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ORIGINAL ARTICLE

Management of early melanoma recurrence despite adjuvant anti-PD-1 antibody therapy☆

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Background: Anti-programmed cell death protein 1 (PD-1) antibodies (PD1) prolong recurrence-free survival in high-risk resected melanoma; however, approximately 25%—30% of patients recur within 1 year. This study describes the pattern of recurrence, management and outcomes of patients who recur with adjuvant PD1 therapy.

Patients and methods: Consecutive patients from 16 centres who recurred having received adjuvant PD1 therapy for resected stage III/IV melanoma were studied. Recurrence characteristics, management and outcomes were examined; patients with mucosal melanoma were analysed separately.

Results: Melanoma recurrence occurred in 147 (17%) of ∼850 patients treated with adjuvant PD1. In those with cutaneous melanoma ($n = 136$), median time to recurrence was 4.6 months (range 0.3—35.7); 104 (76%) recurred during (ON) adjuvant PD1 after a median 3.2 months and 32 (24%) following (OFF) treatment cessation after a median 12.5 months, including in 21 (15%) who ceased early for toxicity. Fifty-nine (43%) recurred with locoregional disease only and 77 (57%) with distant disease. Of those who recurred locally, 22/59 (37%) subsequently recurred distantly. Eighty-nine (65%) patients received systemic therapy after recurrence. Of those who recurred ON adjuvant PD1, none (0/6) responded to PD1 alone; 8/33 assessable patients (24%) responded to ipilimumab (alone or in combination with PD1) and 18/23 (78%) responded to BRAF/MEK inhibitors. Of those who recurred OFF adjuvant PD1, two out of five (40%) responded to PD1 monotherapy, two out of five (40%) responded to ipilimumab-based therapy and 9/10 (90%) responded to BRAF/MEK inhibitors.

Conclusions: Most patients who recur early despite adjuvant PD1 develop distant metastases. In those who recur ON adjuvant PD1, there is minimal activity of further PD1 monotherapy, but ipilimumab (alone or in combination with PD1) and BRAF/MEK inhibitors have clinical utility. Retreatment with PD1 may have activity in select patients who recur OFF PD1.

Key words: adjuvant therapy, immunotherapy, melanoma

INTRODUCTION

Outcomes for patients with advanced melanoma have been transformed in recent years with novel systemic therapies, including anti-programmed cell death protein 1 (PD-1) antibodies (PD1) and anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immunotherapy, and targeted therapy with BRAF and MAPK kinase inhibitors (BRAF/MEKi) in *BRAF*^{V600} mutant melanoma.[1—3] Similar improvements are observed in the adjuvant setting for resected stage III or IV melanoma,[4—6] with phase III trials demonstrating prolonged recurrence-free survival for adjuvant nivolumab versus ipilimumab[4] (hazard ratio 0.65) and pembrolizumab versus placebo[5] (hazard ratio 0.57). Therefore, adjuvant PD1 therapy is a new standard of care for high-risk resected melanoma, however approximately 25%—30% of patients recur within 1 year.

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To date, there are no data regarding patterns of recurrence, management and outcomes of patients who recur having received adjuvant PD1 therapy. In patients who progress on PD1 in the advanced setting, ipilimumab (alone or in combination with PD1) and BRAF/MEKi have activity,[7–9] while those who initially respond to PD1 and then progress while off therapy may also benefit from retreatment with PD1 therapy.[10,11] Whether the efficacy of systemic treatment of patients who recur following adjuvant PD1 therapy is similar to those who progress after PD1 for advanced melanoma is unknown. It is also unknown whether the success of systemic therapy at recurrence is different in patients who recur during (ON) adjuvant PD1 therapy compared with those who recur following (OFF) therapy.

The aim of this study was to describe the nature of recurrence, management and outcomes of patients who recurred ON or OFF adjuvant PD1 therapy for resected melanoma.

