Nature and management of melanoma recurrences following adjuvant anti-PD-1 based therapy

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Nature and management of melanoma recurrences following adjuvant anti-PD-1 based therapy

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ABSTRACT

Introduction: Approximately 50 % of resected stage II-IV melanoma patients develop recurrent disease by 5 years despite adjuvant anti-PD-1 therapy. Data to define best management of recurrences is lacking.
Methods: This was a multicentre, international, retrospective cohort study. Patients with resected stage II-IV melanoma who commenced adjuvant anti-PD-1-based therapy before January 2022 and later recurred were identified. Data on demographics, disease characteristics, recurrence patterns, management and outcomes were collected.
Results: 711 patients from 17 sites were included. Median age was 60 [range 16–92], 64 % were male, 2 % stage II, 91 % were stage III, 7 % stage IV. Median time to recurrence was 6.2 months (0–68.5) and median follow up time from recurrence was 19.8 months (range 0.2–73.1). 63 % recurred on anti-PD-1 therapy, 36 % off therapy [3 % < 6 months, 33 % > 6 months]. Initial recurrences were locoregional (LR) alone in 44 %, distant alone (DR) in 43 %, and 11 % in both sites. LR recurrences were managed with local therapy, alone (62 %) or with "second

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adjuvant" anti-PD-1 (14 %) or BRAF/MEK therapy (23 %); 12 m RFS2 was 25 %, 29 % and 69 % respectively (p = 0.0045). Definitive systemic therapy at first recurrence was given in 16 % LR and 86 % DR, with best outcomes for anti-CTLA4 + anti-PD-1 and trial combinations (24 m PFS 63 % and 69 %, respectively). The 24 m OS for the entire cohort was 65 %.

Conclusion: Most recurrences following adjuvant anti-PD-1 based therapy occur early and while still on drug. Outcomes are poor, regardless of site, timing of recurrence, and subsequent treatment.

1. Introduction

Anti-PD-1 therapy has revolutionised treatment of melanoma[1,2], improving overall survival in patients with stage IV melanoma and reducing the risk of recurrence in resected melanomas both with and without regional nodal involvement[1,3,4].

Despite a 40–50 % reduction in recurrence risk, nearly 50 % of patients still recur at various timepoints, including during adjuvant systemic anti-PD-1 therapy[5]. 'Early' recurrences are defined by convention as recurrences diagnosed during or within 6 months of therapy completion (considered PD-1 resistant), and 'late' as any point thereafter (considered potentially PD-1 responsive)[6]. There are little to no data to support such distinctions, nor the presumed implication of drug resistance. Furthermore, there is a lack of data about this population of patients who progress on adjuvant anti-PD-1 and their defining characteristics[7]. Limited information on retreatment outcomes is available from small cohort studies of real-world experience[8,9] and limited follow-up of clinical trial cohorts[10]. In these, earlier timeframes of recurrence were associated with inferior survival outcomes [10], particularly when recurrences were ON adjuvant anti-PD-1 therapy as opposed to OFF[9]. Reported success of rechallenge anti-PD-1 is generally poor, but higher when paired with ipilimumab or with targeted treatments[8,9].

Several other studies have assessed the success of subsequent therapies following failure of anti-PD-1 therapy, predominantly in the metastatic setting. We have previously described 355 patients treated with ipilimumab either alone or in combination with anti-PD-1 therapy following anti-PD-1 failure, reporting a response rate of 31 % for combination and 13 % for single-agent[11]. This rate was subsequently confirmed in a small prospective study[12].

There is an urgent need to determine the optimal treatment for patients who relapse despite anti-PD-1 based therapy and devise strategies to improve outcomes, not only in the advanced melanoma setting but also following neo/adjuvant treatments. Consequently, we performed a multicentre, retrospective study of patients recurring following adjuvant anti-PD-1 therapy to describe disease recurrence characteristics and subsequent management.

2. Methods

We collected data retrospectively from 17 international sites on patients with resected stage II-IV melanoma who received at least one dose of adjuvant anti-PD-1 therapy between January 2015 and January 2022 and had experienced a recurrence event. Patients who participated in an unblinded clinical trial of adjuvant therapy, and those who received anti-PD-1 adjuvant therapy after prior neoadjuvant treatment were included.

Recurrence events were defined as either local (between the primary site and the draining lymph node basin; LR) or distant recurrence of the melanoma for which the patient received adjuvant therapy (DR). Patients with multisite recurrences, ie both locoregional and distant sites of recurrent disease; were considered part of the distant recurrence group. Development of a second primary melanoma was not considered an event.

