Dabrafenib plus trametinib versus anti-PD-1 monotherapy as adjuvant therapy in *BRAF* V600-mutant stage III melanoma after definitive surgery: a multicenter, retrospective cohort study

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Summary

Background Both dabrafenib/trametinib (D/T) and anti-PD-1 monotherapy (PD-1) are approved adjuvant therapies for patients with stage III *BRAF* V600-mutant melanoma. However, there is still a lack of head-to-head comparative data. We aimed to describe efficacy and toxicity outcomes for these two standard therapies across melanoma centers.

Methods This multicenter, retrospective cohort study was conducted in 15 melanoma centers in Australia, China, Germany, Italy, Japan, UK, and US. We included adult patients with resected stage III *BRAF* V600-mutant melanoma who received either adjuvant D/T or PD-1 between Jul 2015 and Oct 2022. The primary endpoint was relapse-free survival (RFS). Secondary endpoints included overall survival (OS), recurrence pattern and toxicity.

Findings We included 598 patients with stage III *BRAF* V600-mutant melanoma who received either adjuvant D/T (n = 393 [66%]) or PD-1 (n = 205 [34%]) post definitive surgery between Jul 2015 and Oct 2022. At a median follow-up of 33 months (IQR 21–43), the median RFS was 51.0 months (95% CI 41.0-not reached [NR]) in the

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D/T group, significantly longer than PD-1 (44.8 months [95% CI 28.5-NR]) (univariate: HR 0.66, 95% CI 0.50–0.87, P = 0.003; multivariate: HR 0.58, 95% CI 0.39–0.86, P = 0.007), with comparable OS with PD-1 (multivariate, HR 0.90, 95% CI 0.48–1.70, P = 0.75). Similar findings were observed using a restricted-mean-survival-time model. Among those who experienced recurrence, the proportion of distant metastases was higher in the D/T cohort. D/T had a higher incidence of treatment modification due to adverse events (AEs) than PD-1, but fewer persistent AEs.

Interpretation In patients with stage III *BRAF* V600-mutant melanoma post definitive surgery, D/T yielded better RFS than PD-1, with higher transient but lower persistent toxicity, and comparable OS. D/T seems to provide a better outcome compared with PD-1, but a longer follow-up and ideally a large prospective trial are needed.

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Keywords: Adjuvant therapy; BRAF V600 mutation; Melanoma; PD-1; Dabrafenib/trametinib

Research in context

Evidence before this study

We searched PubMed from database until Mar 31, 2023, for articles using the following search terms: 'stage III melanoma' AND '*BRAF*' AND 'adjuvant' AND ('anti-PD-1' OR 'PD-1' OR 'nivolumab' OR 'pembrolizumab' OR 'toripalimab') AND ('dabrafenib and trametinib' OR 'MAPK pathway inhibitors' OR 'MAPKi'). We found 23 articles, among which only 4 studies evaluated clinical outcomes of D/T versus PD-1 in the adjuvant setting. None of these studies have performed multivariate analysis in the *BRAF* V600 mutant stage III melanoma to minimize the effect of confounding factors, nor reported recurrence pattern. Safety comparisons did not delineate transient versus long-term toxicity outcomes. Additionally, the generalizability is limited due to limited geographic distribution of participating centers.

Added value of this study

In this large, retrospective, multicenter, cohort study of 598 patients with stage III *BRAF* V600 mutant melanoma, we showed that in the real-world setting, when treatments reflected clinician and patient choice rather than being protocol-mandated, those who received adjuvant D/T had a longer RFS than did those who received PD-1 monotherapy, with a better long-term toxicity profile. Moreover, these results held true in both Cox and RMST models and D/T remained independently correlated with longer RFS after adjustment for multiple confounders.

Implications of all the available evidence

Adjuvant D/T is associated with better RFS and long-term toxicity data than PD-1 and had comparable OS with PD-1 in patients with stage III *BRAF* V600 mutant melanoma. We also have also identified subgroups of patients that are more likely to benefit from D/T compared to PD-1, which may help facilitate clinical decision-making.

