survival-2 (DMFS2), and overall survival (OS).
- Outcomes for distant recurrences included objective response rate (ORR), duration of response (DOR), PFS and OS.
- Both localised and systemic recurrences were assessed for further PD-1 efficacy for patients recurring ON and OFF anti-PD-1 therapy.
- ON PD-1 was defined as those who were actively receiving drug at the time of recurrence. OFF PD-1 was defined as those who recurred after the last dose of PD-1 regardless of whether cessation was due to treatment completion or other causes.
- Further exploratory analyses of outcomes based on time to recurrence were also performed.

Results

Figure 1. Time-to-recurrence



- 711 pts included
- Median follow-up from commencement of adjuvant 28.4 months (0.7-106.6)
- Median time to recurrence 6.2 months (0.0-68.5)
- 12m OS 81%
- 24m OS 65%

Table 1. Patterns of recurrence.

Total	Local alone	Distant alone	Local + distant
N=711 (100%)	315 (44%)	307 (43%)	78 (11%)

Table 2. Sites of distant (distant alone + multisite) recurrences

	Nodal/soft tissue	Lung	Non-brain other organ	Brain
N (%)	99 (14%)	107 (15%)	133 (19%)	68 (10%)

Table 3. Baseline demographic characteristics

Demographics		N (%)
Total		*711 (100%)*
Age	Median [range]	59.5 [16.0-92.0]
Sex	Male	451 (64%)
Melanoma subtype	Cutaneous non-acral	508 (86%)
	Acral	54 (9%)
	Mucosal	20 (3%)
	Other	10 (1%)
Mutational status	BRAF V600	285 (58%)
Stage	II/IIIA*	66 (9%)
	IIIB	170 (24%)
	IIIC	281 (54%)
	IIID	22 (3%)
	IV	51 (7%)
SNB	yes	536 (75%)
CLND	yes❖	236 (44%)
Adjuvant therapy	PD1	635 (90%)
	PD1 + other†	74 (11%)
Duration of adjuvant	Median [range]	5.5 [0.0-34.0]
Reason for cessation	Completion	142 (20%)
	Toxicity	115 (16%)
	Recurrence	444 (63%)
	Elective	8 (1%)

*20 patients (3%) stage III not otherwise specified. ❖Of 536 patients with prior SLNB. † PD-1 + other includes BRAF + PD-1, PD-1 + bempegaldesleukin, PD-1 + TVEC, PD-1 + mR-4157, PD-1 + CTLA-4.

Table 8. Rechallenge outcomes of anti-PD-1 monotherapy in the overall population

Outcome	All rechallenge (N=88)	Recurrence OFF (N=47)	Recurrence ON (N=41)
TTR§*	8.1 (0.5-64.7)	18.5 (1.4-64.7)	3.1 (0.5-22.8)
ORR (%)	27	34	20
DOR*	9.8 (2.3-35.6)	2.7 (2.3-13.8)	16.8 (9.8-35.6)
PFS*	8.6 (0.7-61.2)	9.5 (2.7-61.2)	7.4 (0.7-54.8)
OS*	16.9 (0.7-76.1)	13.4 (3.3-72.7)	25.5 (0.7-76.1)

*Median [range], in months. § Time to recurrence.

Locoregional recurrences

- 140/315 (44%) had definitive local therapy with surgery +/- radiation.
- After initial locoregional recurrence, 164 (52%) had a further local and 129 (41%) distant recurrence.

Table 4. Treatment modalities for locoregional recurrences.

Treatment type⬥	Locoregional alone [N (%)]
Total	*315 (100%)*
Surgery alone	98 (31%)
Surgery + adjuvant radiation	42 (13%)
Radiation alone	0 (0%)
Definitive systemic	73 (23%)
'Second adjuvant' systemic	86 (27%)

⬥ Some patients received multiple treatments.

'Second' adjuvant treatment

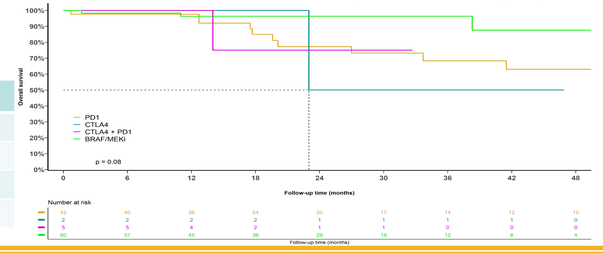
- 119 patients received 'second' adjuvant treatment, comprising 86 (72%) of locoregional recurrences and 25 (21%) distant recurrences.