METHODS

With local institutional board approval, data were collected retrospectively from 16 international sites. Between March 2015 and December 2018, all patients with resected stage III or IV melanoma who received at least one dose of adjuvant PD1 and had melanoma recurrence were included; new primary melanomas were not considered a recurrence. Patients who received adjuvant PD1 therapy on a clinical trial or as standard care were included, as were those who received combination adjuvant nivolumab with ipilimumab[4,5] (NCT03068455). The proportion of recurrence was estimated from the total number of patients that commenced adjuvant PD1 therapy for resected melanoma at all sites by data submission at 31 December 2018. The denominator included 214 patients who remained blinded on 1 : 1 randomised trials, where only one arm included a PD1 agent, which was halved to estimate the actual number receiving adjuvant PD1.

Clinical data regarding disease characteristics before adjuvant therapy, adjuvant treatments received, toxicity, timing and pattern of recurrences, method of detection, subsequent management and patient outcomes were collected. Patients had 12-weekly computed tomography surveillance including brain imaging (computed tomography or magnetic resonance imaging) and medical oncology review for at least 24 months from start of adjuvant therapy or until recurrence. Regional skin, subcutaneous or nodal metastases were reported as locoregional recurrence. Any distant or visceral metastases were reported as distant recurrence, including recurrence at a previously resected distant site. Investigators determined whether recurrence was primarily detected by symptoms, clinical examination or imaging. Patients were divided into those who recurred ON adjuvant PD1 therapy (recurred while receiving adjuvant PD1 or within 1 month of last dose of therapy) and those who recurred OFF adjuvant PD1 (greater than 1 month after last dose of adjuvant PD1). Clinical outcomes after subsequent systemic therapies were assessed using investigator-determined best response according to RECIST 1.1 (unconfirmed), progression-free survival (PFS) and overall survival (OS). Efficacy data [objective response rate (ORR)/PFS] were reported by therapy type, regardless of line of therapy, and OS data were reported from first line of systemic therapy at recurrence. ORR was calculated in assessable patients; patients who had recently commenced therapy <12 weeks, without response assessment and without clinical signs of progression, were recorded as non-assessable and were excluded from the denominator for ORR. Patients with cutaneous, acral or unknown primary melanoma were analysed together and are henceforth termed cutaneous. Patients with mucosal melanoma were analysed independently given the unique biology and inferior outcomes in the metastatic setting.[12]

Descriptive statistics were used (stratified by initial site of recurrence or treatment at recurrence, where appropriate), except for time-to-event outcomes (OS, PFS, recurrence-free survival and distant metastasis-free survival), which were analysed using the Kaplan—Meier method, with the log-rank test used to examine differences between subgroups. Systemic therapy responses were compared descriptively in subgroups and the exact binomial test was used to examine differences between them.

RESULTS

Patient characteristics and adjuvant therapy

From an estimated total of 850 patients treated with adjuvant PD1 therapy, 147 (17%) had melanoma recurrence during or following adjuvant PD1-based therapy (supplementary Figure S1, available at *Annals of Oncology* online). Those who recurred had received adjuvant nivolumab (67 patients, 46%), pembrolizumab (40 patients, 27%), nivolumab with 'low dose' ipilimumab 1 mg/kg every 6 weeks (18 patients, 12%) or nivolumab ± 'low dose' ipilimumab on a blinded trial (22 patients, 15%). Median time from starting PD1 to last follow-up was 13.3 months (range 1.4—42.3). Median time from first recurrence to last follow-up was 7.7 months (range 0.2—33.6).

The majority of patients had cutaneous melanoma ($n = 136$, 93%) and 11 had mucosal melanoma (analysed separately). Most patients (119 patients, 88%) had resected stage III melanoma, 97 (71%) of whom underwent completion lymph node dissection surgery (CLND), and 17 (13%) had resected stage IV melanoma.

Timing and nature of initial recurrence

Median time to first recurrence from starting adjuvant PD1 was 4.6 months (range 0.3—35.7 months). Most patients recurred ON adjuvant PD1 (104 patients, 76%), at a median 3.2 months. Of the 32 patients (24%) who recurred OFF adjuvant PD1, median time to recurrence was 12.5 months. A total of 21/32 patients (66%) had discontinued adjuvant PD1 early for toxicity after a median 2.3 months (range 0.4—11.3), 10 completed 1 year of adjuvant PD1 and one

withdrew consent to continuing adjuvant PD1 after 1 month. In those who recurred OFF adjuvant PD1, median time to recurrence from ceasing adjuvant PD1 was 5.5 months (range 1.0—24.2).