Patient records were reviewed for demographic information, reasons for treatment cessation, toxicity requiring immunosuppressant use, and disease characteristics at the time of adjuvant therapy and at each subsequent recurrence. Site, onset and stage of disease recurrence and method of treatment was obtained. Clinical outcomes following systemic treatment of recurrences were evaluated by each investigator according to RECIST v1.1[13] and at intervals determined by institutional practice or relevant clinical trial protocol. Progression free survival (PFS) and overall survival (OS) were evaluated from the date of initial recurrence as landmark percentages at 1, 2 and 3 years. Second relapse-free survival (RFS2) and distant metastasis free survival (DMFS) were evaluated from the date of commencement of adjuvant therapy to second occurrence of disease for those with first recurrences that were treated by local therapy (either ablative radiotherapy or surgical resection) with definitive intent. This was reported using landmark percentages at 1 and 2 years.

We used descriptive statistics to summarize characteristics of patients and disease, as well as the type of treatment for recurrent disease, dividing these by pattern of recurrence as locoregional versus distant recurrences. Median follow up and time-to-event endpoints (OS, PFS, as well as DMFS and RFS2 in locoregional recurrences) were additionally analysed according to the Kaplan-Meier method, and log rank testing was used to provide hazard ratios estimating treatment effect between groups.

We also assessed outcomes within specific subgroups of interest. These subgroups included (1) patients who received second adjuvant therapy following definitive treatment of a local recurrence; and (2) patients recurring ON anti-PD-1 therapy as opposed to OFF anti-PD-1 therapy, where 'ON-treatment' was defined as recurrence during or within 6 months of completing adjuvant PD-1 therapy.

3. Results

3.1. Features of initial adjuvant therapy

The study included 711 patients across 17 international sites. The median age was 59.5 years (range 16–92), and 259 were female (36 %). Almost all were stage III (N = 641, 91 %), mainly IIIB (N = 170, 24 %) and IIIC 54 % (N = 381, 54 %), while few were stage II (N = 18, 2 %) and IV (n = 51, 7 %) (Table 1). Three-quarters (N = 536, 75 %) of patients underwent sentinel node biopsy prior to anti-PD-1 therapy, and 44 % (N = 236) underwent primary therapeutic or completion nodal dissection.

The majority of patients (N = 635, 90 %) were treated with anti-PD-1 monotherapy as adjuvant therapy, with fewer receiving a combination with anti-CTLA4 or other agents (70 [10 %], and four [1 %], respectively). Median duration of adjuvant treatment was 5.5 months (range 0–34 months; 0.2–148 weeks). Only 142 (20 %) patients completed an entire 12 months of treatment. Treatment cessation in this population occurred due to disease recurrence while on drug in 444 (63 %), for toxicity in 115 (16 %), by patient choice in eight (1 %) and for undocumented reasons in two (<0 %).

3.2. Timing of initial recurrence

Median follow up of all patients following commencement of adjuvant therapy was 28.4 months (range 1–107 months). Almost half the patients (N = 338, 48 %) recurred within 6 months of starting adjuvant therapy, a quarter (N = 166, 23 %) recurred between 6–12 months, and of the remainder 140 (20 %) recurred between 12–24 months and 59 (8 %) recurred after 24 months (Fig. 1**A**). Median time to recurrence was

Table 1
Demographic data at commencement of adjuvant anti-PD-1 immunotherapy.

		N (%)
Age	Median [range]	59.5 [16.0 −92.0]
Sex	Male	451 (64 %)
Melanoma subtype	Cutaneous non-acral	481 (68 %)
	Acral	54 (8 %)
	Mucosal	20 (3 %)
	Occult/unknown	155 (22 %)
Mutational status	BRAF MT	312 (44 %)
Neoadjuvant therapy	Yes	16 (2 %)
	No	690 (98 %)
Stage at adjuvant commencement	IIA	3 (0 %)
	IIB	5 (1 %)
	IIC	11 (2 %)
	IIIA	50 (7 %)
	IIIB	178 (25 %)
	IIIC	389 (55 %)
	IIID	22 (3 %)
	IV	53 (7 %)
Sentinel lymph node biopsy	Yes	536 (75 %)
Completion lymph node dissection	Yes	236 (44 %)
Adjuvant therapy	PD−1 alone	635 (89 %)
	PD−1 + other*	74 (11 %)

* includes CTLA-4, BRAF/MEK inhibitor, TVEC, bempegaldesleukin, mR-4157

6.2 months (range 0–69 months).

Fig. S1 demonstrates the flow of analysis for included patients.

3.3. Sites of disease recurrence

Initial recurrences were LR in 315 (44 %), and distant (DR) in 385 (54 %). A proportion of those with distant recurrences experienced concurrent locoregional and distant disease recurrence (N = 78, 11 %) and data was incomplete for 11 (2 %). Sites of recurrent disease are demonstrated in Fig. 1**B.**

3.4. Locoregional recurrences and "second adjuvant" therapy

For those with LR alone, 220 (70 %) underwent local therapy with the intent rendering them no evidence of disease. A minority of patients (N = 49, 16 %) received systemic therapy alone; the outcome of these patients is analyzed in combination with those with a distant recurrence.