Introduction

BRAF V600 mutation is one of the most common hotspot mutations in melanoma, present in 40–50% of the cutaneous subtype[1] and 10–20% of acral/mucosal subtypes.[2] In the past decade, the prognosis of patients with *BRAF* V600 mutant melanoma has substantially improved thanks to the introduction of both small molecule *BRAF*/*MEK* inhibitors and immunotherapy. *BRAF*/*MEK* inhibitors (dabrafenib/trametinib, D/T) and anti-PD-1 monotherapy (PD-1) have been approved as standard post-definitive surgery adjuvant therapies for stage III *BRAF* V600 mutant melanoma, based on large randomized control trials demonstrating prolonged relapse-free survival (RFS).[3–6] Although emerging real-world data[7,8] with short follow-up suggested that there might be RFS advantage of D/T over PD-1 at 12-month landmark, these were subgroup comparisons between D/T and PD-1 regardless of *BRAF* mutation status and melanoma stage and with no confounder adjustment. In addition, there is still a lack of direct comparison between recurrence pattern and toxicities, especially those with long-term impact (e.g., chronic hormone supplementation). Therefore, the clinical therapeutic choice is still challenging and made on an individual case by case basis due to the lack of direct comparison between these two mainstay therapeutic options.

We therefore performed a large, multicenter, retrospective cohort study to determine the efficacy and safety profiles of adjuvant D/T and anti-PD-1

monotherapy in patients with stage III *BRAF* V600 mutant melanoma after definitive surgery.

Methods

Study design and participants

In this multicenter, retrospective, cohort study, we included patients aged ≥18 years with resected stage III *BRAF* V600-mutant melanoma, who received either D/T or PD-1 in the adjuvant setting after definitive surgery between Jul 2015 and Oct 2022, at 15 melanoma centers in Australia, China, Germany, Italy, Japan, UK, and the US. Recurrence was defined by radiological evaluations (RECIST v1.1) and according to the treating physicians' best clinical judgement. Patients with uveal melanoma were excluded. Patients who received neoadjuvant therapy before surgery or had any prior PD-1 or MAPK pathway inhibitor exposure were excluded.

Ethics

This overall study was approved by IRB of Peking University Cancer Hospital & Institute (2021KT131) with individual patient consent waived due to its retrospective nature and was conducted in accordance with Declaration of Helsinki. Local IRB approvals and/or informed consent from participant centers were obtained when needed according to local regulations. Specifically, this study was approved by IRB without individual patient consent at the following centers due to its retrospective nature: Alfred Health, Peking University Cancer Hospital, Vanderbilt University Medical Center, National Cancer Center Hospital Japan, Saitama Medical University International Medical Center, UPMC. This study was approved as a clinical audit (reference number 3409) at University of Manchester and Christie NHS Foundation Trust; as an internal audit under Caldicott Guidelines at Newcastle University Centre for Cancer. It was approved by Istituto Pascale's Ethical Committee with the protocol DSC 33/22 oss (all patients signed an informed consent, which allowed the use of clinical data for research purposes and analysed in an anonymous manner. The deidentified data from Istituto Pascale presented in this study are available in a public, open-access repository at https://zenodo.org/record/7795552). All patients from MGH were consented to DF/HCC protocol 11–181. This study was approved by IRB and patients gave informed consent for data collection at University of Turin Medical School. The melanoma group at University of Perugia has an overall EC approval to collect info of melanoma patients and a consent to collect info for research purposes, which covered this study. All MIA patients were consented according to the following protocol: Protocol No X15-0311 & 2019/ETH06854—"Melanoma Institute Australia: Melanoma Research Database" approved by SLHD HREC (RPAH Zone). At the University Medical Center Hamburg-Eppendorf (UKE) there was an IRB approval and all documented patients gave their informed consent. The data from Royal Marsden NHS Foundation Trust was generated via an approved service evaluation, with no requirement for patient consent.

Procedures

All patients included in this study had definitive surgery before the initiation of either adjuvant D/T or PD-1. Patients then received either D/T or PD-1 monotherapy (pembrolizumab, nivolumab, or toripalimab) based on access to therapies, treating physician and/or patient choice.

