Efficacy and safety of "second adjuvant" therapy with BRAF/MEK inhibitors after resection of recurrent melanoma following adjuvant PD-1-based immunotherapy

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Background

- Adjuvant therapy reduces risk of recurrence in resected Stage II-IV melanoma[1,2,3,4].
- Despite adjuvant therapy, many patients still recur and recurrence may be resectable[5,6].
- The utility of 'second adjuvant' therapy is unknown[7].

Objectives

- To explore the efficacy and safety of 'second adjuvant' BRAF/MEKi in BRAFV600 patients who recurred despite adjuvant PD-1 based immunotherapy

Methods

- Retrospective study
- 13 international centres

Results – Adjuvant PD-1

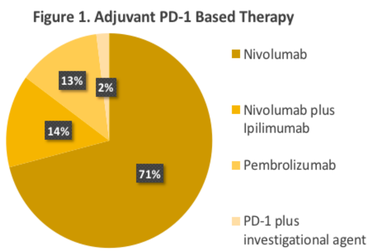
Table 1. Baseline Characteristics

	N=55
Gender	
Male	26 (47%)
Female	29 (53%)
BRAF mutation	
V600E	48 (91%)
V600K	3 (6%)
Other	2 (4%)
Primary histology	
Cutaneous	48 (92%)
Acral	3 (6%)
Mucosal	1 (2%)

Table 2. Characteristics of first adjuvant PD-1 based therapy

	N=55
Age at commencement	
Median	52.8 years
ECOG at commencement	
0	51 (93%)
1	1 (2%)
unknown	3
Stage (AJCCv8) at commencement	
IIIA	3 (5%)
IIIB	23 (42%)
IIIC	24 (44%)
IIID	1 (2%)
IV	4 (7%)
Surgical management prior to adjuvant therapy	
SNB	13 (25%)
ITM resected	9 (17%)
CLND	26 (49%)
Resection of metastasis	3 (6%)
Other	2 (3%)
Time on adjuvant therapy	
Median	5.0 months 95% CI 3.2-6.9
Reason for cessation	
Completed	10 (19%)
Recurrence	35 (65%)
Toxicity	9 (17%)
Ongoing	0 (0%)

Figure 1. Adjuvant PD-1 Based Therapy



Recurrence after adjuvant PD-1:

- Median 8.4 months (95% CI 6.9 -10.8). Most during adjuvant treatment (65%).

Results – Second Adjuvant BRAF/MEKi

Figure 2. Second Adjuvant BRAF/MEKi

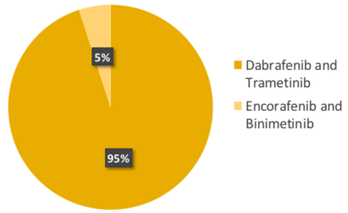


Table 3. Characteristics at start of second adjuvant BRAF/MEKi

	N=55
Age	
Median	54.0 years
ECOG	
0	48 (87%)
1	3 (5%)
unknown	4
Stage (AJCCv8)	
IIIA	0 (0%)
IIIB	16 (29%)
IIIC	29 (53%)
IIID	2 (4%)
IV	8 (15%)
Surgical management prior to second adjuvant therapy	
CLND	20 (36%)
ITM resected	18 (33%)
Limited nodal resection	6 (11%)
Resection of metastasis	7 (13%)
Other	4 (7%)

Safety of "Second Adjuvant" BRAF/MEKi:

- Most common toxicity was pyrexia (43%)
- 21% experienced G3-4 adverse event
- 12% experienced an adverse event requiring hospitalisation
- No new safety signals in this setting

Efficacy of "Second Adjuvant" BRAF/MEKi:

Median FU 21.4 months (19.7-25.4)