Of those undergoing local therapy, 95 (43 %) had surgery alone, and 42 (19 %) had surgery with adjuvant RT alone. One third (N = 83, 37 %) received local therapy and then "second adjuvant" systemic treatment. Median follow up from local recurrence was 18.9 months (range 0–76.9).

Second adjuvant therapy included further anti-PD-1 agents in 30 (28 %) patients, combination BRAF/MEK therapy in 49 (46 %) patients, and other agents in 15 (14 %) patients, involving combinations of anti-PD-1 and either anti-CTLA-4 agents or injectables. Due to concerns about whether this was true second adjuvant treatment, we did not include the latter group in our analysis. Second adjuvant anti-PD-1 therapy was a continuation of prior agents in 22 patients (73 %) and rechallenge in 8 (27 %). Table S1 provides demographics for patients who had local therapy with and without second adjuvant therapy. With a median follow up time from first recurrence of 19.8 months (range 0.2–73.1), the landmark 12 month RFS2 was 25 % (95 % CI 17–37) for those receiving definitive local therapy alone, inferior to those receiving further anti-PD-1 (29 %, 95 % CI 14–61) and those receiving adjuvant BRAF/MEK (69 %, 95 % CI 49–96, p = 0.0045) (Figure 2A). Distant metastasis-free survival at 12 months was 43 % (95 % CI 32–57) for local therapy alone but improved with either modality of second adjuvant therapy (73 % (95 % CI 53–100) anti-PD-1, 85 % (95 % CI 68–100) BRAF/MEK respectively (p = 0.0052) (Figure 2B).

The efficacy of second adjuvant anti-PD-1 therapy could be influenced by the interval between adjuvant anti-PD-1 and initial recurrence. Most (N = 22, 73 %) patients receiving second adjuvant anti-PD-1 therapy had recurred within 6 months of last PD-1 therapy. Despite limited numbers, RFS2 at 12 months was similar at 29 % (95 % CI 12–65) in the on-treatment recurrences and 33 % (95 % CI 67–100 %) in the off-treatment recurrences (p = 0.29, Figure 2C).

After an initial LR, 170 (54 %) had a further recurrence. Of these, 54 (32 %) were locoregional and 99 (58 %) were distant. Median time to second recurrence was 6.7 months (0–61.2). Of those that recurred with distant disease, 29 (29 %) M1b, 44 (44 %) M1c and 26 (26 %) M1d (Fig. S3).

3.5. Distant recurrences

Of those who first recurred with distant disease, 107 (15 %) were M1b, 133 (19 %) M1c, and 68 (10 %) M1d. For those with M1c disease, 66 (50 %) involved liver, 57 (43 %) bone, 8 (6 %) bowel, and 35 (26 %) other viscera. A minority of patients whose initial recurrence was at distant sites received local therapy alone with either curative (resection to NED, ablative radiotherapy, surgery and adjuvant radiotherapy; N = 28, 9 %) or palliative intent (N = 15, 5 %). The majority received systemic therapies with or without additional local therapies (N = 79 (21 %) and N = 250 (65 %) respectively). Median follow up time from distant recurrence was 14.2 months (range 0–70.7).

Forty-nine (15 %) patients with DR received further anti-PD-1 monotherapy, 131 (41 %) received combination anti-CTLA-4 + anti-