Patient demographics (e.g., sex, age, self-identified ethnicity), disease (melanoma subtype, primary anatomic site, thickness, ulceration, mitotic rate, stage per AJCC 8th edition,[9] surgery type [the last surgery prior to the initiation of adjuvant therapy] [wide resection, sentinel lymph node biopsy, completion lymph node dissection, adjuvant radiotherapy, etc.) and baseline characteristics, as well as adjuvant pertinent information (e.g., treatment duration, cessation, dose modification and corresponding reasons) were collected and analysed. Safety data were collected continuously from the initiation of either D/T or PD-1 until 1 year after the final dose if no further systemic treatment was given, or the beginning of the next systemic therapy, or the data cutoff (Feb 17, 2023), whichever came first. Adverse events (AEs) were graded at the time of event by treating physicians, and all AE data were independently reviewed, quality controlled, and attributed to study treatment by an independent medical oncologist, and afterwards confirmed by another to ensure consistency across different centers. The severity of treatment-related AEs were graded via the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. As per JITC immune-related adverse event (irAE) consensus definition,[10] we considered persistent irAEs those which remained present longer than three months following treatment discontinuation. The same criteria were used for D/T-related adverse events. Patients were followed-up independently by each center.

Outcome

The primary endpoint of this study was RFS, defined as the period between the definitive surgery and the development of local recurrence and/or distant metastasis or death or last follow-up, whichever came first. The secondary endpoints included overall survival (OS), defined as the period between the definitive surgery and death or last follow-up, whichever came first; furthermore, recurrence pattern and toxicity to D/T versus PD-1 monotherapy. Toxicities were described based on organ/system affected, grades, whether led to adjuvant therapy modification (permanent termination versus treatment modification [including schedule interruption and/or dose reduction]) and outcomes (persistent versus

not). Recurrence pattern was categorized by distant metastasis versus local recurrence.

Statistics

Sample size calculation was performed using the Cox proportional hazard model (thresholds: alpha = 0.05, power = 0.8, HR = 0.7, D/T:PD-1 = 2:1). In total, 278 events were required. Assuming that 50% of the patients had RFS events, and taking into account 5% loss of follow-up, in total 584 patients were required. The UCSF sample size calculators for designing clinical research were employed for this calculation [https://sample-size.net/sample-size-survival-analysis/].

Categorical variables (e.g., sex) were summarized by frequency and percentage, and continuous variables (e.g., age) were summarized by median and IQR. Baseline characteristics were compared between the two treatment groups using Wilcoxon rank sum test for continuous variables and Pearson's Chi-square test with Yates' correction (or Fisher's exact test if expected count per cell < 5) for categorical variables. All primary and secondary endpoints were assessed in the entire cohort. Univariate tests for survival outcomes (both RFS and OS) were performed through Kaplan–Meier survival curves using the log-rank test and Cox proportional hazards regression model. Multivariable Cox proportional hazard models were performed to assess the adjusted difference between the two treatments. First, a univariable Cox regression was performed on each baseline variables and those with a moderate association with outcome, defined as P-value < 0.2 [for categorical variables with >2 categories, at least 1 category with P-value < 0.2], were included in the multivariable analysis as adjustment factors for adjuvant therapy effect. To account for potential management differences between sites that may impact patients' outcomes, site was included as a stratification factor in all Cox models. Multivariable analyses were performed based on complete case analysis with the frequency of missing values and total sample reported for transparency. Restricted mean survival time (RMST) is a nonparametric measure when the proportional hazards assumption cannot be made. RMST is defined as the area under the survival curves between groups up to a preset time.[11] With the concern that the proportional hazard assumption of Cox model may not hold, a pre-planned secondary analysis using RMST[12] model at a preset landmark of 2-year was performed for both RFS and OS.

A subgroup analysis comparing RFS between D/T and PD-1 was planned for clinically relevant pre-specified subgroups, including sex, age, ethnicity (Caucasian and Asian), melanoma subtypes (non-acral-cutaneous/unknown primary (NAC/UP) and acral/mucosal), *BRAF* V600 mutation types (V600E and V600K), surgery types (sentinel lymph node biopsy, SLNB; complete lymph node dissection, CLND), and the American Joint Committee on Cancer (AJCC) staging; and also anatomic locations of the primary sites within the NAC/UP subgroup. Subgroup analyses were performed based on complete case analysis and were not adjusted for multiple comparison, thus considered to be exploratory. Subgroup results were displayed via forests plots including median time of event for each subgroup category and treatment, the HR (95% CI) between treatment within each subgroup category and the P-value of the interaction between subgroup and treatment.