Across the cutaneous cohorts ($n = 136$), initial recurrences were locoregional alone in 59 (43%), distant alone in 55 (40%) and concurrent locoregional and distant recurrence in 22 (16%) (supplementary Table S1, available at *Annals of Oncology* online).

In the cohort with stage III melanoma at baseline ($n = 119$), 60 (50.4%) developed distant metastases at initial recurrence, including 12 (20%) with brain metastases (Figure 1A—C). Distant metastases were more frequent in those with macroscopic versus microscopic nodal disease at baseline ($P = 0.04$, supplementary Table S1, available at *Annals of Oncology* online) and in older patients (median age 59 years versus 54 in those with only locoregional metastases, $P = 0.01$). Of the 52 patients with microscopic nodal disease identified on sentinel node biopsy who recurred, 39 had a prior CLND of whom 15 (38%) recurred in the nodal basin, and 13 did not have a prior CLND of whom six (46%) recurred in the nodal basin.

The method of detection of first recurrence differed by the pattern and type of recurrence in patients with resected stage III at baseline (Figure 1B). Most distant recurrences were identified solely on imaging (65%, 39/60 patients), especially in those without concurrent locoregional recurrence (78%, 32/41 patients).

Of the 59 patients who recurred initially with only locoregional metastases, 22 (37%) later developed distant metastases, at a median follow-up of 8.3 months (range 1—31) from first recurrence. At the end of the study period, of the patients with stage III melanoma at baseline, 82 patients had stage IV disease (69%) and 37 still had stage III disease (31%).

Management of resectable locoregional recurrence

Across the cutaneous stage III and IV cohorts ($n = 136$), at first recurrence, 59 patients had locoregional recurrence alone, and 48 (81%) of these were resectable. All patients with resectable locoregional recurrence had surgery, either alone (29, 49%), with adjuvant PD1 (eight, 14%), with adjuvant radiotherapy (12, 20%) or with adjuvant BRAF/MEKi (four, 7%) (Figure 2). Median follow-up from resectable locoregional recurrence was 8.3 months (range 1—31) and 27/48 (56%) resected patients had further recurrence, with distant metastases in 18 (38%). Of four patients treated with adjuvant BRAF/MEKi following initial recurrence, none have yet recurred at a median follow-up of 6.5 months (range 0—8).

Management of distant and unresectable locoregional recurrence

In total, 108 (79%) patients developed unresectable locoregional or distant disease during the study. At data cut, median OS from unresectable locoregional or distant recurrence was 21.3 months [95% confidence interval (CI) 12.3—not reached (NR)] and 26 patients (24%) had died, at a median follow-up of 6.5 months (range 0—31).

Of 105 patients who received treatment, 35 (33%) had ipilimumab-based therapy first line (10 had monotherapy, 25 had combination with PD1), 32 (31%) had BRAF/MEKi, 16 (15%) had PD1 alone or in combination with an investigational agent (11 PD1 monotherapy, 5 on an PD1/L1-based combination trial) and 22 (21%) had local therapy for distant recurrence to render the patient free of measurable disease. Differences were observed between the treatment groups (supplementary Table S2 and Results S1, available at *Annals of Oncology* online).

Median follow-up from start of systemic therapy for recurrence ranged from 5.5 to 8.4 months, depending on