Table 5. Survival outcomes for patients receiving 'second' adjuvant

Second adjuvant (N=119)	RFS2*†	DMFS2*†	OS*
BRAF/MEKi (N=62)	24.9 (7.8-66.0)	16.2 (5.0-42.3)	23.4 (1.3-56.8)
PD1 (N=42)	11.7 (2.9-58.1)	3.7 (1.3-24.3)	19.9 (0.7-76.1)
(ON PD1; N=23)	3.2 (0.5-22.8)	18.1 (0.7-76.1)	27.0 (0.7-76.1)
(OFF PD1; N=19)	17.5 (2.6-52.5)	17.5 (2.6-72.7)	16.6 (5.5-72.7)

† From start of 'second' adjuvant. *Median [range], in months.

Figure 2. Overall survival for second adjuvant treatment groups.



Distant recurrences

- 296/385 (77%) received definitive systemic therapy. Radiotherapy was palliative in 10 (71%) and ablative in 4 (29%).
- Median OS for distant recurrences was 14.2 (0.0-70.7), compared to 19.9 (0.2-76.1) for locoregional recurrences.

Table 6. Treatment modalities for distant recurrences‡

Treatment type⬥	Distant recurrence [N (%)]
Total	*385 (100%)*
Surgery alone	21 (5%)
Surgery + radiation	9 (2%)
Radiation alone	15 (4%)
Definitive systemic	296 (77%)
'Second adjuvant' systemic	25 (6%)

‡Numbers for distant alone + multisite.

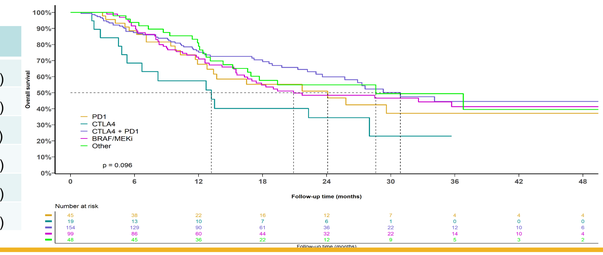
Definitive drug outcomes

Table 7. Survival outcomes for definitive systemic therapy.

Definitive systemic (N=378)	ORR (%)	DOR*	PFS*	OS*
PD1 alone (N=46)	24	6.3 (2.7-14.4)	17.4 (2.3-44.3)	15.2 (1.0-69.7)
(ON PD1, N=18)	17	11.9 (9.8-14.0)	9.4 (1.4-54.8)	21.3 (3.0-54.8)
(OFF PD1, N=28)	32	-	7.9 (2.7-34.0)	11.5 (3.3-51.1)
CTLA4 alone (N=19)	11	-	9.8 (4.9-50.5)	12.7 (2.0-35.7)
CTLA4 + PD1 (N=157)	34	5.6 (0-21.7)	13.5 (1.9-55.3)	14.4 (1.0-69.7)
BRAF/MEKi (N=105)	65	3.4 (0-29.3)	14.8 (0.6-73.5)	15.6 (1.3-67.4)

† From start of adjuvant. *Median [range], in months. ⬥ Some patients received multiple treatment modalities.

Figure 3. Overall survival for definitive systemic treatment groups.



Conclusions

- **Almost 50% of recurrences occur within 6 months of starting therapy, with similar rates of local and distant recurrence.**
- **Following local recurrence, despite local therapy and often additional adjuvant therapy, 52% develop further local and 41% distant disease.**
- **'Second adjuvant' BRAF/MEKi appears to have greater efficacy than resuming or continuing PD1 therapy**
- **Following distant recurrence, most receive CTLA4+PD1 or BRAF/MEKi, but survival remains poor with mOS <2 years.**

References

1. Weber J, Mandala M, Del Vecchio M, *et al.* Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. New England Journal of Medicine 2017;377(19):1824-1835
2. Ng G, Xu W, Atkinson V. Treatment Approaches for Melanomas That Relapse After Adjuvant or Neoadjuvant Therapy. Current Oncology Reports 2022;24(10):1273-1280.

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