All statistical tests were two-sided (or double-one-sided for Fisher's exact tests), and P < 0.05 was considered to be of statistical significance. Univariate comparisons of recurrence pattern and the development of different AEs were carried out via Fisher's exact or chi-square test in a context-dependent way. All analyses were performed using R version 4.2.2.

Role of the funding source

Dr. Xue Bai was supported by the Beijing Hospitals Authority Youth Programme (QMS20211101) for her efforts devoted to this study. Dr. Keith T. Flaherty was funded by Adelson Medical Research Foundation for the efforts devoted to this study. The Funders had no role in study design, data collection, data analyses, interpretation, or writing of report.

Results

We included 598 patients with resected stage III *BRAF* V600 mutant melanoma who received either D/T (n = 393, 66%) or PD-1 (n = 205, 34%) between Jul 2015 and Oct 2022 after definitive surgery. The groups were well balanced for most characteristics at the start of adjuvant D/T or PD-1, with the discrepancy for *BRAF* mutation types largely driven by different test methods between institutes; as well as surgery types and post-surgery radiotherapy (Table 1).

Efficacy

At a median follow-up of 33 months (IQR 21–43) (D/T group 29 months [IQR 18–40], PD-1 group 38 months [IQR 29–50]), the RFS was significantly longer in the D/T group than PD-1 (HR 0.66, 95% CI, 0.50–0.87, P = 0.003), but this did not translate into an OS advantage (HR 1.00, 95% CI 0.65–1.55, P = 0.99) (Fig. 1 and Table 2). In a multivariate analysis adjusting for covariates with moderate correlation with survival outcomes (P-value < 0.2), D/T was independently correlated with better RFS (HR 0.58, 95% CI 0.39–0.86, P = 0.007), but not with OS (HR 0.90, 95% CI 0.48–1.70, P = 0.75) (Supplementary Tables S1 and S2).

The 2-yr restricted mean survival time (RMST) for RFS in the D/T cohort was 21.8 months (95% CI 21.3–22.3); significantly longer than the PD-1 cohort, which was 19.0 months (95% CI, 17.9–20.0) (P < 0.001). D/T was independently correlated with better RMST

	D/T group (n = 393)	PD-1 group (n = 205)	P value
Age, years			0.5[b]
Median	56	55	
IQR	(44–65)	(42–66)	
Sex			0.2[c]
Male	207 (53%)	119 (58%)	
Female	186 (47%)	86 (42%)	
Melanoma subtype			0.6[d]
Non-acral cutaneous	352 (90%)	178 (87%)	
Unknown primary	21 (5%)	16 (8%)	
Acral	18 (5%)	9 (4%)	
Mucosal	2 (1%)	2 (1%)	
Ethnicity			0.1[d]
Caucasian	342 (87%)	172 (84%)	
African	0	1 (0%)	
Asian	42 (11%)	31 (15%)	
Hispanic	2 (1%)	0	
Unspecified	7 (2%)	1 (0%)	
BRAF mutation type			0.002[d]
V600E	323 (82%)	178 (87%)	
V600K	35 (9%)	22 (11%)	
Others[a]	5 (1%)	3 (1%)	
Unknown	30 (8%)	2 (1%)	
Stage			0.9[d]
IIIA	60 (15%)	26 (13%)	
IIIB	120 (30%)	62 (30%)	
IIIC	189 (48%)	106 (52%)	
IIID	20 (5%)	9 (4%)	
III unspecified	4 (1%)	2 (1%)	
SLNB			0.001[d]
Yes	269 (68%)	111 (54%)	
No	124 (32%)	93 (45%)	
NA	0	1 (0%)	
CLND			0.04[c]
Yes	146 (37%)	95 (46%)	
No	247 (63%)	110 (54%)	
Adjuvant radiotherapy			0.002[d]
Yes	4 (1%)	11 (5%)	
No	387 (98%)	191 (93%)	
Unspecified	2 (1%)	3 (1%)	

[a]Included 5 V600R, 1 V600D, 1 V600M, and 1 V600Q. SLNB: sentinel lymph node biopsy; CLND: complete lymph node dissection; NA, not available. [b]Wilcoxon rank sum test. [c]Chi-square test with Yates' correction. [d]Fisher's exact test.