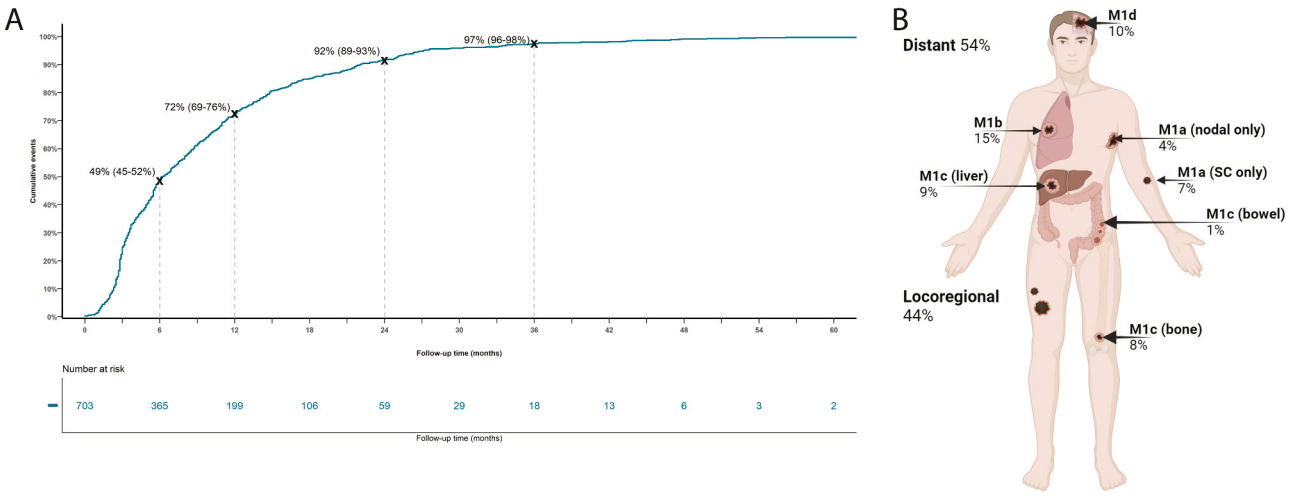

Fig. 1. : (A) Time to recurrence for the total population (n = 711); **(B)** Sites of recurrent disease.

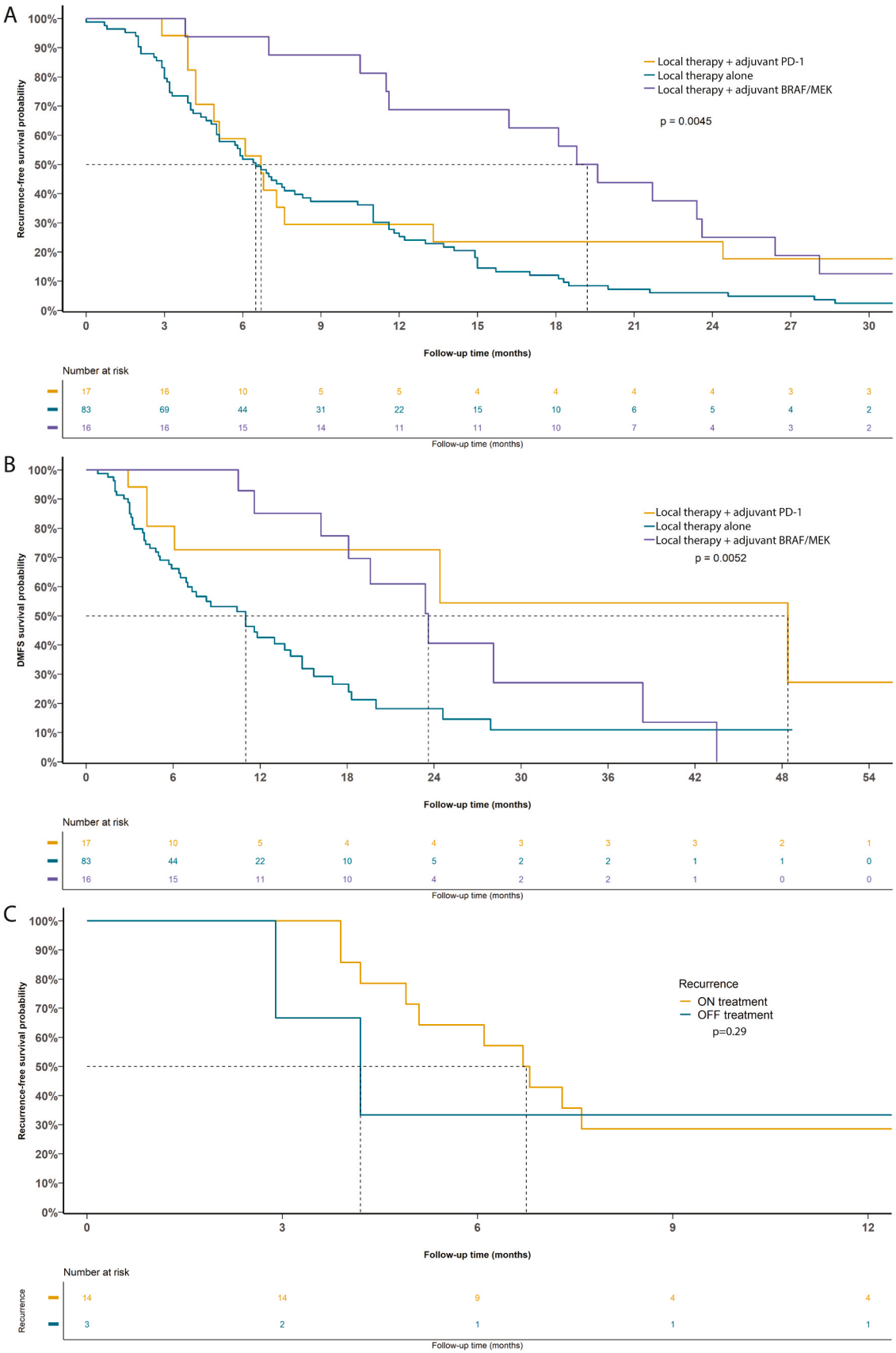

Fig. 2. Kaplan-Meier curves for **(A)** second relapse-free survival (RFS2),**(B)** distant metastasis-free survival (DMFS2) for locoregional recurrences by treatment group, and **(C)** RFS2 by on/off anti-PD-1 recurrences.