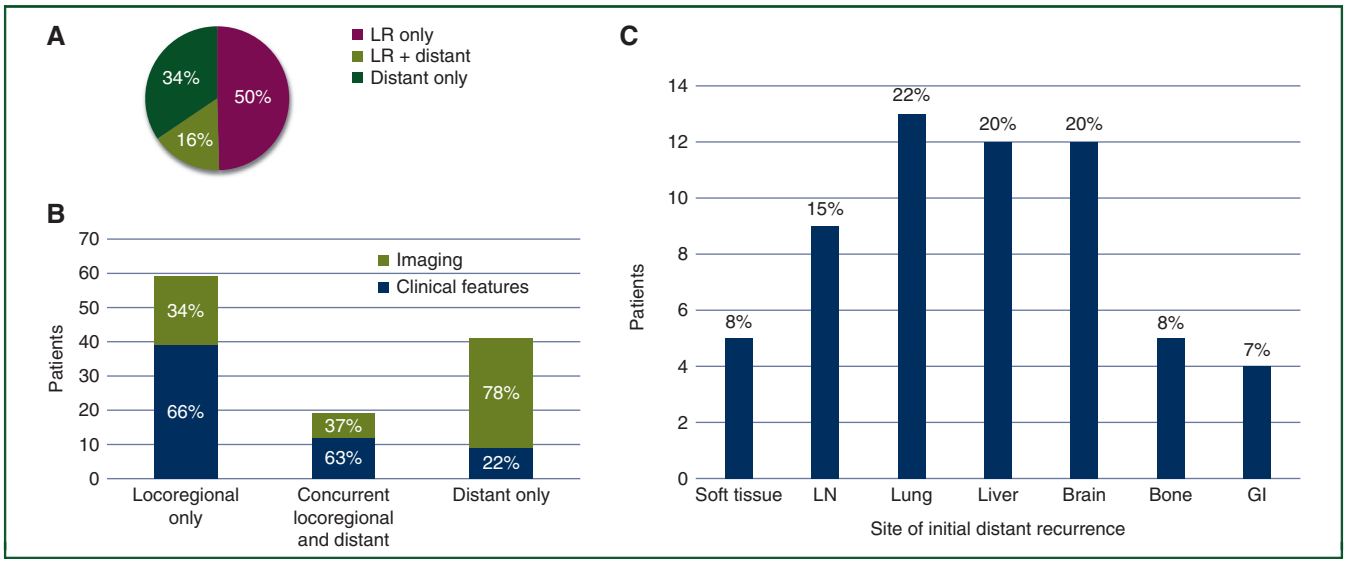

Figure 1. Pattern of initial recurrence in 119 patients with resected stage III at baseline in (A), including primary method of detection ($n = 119$) in (B) and organ site in those with distant metastases at initial recurrence ($n = 60$) in (C), classified by most advanced site (by AJCC M category) in those with multiple sites.
All patients had computed tomography staging and brain imaging at recurrence.
GI, gastrointestinal; LN, lymph node; LR, locoregional.

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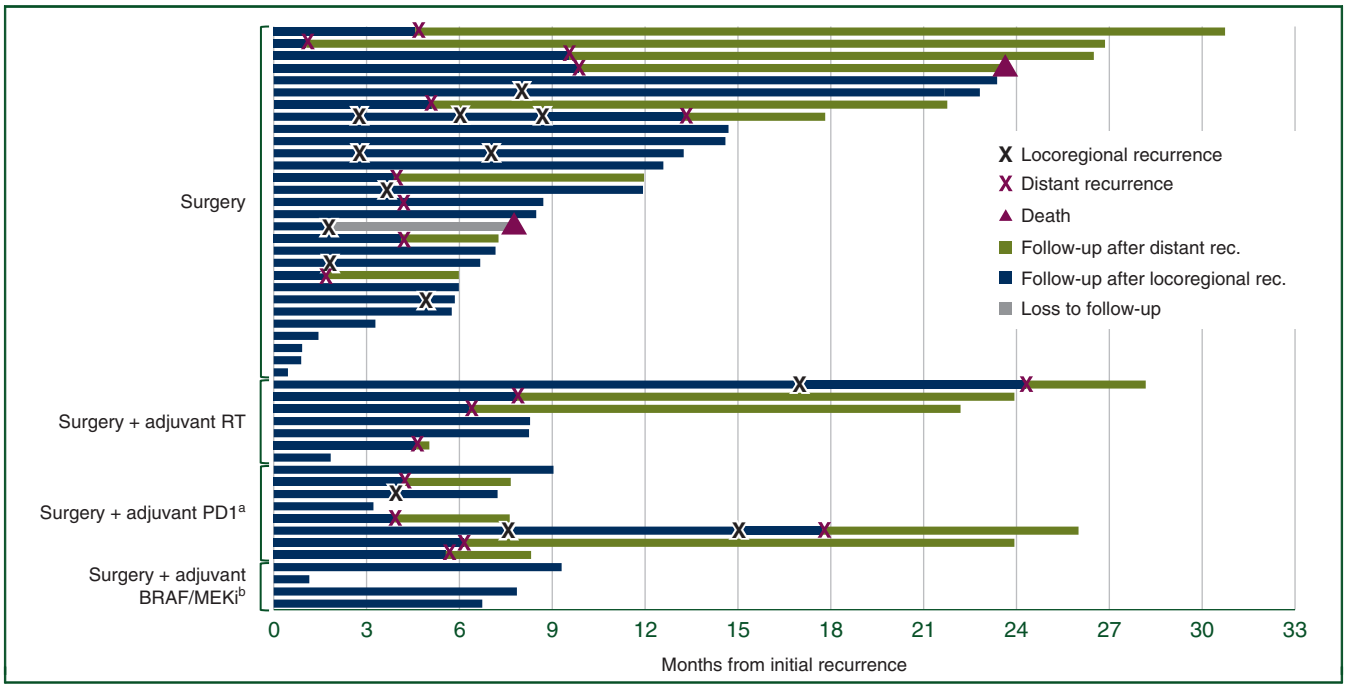