Table 1: **Patient characteristics.**

after the adjustment covariates with moderate correlation with survival outcomes (P-value < 0.2) (Supplementary Table S3). The 2-year RMST for OS was not different between the D/T and PD-1 cohort (Supplementary Table S4).

Preplanned subgroup analyses of the primary endpoint RFS were performed based on age, sex, ethnicity, melanoma subtype, *BRAF* V600 mutation type, stage, and surgery types. D/T provided substantial survival benefit in most subgroups with varying statistical significance (Fig. 2). Sex seemed to be an effect modifier with female patients gaining more RFS benefit than male without adjustment for multiple comparison (Fig. 2). Within the NAC/UP subgroup, patients with head/neck seemed to benefit more significantly from D/T than PD-1, but the anatomic site of the primary lesion was not a statistically significant effect modifier (P = 0.11) (Supplementary Table S5).

By last follow-up, 109 and 93 patients had disease progression in the D/T and PD-1 group, respectively. The rate of distant metastasis was higher (79/109 [72%] versus 54/93 [58%], P = 0.045) in the D/T group

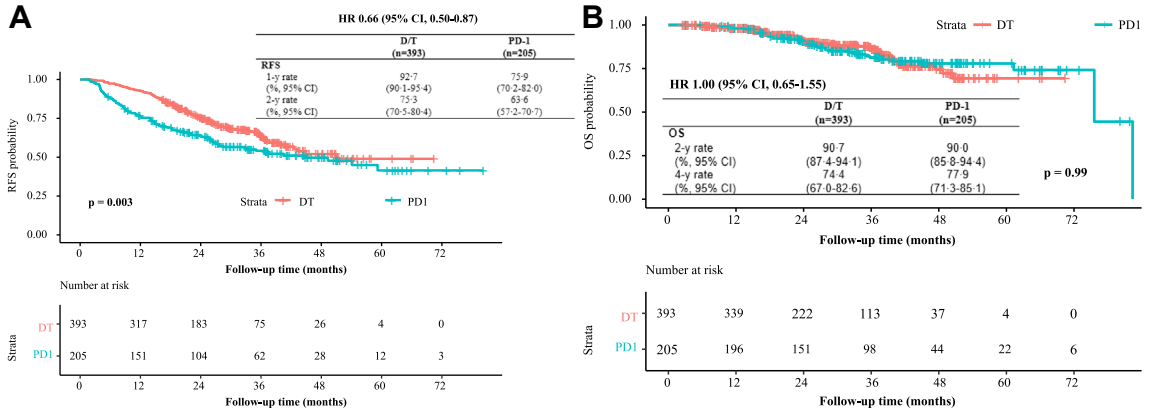

Fig. 1: Survival outcomes of adjuvant D/T and PD-1 treated patients with resected *BRAF* V600 mutant melanoma. A) RFS between D/T and PD-1 (P = 0.003). B) OS between D/T and PD-1 (P = 0.99). D/T, dabrafenib/trametinib; PD-1, anti-program death-1 antibody; RFS, relapse free survival; OS, overall survival.

compared to the PD-1 group. Local recurrence rate in the D/T group was numerically lower, although statistical significance was not achieved (46/109 [42%] versus 52/93 [56%], P = 0.07). The proportion of patients who received further local (surgery, radiation therapy, or cryoablation) and/or systemic therapies were similar in both cohorts (Supplementary Table S6). Those who received D/T in the adjuvant setting were more likely to receive immunotherapy (55/109 [50%] versus 24/93 [26%], P < 0.001), and those who received PD-1 in the adjuvant setting were more likely to receive MAPK pathway inhibitors as subsequent systemic therapy after recurrence (51/93 [55%] versus 24/109 [22%], P < 0.001) (Supplementary Table S6).