Figure 3a. Recurrence Free Survival

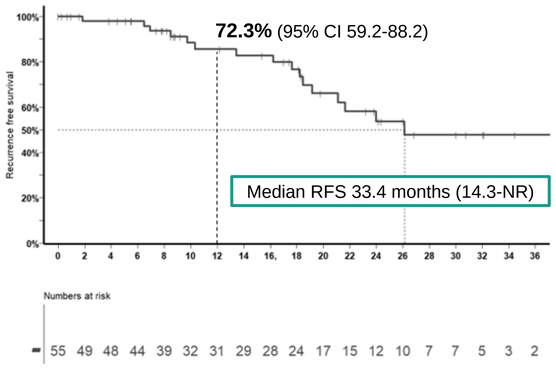


Figure 3b. Distant Metastasis Free Survival

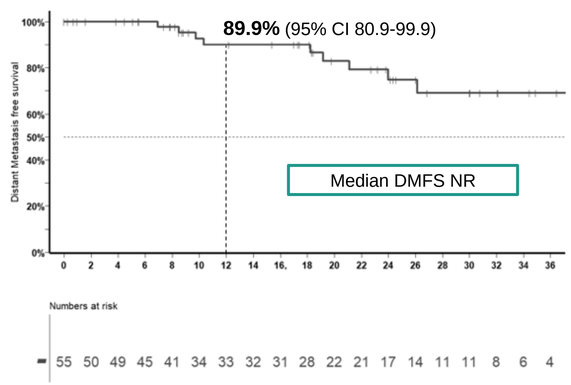


Figure 3c. Overall Survival

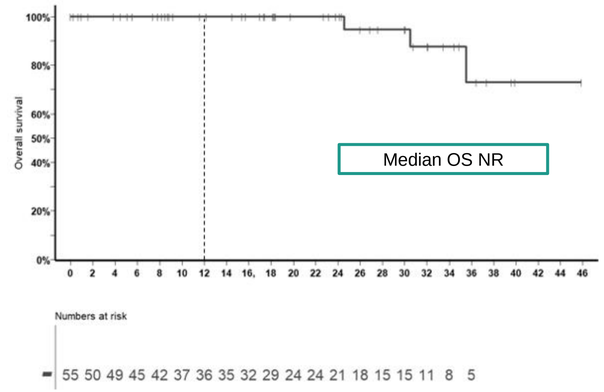


Table 4. Outcomes of Second Adjuvant BRAF/MEKi

Time on adjuvant therapy	N=55
Median	10.1 months 95% CI 7.8-12.0
Reason for cessation	N=55
Completed	21 (38%)
Recurrence	4 (7%)
Toxicity	11 (20%)
Ongoing	19 (35%)
Recurrence on/after BRAF/MEKi	17 (31%)
Locoregional	6 (35%)
Distant	11 (65%)
Recurrence on therapy	4 (24%)
Recurrence off therapy	13 (76%)

Conclusions / Future Directions For Research

- First study examining outcomes of patients receiving second adjuvant therapy for melanoma.
- RFS appears shorter compared to first line trials but higher risk group (15% had resected stage IV disease)
  - COMBI-AD showed for resected stage III BRAF600 patients; RFS at 12 months was 95% for those receiving adjuvant BRAF/MEKi and 56% for placebo group[1] compared to our study showing RFS at 12 months is 72.3%.
- For patients with re-resected BRAF mutant melanoma, second adjuvant treatment with BRAF/MEKi is safe.
- Recurrences in the first year are rare but approximately 50% recur by 2 years. Second adjuvant treatment does not prevent further recurrence in a significant proportion of patients.
- Further data on sequencing adjuvant therapies are needed.

References

1. Dummer R *et al.* NEJM 2020
2. Ascierto PA *et al.* Lancet 2020
3. Eggermont AMM *et al.* JCO 2020
4. Luke JJ *et al.* Lancet 2022
5. Owen CN *et al.* Ann Oncol 2020
6. Bhave P *et al.* JCO 2020
7. Dimitriou F *et al.* Ann Oncol. 2021

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