Figure 2. Management of resectable locoregional recurrence ($n = 48$), with individual patients grouped according to treatment at recurrence (y-axis), showing follow-up in months after surgery for initial recurrence (x-axis), and subsequent locoregional or distant relapse or death according to key.

[a] Three patients had adjuvant anti-programmed cell death protein 1 antibodies (PD1) and adjuvant radiotherapy (RT).

[b] Two patients had adjuvant BRAF/MEK and adjuvant RT.

treatment group (Table 1). The overall response rate to ipilimumab-based therapy was 26%, 10/38 [95% CI 14%—43%, three complete responses (CRs)], and to BRAF/MEKi was 82%, 27/33 [95% CI 64%—93%, 12 complete responses (CRs)]. The 6-months PFS was 40% and 70%, respectively (Figure 3A). Ipilimumab-based therapy had efficacy in those who recurred ON adjuvant therapy [8/33, 24% (supplementary Table S3, available at *Annals of Oncology* online)] and in those who recurred OFF adjuvant therapy (2/5, 40%), as did BRAF/MEKi (18/23, 78% ON therapy, 9/10, 90% OFF therapy), with similar PFS in those who recurred ON versus OFF adjuvant therapy for ipilimumab and BRAF/MEKi (Figure 3B and C). Ipilimumab activity appeared similar whether used as monotherapy or combined with PD1 (supplementary Results S2, available at *Annals of Oncology* online).

Notably, there were no responses (0/6) to PD1 therapy in patients who recurred ON adjuvant PD1, while two out of five (40%) patients who recurred OFF adjuvant PD1 responded to retreatment PD1 therapy at recurrence. Retreatment of patients who recurred ON adjuvant PD1 with PD1 was associated with inferior PFS to those OFF adjuvant PD1 (median 2.3 months versus NR, Figure 3D). The two patients who recurred OFF treatment and

Table 1. Responses to first-line and subsequent systemic therapies for unresectable locoregional or distant recurrence

	Ipilimumab (±PD1)	BRAF/MEKi	PD1 monotherapy	PD(L)1 + novel agent[c]
N	44[a]	40[b]	14	11
Recurred ON PD1	38	27	9	10
Recurred OFF PD1	6	13	5	1
Median F/U (months)	8.4	5.5	8.4	6.4
ORR, % (95% CI)[d]				
Total	26 (14—43)	82 (64—93)	18 (2—52)	11 (0—48)
Recurred ON PD1	24 (12—43)	78 (56—93)	0 (0—46)	13 (0—53)
Recurred OFF PD1	40 (5—85)	90 (55—100)	40 (5—85)	0 (0—96)
6-Month PFS, % (95% CI)	40 (26—58)	70 (52—93)	26 (10—68)	18 (3—93)
Median OS[e], months (95% CI)	21.3 (17.6—NR)	12.3 (8.7—NR)	NR	5.5 (4.2—NR)

Efficacy data (ORR/PFS) by drug in total cohort regardless of line of therapy. ORR reported for each systemic agent and in those who recurred during or following adjuvant PD1.
CI, confidence interval; IDOi, indoleamine 2,3-dioxygenase inhibitor; NR, not reached; ORR, objective response rate; OS, overall survival; PD(L)1, anti-programmed cell death (ligand) 1 antibodies; PFS, progression-free survival.