For patients who developed distant metastasis and received systemic therapy, those who received PD-1 in the adjuvant setting had higher objective response rate than D/T to the subsequent *BRAF*/*MEK* combo, but no substantial progression-free survival (PFS) benefits were observed; those who received D/T in the adjuvant setting seemed to respond better to subsequent PD-1 monotherapy, but the statistical power was limited due to sample size. Both adjuvant treatment groups demonstrated good response rates to PD-1/CTLA-4 combo, but PFS was shorter than *BRAF*/*MEK*i combo in both groups in this post-adjuvant setting. However small numbers limit conclusions which can be drawn. Details are listed in Supplementary Table S7.

	D/T (n = 393)	PD-1 (n = 205)
RFS		
Median (months, 95% CI)	51.0 (41.0-NR)	44.8 (28.5-NR)
1-y rate (%, 95% CI)	92.7 (90.1–95.4)	75.9 (70.2–82.0)
2-y rate (%, 95% CI)	75.3 (70.5–80.4)	63.6 (57.2–70.7)
3-y rate (%, 95% CI)	63.1 (57.1–69.8)	54.1 (47.2–62.0)
P-value	0.002	
OS		
2-y rate (%, 95% CI)	90.7 (87.4–94.1)	90.0 (85.8–94.4)
3-y rate (%, 95% CI)	86.2 (81.8–90.7)	81.2 (75.4–87.4)
4-y rate (%, 95% CI)	74.4 (67.0–82.6)	77.9 (71.3–85.1)
P-value	0.99	

NR, not reached.

Table 2: **RFS & OS by different adjuvant therapies (D/T versus PD-1).**

Adverse events (AEs)

Of the entire cohort, 97 (16%) patients discontinued adjuvant therapy due to toxicity, 250 (42%) had treatment modification (either treatment schedule interruption or dose reduction), and 66 (11%) had persistent AEs. D/T had a numeric higher incidence of treatment discontinuation or treatment modification than PD-1, but fewer long-lasting persistent AEs (Table 3).

The AE profiles of D/T and PD-1 differed substantially. The most common AEs that led to different consequences are listed in Supplementary Tables S8 and S9. Fever/chills and GI tract toxicity were the most commonly seen AEs that contributed to either permanent treatment discontinuation (26/393 [7%] and 13/393 [3%], respectively) or treatment modification (176/393 [45%] and 44/393 [11%], respectively) in the D/T cohort. Besides, other toxicities that contributed to permanent discontinuation in the D/T cohort included cardiovascular and liver toxicities (11/393 [3%] and 10/393 [3%], respectively); and those lead to treatment modifications included musculoskeletal (38/393, 10%), skin (33/393, 8%), and liver (31/393, 8%) toxicities. In contrast, the most common AE that led to permanent PD-1 discontinuation or dose interruption was immune-related hepatitis (9/205, 4%), followed by GI and skin toxicities (5/205 [2%], 4/205 [2%], respectively). A substantial percent of PD-1 patients developed persistent AEs