PD-1, 19 (6 %) received anti-CTLA-4 monotherapy, 92 (28 %) received combination BRAF/MEK inhibition and 32 (10 %) received other therapies, most through clinical trials. For PFS, both 12 month and 24 month landmarks were better for patients receiving investigational agents, dual immunotherapy and BRAF/MEK inhibitors compared to anti-PD-1 or anti-CTLA4 monotherapy ($p = 0.005$) (Fig. 3A and B, Table S2). Although the 12 month OS was comparable for all systemic therapies (anti-PD-1 75 % (95 % CI 63–89); combination anti-CTLA4/anti-PD-1 71 % (95 % CI 63–79); BRAF/MEK inhibition 71 % (95 % CI 62–81); investigational agents 69 % (95 % CI 54–87)), the 24-month OS showed greater differences. Dual immunotherapy and BRAF/MEK inhibitors demonstrated the highest 24-month landmark OS (53 % (95 % 44–65) and 54 % (95 % CI 44–66) respectively), whilst anti-PD-1 therapy and investigational agents decreased substantially (41 % (95 % CI 27–61) and 41 % (95 % 27–63), respectively), although overall did not meet statistical significance ($p = 0.2$). ORR and DOR are presented in Table S2.

For patients who received further anti-PD-1 therapy for distant non-resectable recurrences, 27 (55 %) recurred ON prior adjuvant anti-PD-1 agents, and 22 (45 %) OFF prior adjuvant anti-PD-1 agents. There was a numerically higher overall response rate (ORR) (32 % versus 17 %) and improved 12-month PFS (72 % versus 36 %) in patients who recurred OFF initial adjuvant treatment, although numbers were small and neither met significance ($p = 0.127$ and $p = 0.052$, for ORR and PFS respectively). (Figure 3C).

Numbers were too small to assess outcomes of systemic treatment for mutational subtypes.

3.6. Overall survival

Landmark overall survival from the time of initial recurrence of the entire cohort was 81 % at 12 months and 65 % at 24 months respectively (Fig. S2A). For those that recurred ON therapy, there was a tendency towards reduced OS compared to those recurring OFF therapy; 12 month OS 69 % vs 84 % and 24 month OS of 35 % vs 52 %, $p = 0.083$ (Fig. S2B).

Patients with local disease only as first manifestation of recurrence had improved OS compared to distant or multisite disease ($p < 0.001$) (Fig. S2C).

4. Discussion

For patients recurring after adjuvant anti-PD-1 therapy, early recurrences are common, occurring predominantly during adjuvant treatment and as an even distribution of local and distant disease. Limited numbers made it difficult to draw conclusions regarding recurrences ON and OFF adjuvant anti-PD-1 and the influence of different mutations, however outcomes were poor regardless of the treatment regimen utilized for disease recurrence, intention of the systemic treatment and the timing of recurrent disease. Slight exceptions to this were an apparent short-term benefit of second adjuvant BRAF/MEK treatment and improved survival for those with a locoregional distribution of disease at first recurrence.

Rates of locoregional recurrence were similar in our population as reported in studies of adjuvant anti-PD-1 [5,14,15]. Notably, this equivalence was in spite of mandated CLND prior to adjuvant treatment in these trial populations for those with sentinel node positivity[2,3] and omission of SLNB in a substantial number of our included patients, with acknowledged concerns for the accuracy of staging[16]. Nearly 80 % of patients received local therapies, many also receiving a further course of adjuvant therapy. 'Second adjuvant' BRAF/MEK, when compared to other agents demonstrated benefit in the short-term, however the high rate of subsequent recurrences, poor RFS2 and DMFS despite optimal management suggests this population may require alternative approaches or treatment sequencing, inclusive of neoadjuvant administration. Indeed, with regulatory approval of neoadjuvant immunotherapy, many of the patients included in our overall population may have been contemporary candidates for a neoadjuvant approach.

We observed similar frequency and sites of distant disease recurrence to those reported in the EORTC-1325/Keynote-054 clinical trial of adjuvant pembrolizumab therapy[14], as well as the more recent CHECKMATE-238 comparison of adjuvant nivolumab versus ipilimumab[10]. For patients with distant disease at recurrence, systemic therapy is the backbone of treatment, although outcomes were generally poorer for all modalities of systemic therapy compared to anti-PD-1 naïve patients. Differences were slightly less for BRAF/MEK combinations, with outcomes approximating those reported in registration trials [17–19], as well as ipilimumab monotherapy where there was consistency with reported numbers for response and survival[20–23].

However, while reported rates of response to first-line anti-PD-1 monotherapy in the metastatic setting range between 32.9–45 % [21–24] and 58 % for combination[1,23,25,26], our rates were 24 % and 34 % respectively, with a median duration of response barely meeting 6 months. This was improved marginally for patients recurring outside of the 6 month 'window' compared to those recurring ON anti-PD-1, although these differences failed to meet significance and small numbers limited our ability to draw definitive conclusions.