[a] Includes one who was treated on a clinical trial with ipilimumab, nivolumab and IDO-inhibitor and one treated with ipilimumab + TLR9-agonist.

[b] A total of 38/40 patients had dabrafenib and trametinib, one patient had vemurafenib and cobimetinib, one patient had encorafenib and binimetinib.

[c] PD1 + novel agents included PD1/-LAG3, -PDL1/MEKi, PD1/TLR9-agonist and PD1/IDOi.

[d] 95% CI for ORR are based on exact binomial test.

[e] OS reported for first-line therapy only.

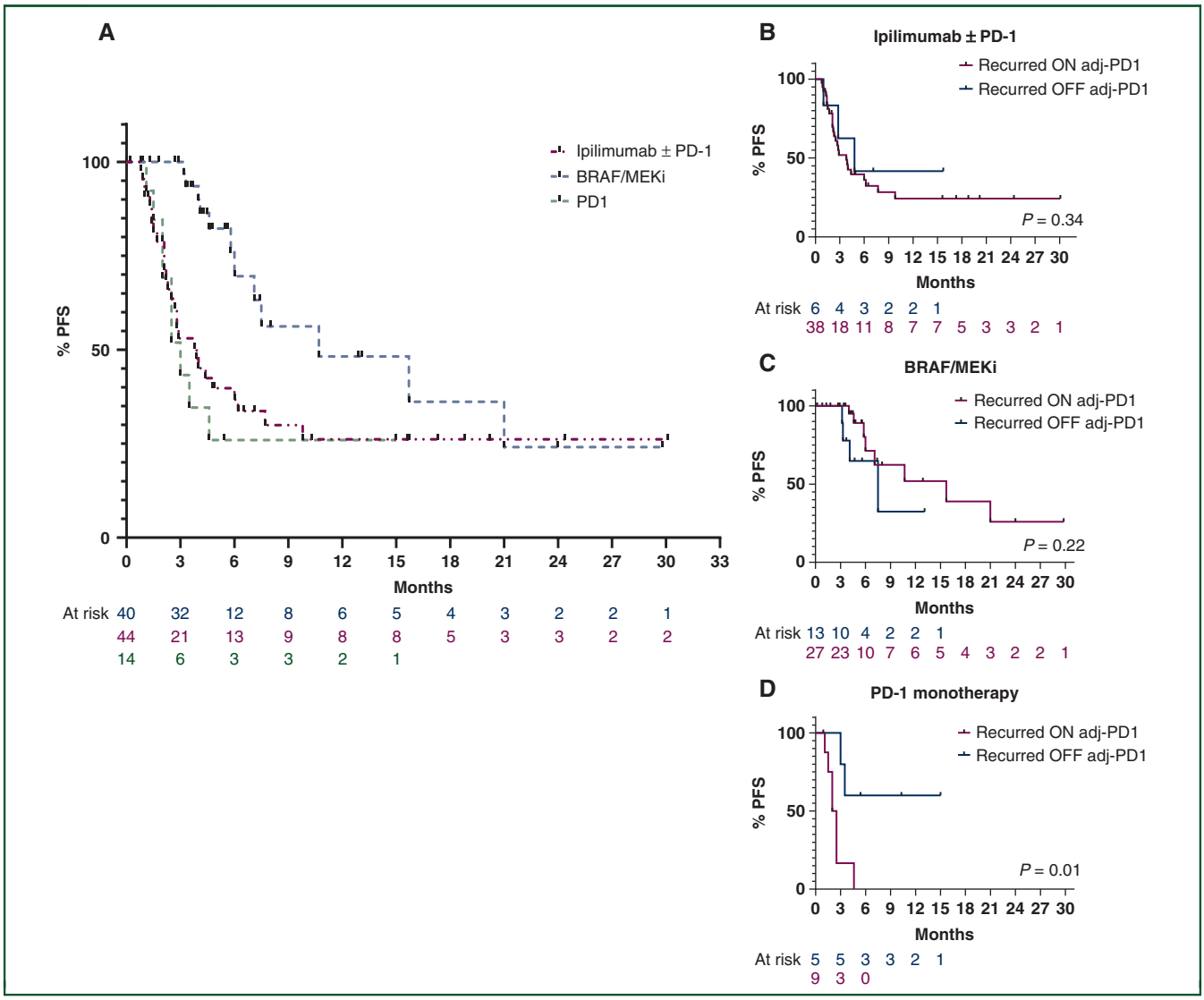

Figure 3. Progression-free survival for standard systemic therapies at recurrence (first-line and subsequent therapies, *n* = 98) (A) and by systemic therapy, according to recurrence ON or OFF adjuvant PD1 (B—D).
Adj, adjuvant; PD-1, programmed cell death protein 1; PD1, anti-programmed cell death protein 1 antibodies; PFS, progression-free survival.

responded to retreatment with PD1 had completed the 1-year standard adjuvant treatment, recurred 5.6 and 13.5 months following PD1 cessation, and remain in response on PD1 after 10.3 and 5.4 months of treatment, respectively.

In 25 patients who underwent definitive local therapy for distant recurrence without systemic therapy (as first-line or subsequent treatment), median follow-up from local therapy was 16.7 months (range 0—26) and 17 (68%) have progressed.

Mucosal melanoma recurrence

Eleven patients with primary mucosal melanoma recurred following adjuvant PD1 therapy. Before adjuvant PD1, five patients had resected stage IV melanoma and six had resected stage III. One patient had a *BRAF*^{V600E} mutation. Median time to recurrence from starting adjuvant PD1 therapy was 3.1 months (range 0.4—7.9), 10/11 (91%) recurred ON adjuvant PD1 and one recurred OFF adjuvant PD1, having discontinued for toxicity after 2.7 months. All 11 patients had distant metastases at recurrence, including four with concurrent locoregional metastases. At recurrence, seven patients received ipilimumab-based therapy; all with evaluable responses (5/5) had progressive disease. Of the remaining four, two had palliative radiotherapy alone, one patient had a partial response with BRAF/MEKi and one patient had progressive disease on PD1 monotherapy. Median follow-up from initial recurrence was 4.8 months (range 0.5—33.6 months); three patients have died, with estimated median OS from initial recurrence 9.2 months (95% CI 6.9—NR).