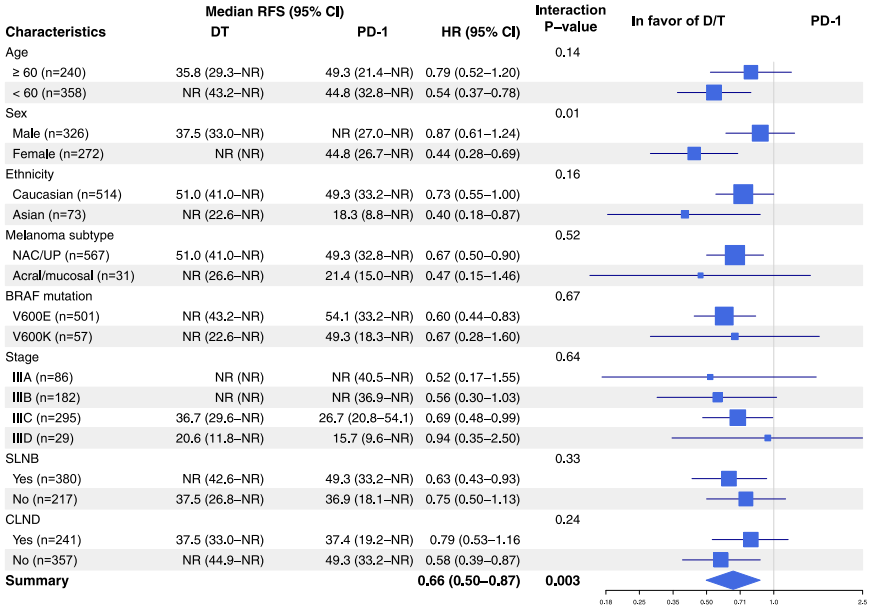

Fig. 2: Forest plot of subgroup analysis using Cox PH model for RFS. D/T, dabrafenib/trametinib; PD-1, anti-program death-1 antibody; RFS, relapse free survival.

(defined as remained present >3 months following treatment discontinuation), including endocrine (29/205, 14%), skin (11/205, 5%), and musculoskeletal (7/205, 3%) immune-related adverse events; whereas persistent AE was rare in the D/T group.

Discussion

This cohort study demonstrated that patients with stage III *BRAF* V600 mutant melanoma who received adjuvant D/T had better RFS than those receiving PD-1 with the median follow-up of 33 months. Although D/T-treated patients have a higher incidence of treatment modification and termination due to AEs during the on-treatment window, these AEs are more short-lived and the incidence of persistent AEs is lower.

Subgroup analyses from two previous real-world study with smaller D/T sample size and shorter follow-up time comparing D/T to PD-1, regardless of stage and mutation status, showed that 1-yr RFS rate was 65–78% in the PD-1 group and 87–95% in the D/T group.[7,8] In this study we observed a similar 1-yr RFS rate (76% in the PD-1 group and 93% in the D/T group).

This cohort study suggests D/T is potentially a superior adjuvant option than PD-1 with an RFS benefit most substantial within the first 3 years post definitive surgery in resected stage III *BRAF* V600 mutant melanoma. Although this study was prospectively designed and powered and with large sample size, these results need to be interpreted with caution given its retrospective and non-randomized nature. There may be potential selection biases, seen as differences in some baseline characteristics between groups, e.g., *BRAF* mutation status, surgery types, and adjuvant radiotherapy. Although the *BRAF* mutation status discrepancies largely derived from differences in test methods (whether to specify substitute amino acid for *BRAF* V600 mutation or not) across different centers, the imbalanced surgery types and radiotherapy and other unobserved biases (e.g., different radiological schedule between different therapies and across different centers) may serve as confounders. Also, being informed by the results of prior trials in the metastatic setting, we suspected that the proportional hazards assumption might be violated when comparing targeted therapy against immunotherapy, and, therefore, a preplanned RMST

	D/T	PD-1	P-value
AE led to treatment discontinuation (n) (%, 95% CI)	71, 18.1% (14.4–22.2%)	26, 12.7% (8.5–18.0%)	0.11
AE led to treatment modification[a] (n) (%, 95% CI)	235, 59.8% (54.8–64.7%)	15, 7.3% (4.2–11.8%)	<0.001
AE persistent (n) (%, 95% CI)	12, 3.1% (1.6–5.3%)	54, 26.3% (20.5–32.9%)	<0.001

[a]Including both dose reduction (D/T only) and treatment interruption (both D/T and PD-1).

Table 3: **AEs with consequence between D/T and PD-1 cohorts.**

model with a preset 2-yr landmark was performed to compensate. Due to the concern of violation of the proportional hazard assumption, the exact HR value of RFS should be cautiously interpreted. Also, with a median follow-up time of 33 months, our study is limited in providing long-term (e.g., >5 years) outcomes of these patients. Besides, the PD-1 group was with a longer follow-up time than the D/T group, largely due to timing of agent availability across different countries. Therefore, longer follow-up is needed. Also, by study design, we did not tract the development of distant metastasis in patients who developed local recurrence first, thus distant metastasis free survival data was not available. Despite these biases and caveats, the multivariable analyses, which included these confounders, showed that D/T was an independent predictor of better RFS compared with PD-1 in both Cox PH and RMST models. Of note, these RFS advantage did not translate into OS, with balanced use of immunotherapy in the first-line metastatic setting for patients who had received adjuvant D/T and vice versa.