Two prior retrospective studies have assessed post-PD-1 treatment efficacy, presenting 355[11] and 147[8] patients progressing on anti-PD-1 therapy in metastatic and adjuvant settings respectively. Of these patients, responses were observed to both ipilimumab monotherapy and combination, consistent with our results and suggesting alternative mechanisms for anti-CTLA4 resistance from those mediating resistance to anti-PD-1 therapy. High response rates to combination BRAF/MEK therapy were also noted, and an absence of benefit to further anti-PD-1 therapy for those defined as recurring on drug. This heterogeneity of responses to further anti-PD-1 across studies for those progressing through anti-PD-1, would suggest use of the 6 month 'window' to be a crude measure for anti-PD-1 sensitivity, likely capturing tumors with heterogeneous biology, and the need to characterize disease resistance on more objective measures.

Our study has limitations. Many of the subgroup analyses included small numbers of patients, thus lacking statistical power to confirm numerical trends and limiting assessment of important subgroups. Furthermore, patients were subject to treatment selection bias regarding management of recurrence, with significant heterogeneity of treatments compromising accuracy of outcome estimates. Similarly, there was heterogeneity in the adjuvant treatment undertaken, with inclusion of various anti-PD-1 combinations and neoadjuvant therapy. While limited by small numbers and being reflective of a real-world population, this could also impact measurement of outcomes. Early recurrences predominated, introducing uncertainty as to whether late recurrences would demonstrate different features, these being more likely secondary rather than primary anti-PD-1 resistance. Finally, despite being a high quality retrospective cohort study, there will be inherent non-measurable biases as well as potential reporting errors and missing data based on quality of medical record keeping.

Notably, this was exclusively a population of patients who recurred and therefore we cannot assess for differences between this population and those not suffering a recurrence. Nevertheless, the general decline in outcomes suggests that failure of adjuvant anti-PD-1 therapy portends a worse prognosis and strategies to improve the efficacy of adjuvant immunotherapy should be a research priority. Furthermore, this high-risk population should be prioritized in studies of novel therapies such as TIL administration following confirmation of a recurrence. For those who do develop distant disease, outside of novel drugs and clinical trials, use of BRAF/MEK combinations and integration of anti-CTLA4 offer better survival outcomes than further anti-PD-1 monotherapy. Similarly, for locoregional disease, 'second adjuvant' BRAF/MEK may benefit patients in the short term, although novel treatment sequencing such as a neoadjuvant or even a 'second neoadjuvant' approach is worthy of consideration.