DISCUSSION

The nature and best management of patients with melanoma who recur early, either during (ON) or following (OFF) adjuvant PD1 therapy, has not been reported to date, and is challenging as most landmark trials have been carried out in

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systemic treatment-naïve patients. Given the extraordinary impact PD1 therapy has had across a range of advanced-stage cancers, these results in the adjuvant setting in melanoma will likely have broad implications for other solid tumours likely soon to be treated with adjuvant PD1. This multicentre, retrospective analysis of 147 patients showed that those who recur locoregionally and have local therapy often develop distant recurrence shortly thereafter. There was a lack of activity of PD1 monotherapy in those who recur ON adjuvant PD1, while further PD1 monotherapy may have activity in those who recur OFF adjuvant PD1.

In patients with melanoma recurrence despite adjuvant PD1, systemic therapy can be active, but response rates appear to vary by drug class and whether patients recur ON or OFF therapy. Ipilimumab-based immunotherapy and BRAF/MEKi are most active, with response rates of 26% and 82%, respectively. Ipilimumab activity was comparable to both that observed in advanced melanoma after PD1 progression, and that of single-agent ipilimumab in the PD1-naïve setting,[1,2] suggesting that PD1 resistance may not necessarily confer CTLA-4 resistance.[7] In our study, a limited number of patients had also received prior anti-CTLA-4 (low dose and 8-weekly) in combination with PD1 as adjuvant therapy, and higher doses of ipilimumab may be important for response, especially given the dose-response relationship observed in the metastatic setting.[13] Response rates to ipilimumab alone or in combination with PD1 were similar in this study, whereas retrospective data in advanced melanoma suggests higher activity of combination therapy than single-agent ipilimumab following PD1 progression.[8] Prospective data are needed (NCT03179436, NCT03033576).

For patients with *BRAF*^{V600}-mutant melanoma, BRAF/MEKi are an alternative subsequent therapy, with a high response rate (82%), however durable survival will likely be achieved only in a small subgroup of patients given data from metastatic trials.[14] For patients who recur OFF adjuvant PD1, rechallenge with single-agent PD1 therapy may be considered, however the small numbers of patients treated with this approach prevent the identification of a specific window period between cessation, recurrence and retreatment where this is effective. A few patients who recurred ON PD1 continued PD1 monotherapy at recurrence and predictably none responded; these cases had mostly recurred very early on adjuvant therapy, and PD1 therapy was likely continued in case of an emergent delayed response. The small group of patients with mucosal melanoma included did not benefit from subsequent therapies (most often CTLA-4 blockade). This supports genomic data indicating that mucosal melanoma is a different from cutaneous melanoma, and remains an area of high unmet clinical need.[15,16]

In our study, 50% of the recurrences in patients with stage III melanoma were distant at first relapse, which is consistent with historical data in the era before effective adjuvant therapies,[17] and clinical trial data of PD1 and BRAF/MEK therapies.[4–6] The most common sites of initial distant recurrence were lung, liver and brain. The rate of brain metastases at initial recurrence (20%) appears higher than that reported in the era pre-effective systemic therapies,[17] however this is likely attributable to changes in clinical practice, whereby regular surveillance brain imaging is now routine, resulting in a higher rate of detection of asymptomatic brain metastases. Consistent with historical data,[17] most distant recurrences were identified on surveillance imaging, whereas most locoregional recurrences were clinically evident. Therefore, regular surveillance imaging (including brain imaging) remains worthwhile to detect distant recurrence before symptoms developing, particularly within 12 months, during which 88% of recurrences occurred in our study.

Most patients who recurred locoregionally underwent resection. Despite this, there was a high rate of subsequent relapse both locoregionally and distantly. These data suggest that systemic therapy is not only required after distant recurrence, but also after resected locoregional recurrence. Of note, no subsequent relapses were observed in four patients treated with BRAF/MEKi; however, follow-up is limited (median 6.5 months). In the COMBI-AD trial, recurrence was uncommon in the first 12 months while patients were on dabrafenib and trametinib, but sharply increased in the first year off therapy.[6]

The majority of patients with micrometastatic nodal involvement underwent CLND before adjuvant PD1 in our study, which is no longer standard practice following the DeCOG-SLT and MSLT-II trials.[18,19] This change of practice may impact contemporary recurrence patterns; locoregional recurrence in the nodal basin may become more frequent as most patients no longer undergo CLND, although we saw no difference in nodal recurrence between those who did or did not undergo CLND in our study with short follow-up.

The majority of patients in this study recurred early, ON adjuvant PD1 therapy, and follow-up post-recurrence is relatively short (median 7.7 months). Similarly, some patients had short follow-up from commencement of salvage therapy such that robust response assessments could not be made. As such, this study largely represents early recurrence, which likely shares similar resistance mechanisms to those seen with primary resistance in the metastatic setting. Melanoma that recurs later, for example, many years following adjuvant therapy, may have a different biology and response to systemic treatment. Given the short follow-up and minority of recurrences OFF adjuvant PD1 (many of which were still within a few months of cessation of therapy, and due to long receptor binding time, could still be considered similar to those ON therapy), it will be particularly important to study those with late recurrence (beyond 1 year), especially since our data suggest that clinical activity of systemic therapies in this setting, particularly retreatment PD1, may be clinically relevant.

In conclusion, this is the first study exploring the nature and management of recurrence during or following adjuvant PD1 therapy in melanoma. With adjuvant PD1 therapy being a standard of care for high-risk resected melanoma, and now being tested in trials across a range of cancers, these data are crucial to guiding clinical management. The poor outcome of patients who recur ON adjuvant PD1

identifies a patient group in great need of new therapeutic options. Clinical trials in advanced melanoma should not exclude this growing group of patients. Furthermore, these data serve as an important framework as adjuvant PD1 therapy is introduced more broadly across oncology.

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Ethics committee approval

All participating sites have local Human Research Ethics Committee approval.

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