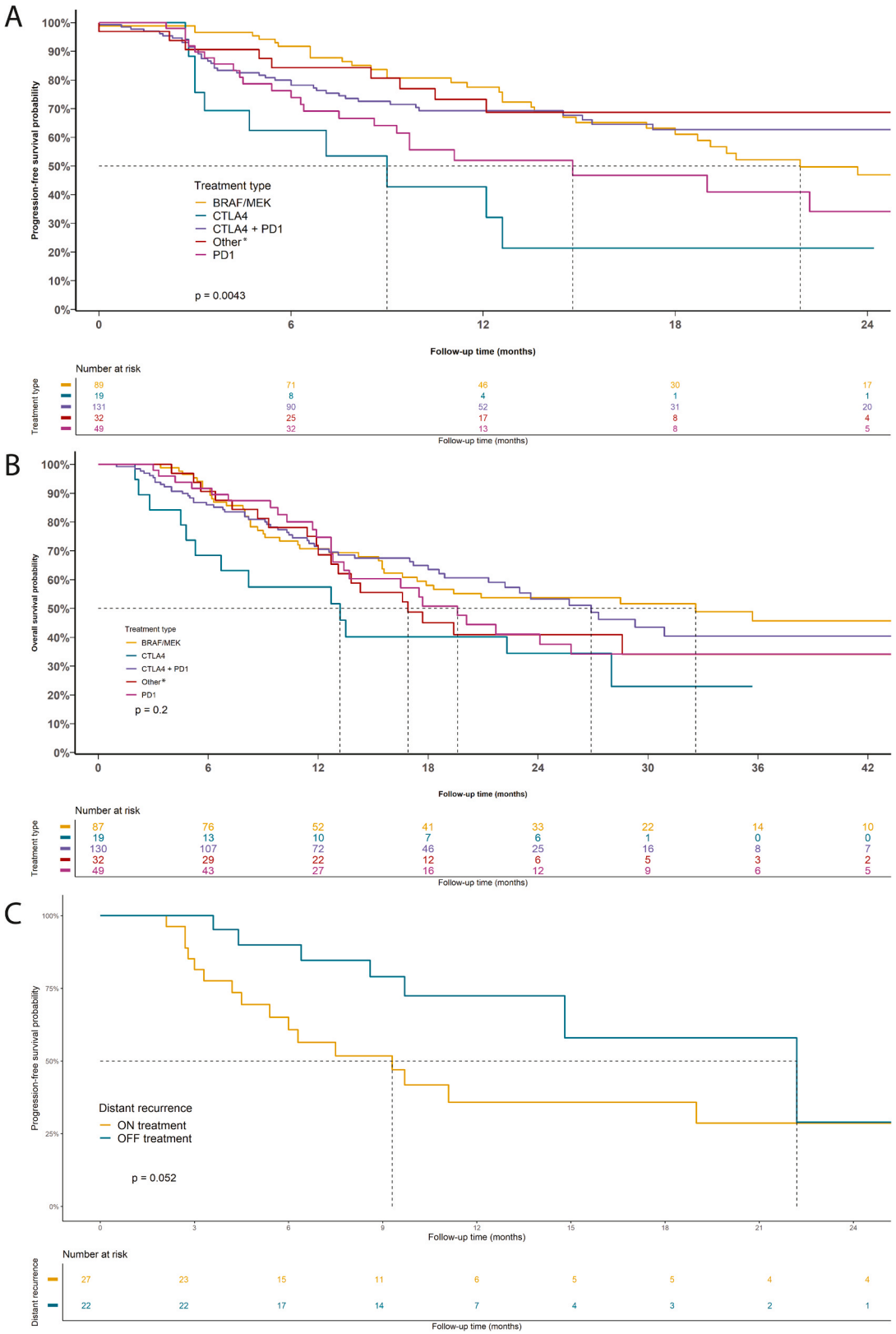

Fig. 3. Kaplan-Meier curves for **(A)** progression-free survival (PFS) by treatment modality for distant recurrences receiving definitive systemic treatment, **(B)** overall survival (OS) by treatment modality for distant recurrences receiving definitive systemic treatment, and **(C)** PFS for distant recurrences occurring on- and off-adjuvant anti-PD-1. * 'Other' includes investigational therapies, including pembrolizumab + lenvatinib, cobimetinib + atezolizumab, carboplatin + paclitaxel, pembro + BO-112, anti-PD-1 + WNT inhibitor, pembrolizumab + TIGIT + MK1308, LXH254 + LTT, imatinib, MK7902–003, pembrolizumab + Lenvatinib + MK1308, cemplimab + SAR, sitravatinib + tiselizumab, TIL, MK1308A, IMCgp100, bevacizumab, pembrolizumab + TVEC, ipilimumab + nivolumab + relatlimab, nivolumab + relatlimab, dasatinib, MVR T3011, MK3475 + MK1308 + MK7684, MK1308 + MK3475 + Lenvatinib, anti-PD-1 + anti-TIM3 + anti-LAG3, CV8102, atezolizumab + vemurafenib + cobimetinib, spartalizumab + ribociclib, pembrolizumab + iNEST vaccination, TVEC.

These data are drawn from the largest population of patients with disease recurrence after adjuvant anti-PD-1 to date and support evidence already reported in smaller cohorts. While this data requires prospective evaluation, our preliminary results can guide clinicians and patients regarding efficacy of subsequent therapies.

5. Conclusion

For patients recurring after adjuvant anti-PD-1 therapy, early recurrences are common, frequently occurring while still on drug. Outcomes are generally poor, regardless of the time frame for disease recurrence and often irrespective of subsequent treatment. Novel drug therapies and clinical trials are urgently required to identify and address primary and acquired resistance to anti-PD-1 therapy.

Statement of ethics

Ethics approval was not required in the formulation of this manuscript.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AMM has served on advisory boards for BMS, MSD, Novartis, Roche, Pierre-Fabre, and Qbiotics. JK has received research funding from LEO Pharma, honorium from BMS, Amgen, Janssen; and educational funding from MSD, Janssen and Astra Zeneca. RRT has served on advisory boards for BMS, MSD, Amgen, Pierre-Fabre, Astra Zeneca and Roche. CL has received research funding from BMS, Roche, consulting fees from BMS, Pierre-Fabre, Sanofi, Novartis, MSD, Amgen, Merck Serono, Roche and Iflax; speaking fees from Amgen, BMS, Pierre-Fabre, Sanofi, Novartis, MSD, Incyte, Pfizer, Roche; and travel funding from BMS, MSD, Novartis, Pierre-Fabre, Roche, Sanofi and served on advisory boards for BMS, Pierre Fabre, Sanofi, Novartis, MSD, Magen, Merck Serono, Roche and Inflax. CA has received travel funding from BMS, Roche and Amgen and speaking fees from Novartis. RJS has served on advisory boards for Merck, Novartis, Pfizer, and Replimune and receives grant funding from Merck. CR has served on advisory boards for Pierre Fabre, Sanofi, BMS, MSD, Novartis, Merck, Roche, Pfizer, Sun Pharma, Ultimovacs, Regeneron, Egle, Philogen, Maat Pharma; involved in steering committees for Novartis, Regeneron, Pfizer and IO Biotech and a consultant IDMC for Ultimovacs; received speaking fees from Pierre Fabre, Sanofi, BMS, MSD and Novartis and travel funding from Pierre Fabre. JM has intermittent project focused consultant or advisory relationships with Merck Sharp & Dohme, Novartis, Bristol Myers Squibb, Johnson & Johnson, and Pierre Fabre and has received travel support from L′ Oreal, Merck Sharp & Dohme, Bristol Myers and Squibb and Pierre Fabre outside of the submitted work. MSC has served on advisory boards or as a consultant for Amgen, BMS, Eisai, Ideaya, MSD, Nektar, Novartis, Oncosec, Pierre Fabre, Qbiotics, Regeneron, Roche, Merck, and Sanofi and received honoraria from BMS, MSD, and Novartis. DBJ has served on advisory boards or as a consultant for AstraZeneca, BMS, The Jackson Laboratory, Mallinckrodt, Merck, Mosaic ImmunoEngineering, Novartis, Pfizer, Targovax, and Teiko, and has received research funding from BMS and Incyte. BN has received financial compensation from Novartis, Roche, BMS, MSD, and Pierre-Fabre for service on advisory boards and speaking engagements; and institutional research funding from Pfizer, Novartis, Roche and Merck-Serono. VR has received honoraria from AstraZeneca and has received travel and education funding from MSD and Novartis. PAA has served as a consultant for BMS, MSD, Roche-Genentech, Ventana, Novartis, Amgen and Array and received research funding from BMS, Roche-Genentech and Ventana. JW has served as a consultant for Merck, Genentech, AstraZeneca, GSK, Novartis, Nektar, Celldex, Incyte, Biond, Moderna, ImCheck, Sellas, Evaxion, Pfizer, Regeneron, EMD Serono, and Bristol Myers Squibb; has had equity roles in Biond, Evaxion, OncoC4, and Instill Bio; received institutional research support from Bristol Myers Squibb, Merck, GSK, Moderna, Pfizer, Novartis, and AstraZeneca; served in scientific advisory roles with CytomX, Incyte, ImCheck, Biond, Sellas, Instill Bio, OncoC4, and NexImmune; and holds patent agreements with Moffitt Cancer Center and Biodesix. PR has received honoraria from BMS, MSD, Novartis, Pierre-Fabre, Merck and Sanofi; and served in an advisory capacity for MSD, BMS, Sanofi, Pierre-Fabre, Blueprint Medicines and Philogen. GAM has received institutional research funding through Roche-Genentech, MSD, Roche, and BMS and other funding through Novartis and BMS. SH has served as a consultant for Amgen, Genmab, Xencor, Astellas Pharma, Regeneron, and Nektar. AA has served as a consultant for BMS, Roche, Novartis, Pierre Fabre, MSD, Merck, Sanofi; received speaking fees from Pierre Fabre, Novartis, MSD, BMS, Roche, Merck, Sanofi; institutional funding from Pierre-Fabre, Novartis, Roche, BMS, MSD, Merck and Sanofi; and travel funding from BMS, MSD, Novartis, Pierre-Fabre. AH has served on an advisory board for BMS, MSD and Novartis. RD has received honoraria from Roche, Novartis, Bristol Myers Squibb, MSD, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, CatalYm, Second Genome, Regeneron, Alligator Bioscience,

MaxiVax, touchIME, T3 Pharmaceuticals, Pfizer; served as a consultant for Roche, Bristol Myers Squibb, MSD, Novartis, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, CatalYm, Second Genome, Alligator Bioscience, touchIME, MaxiVax, Regeneron, Pfizer, T3 Pharmaceuticals and received institutional research funding from Roche, BMS, Novartis, MSD and Amgen. CUB has served as a consultant for AstraZeneca, Bristol-Myers Squibb, GenMab, GlaxoSmithKline, Lilly, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Roche/Genentech, and Third Rock Ventures; received institutional research funding from SC, Bristol-Myers Squibb, NanoString Technologies, and Novartis; provided expert testimony for Freshfields Bruckhaus Deringer; received travel funding from BMS; and has ownership interest in Immagene and Signature Oncology. GVL has received honoraria from BMS, Pierre-Fabre and received served as a consultant for Agenus, Amgen, Array BioPharma, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion Biotech, Hexal AG (Sandoz Company), Highlight Therapeutics, Innovent Biologics USA Inc, Merck Sharp & Dohme, Novartis, OncoSec Medical Australia, PHMR Limited, Pierre Fabre, Provectus, QBiotics, Regeneron, and AstraZeneca. The remaining authors have nothing to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115055.

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