In subgroup analyses (caution should be taken as the sample size of each subgroup was small), we noted that although D/T was associated with substantial RFS benefit in most subgroups, namely across ethnicities, and in younger patients, female, NAC/UP subtype, V600E mutation, stage IIIC, and those who received SLNB rather than CLND. The only significant effect modifier observed was sex, specifically, male yielded less RFS benefit from D/T than female (interpretation with caution advised as no adjustment for multiple comparison). This may relate to the known association between male sex, and less immune pressure during tumor evolution,[13] therefore, PD-1 may be more effective in males, as opposed to females. Although the limitation of small sample should be taken into consideration and further studies are in need, we noted that the numeric HR values between D/T and PD-1 gradually approached 1 as the stages advanced from IIIA to IIID, which may indicate that the largest benefit from D/T was yielded in patients with melanoma of a relatively earlier stage. It remains unknown whether this can be extrapolated into stage II melanomas, given that stages IIB/C demonstrates a poorer OS than stage IIIA per AJCC 8th edition.[9] With a success of PD-1 in patients with completely resected stage IIB/C melanoma,[14] the data of MAPKi will come out from the ongoing Columbus-AD trial in a foreseeable future (NCT05270044). The lack of D/T RFS advantage in acral/mucosal melanoma subtypes is likely due to the limited sample size and therefore the study is statistically underpowered to draw any conclusions in this regard. Of note, we observed the greater benefit of D/T over PD-1 in patients with head-and-neck originated melanomas. This is against instinct as it has been shown that head-and-neck primaries had greatest benefit with PD-1 in the metastatic setting.[15] Underlying mechanisms remain unclear.

Of note, among those who experienced disease recurrence, the proportion of distant metastasis was higher and that of local recurrence was numerically lower in the D/T group than PD-1. Although the rate of local therapy use was similar between D/T and PD-1, our study design does not allow us to compare the biopsy and resection rates triggered by commonly observed enlargement of lymph nodes, especially in the setting of PD-1 therapy, nor to describe the rate of biopsies and resections in which recurrences were found. For patients who developed distant metastasis and received systemic therapy in the metastatic setting, those who received D/T or PD-1 in the adjuvant setting had a poorer response to the same therapeutic agent in first line metastatic setting, and *BRAF*/*MEK*i and PD-1/CTLA-4 combo seemed to be good choices for patients from both cohorts.

Overall, we observed more treatment modification due to toxicity, but fewer persistent AEs in the D/T group than PD-1. The detailed AE profiles of D/T and PD-1 differed substantially. Toxicities that were largely transient dominated in the D/T cohort, e.g., fever/chills, GI, musculoskeletal, skin, and liver toxicities. On the contrary, irAEs to PD-1 that persisted were commonly observed, including endocrine, skin, and musculoskeletal. The D/T AE profile is therefore considered favourable, as a proportion of patients would have been cured by surgery alone. The higher likelihood of long-lasting AEs associated with adjuvant PD-1 is a disadvantage.

Our data suggest that D/T may be superior to PD-1 in patients with resected stage III *BRAF* mutant melanoma, given its substantial RFS benefit and lower persistent toxicity. Longer follow-up is required to be certain of these results, given the very different mechanisms of action of these therapies. Also, ideally, a large prospective randomized control trial should be performed to confirm our result.

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Data sharing statement

Data from different centers will be shared differently according to different local regulatory requirements. Those deidentified data that are not readily shared will be made available upon reasonable request and provided in accordance to corresponding regulatory requirements.

Declaration of interests

Dr. Alexander Menzies is on advisory boards of BMS, MSD, Novartis, Roche, Pierre-Fabre, QBiotics.

Dr. Andrew J.S. Furness has a patent (WO2019008375A1) (co-inventor of methods for identifying responders to cancer treatment), has participated on Data Safety Monitoring Boards or advisory boards of Achilles Therapeutics, GSK, Immunocore and Neogene; and has speaker's bureau and educational events from BMS, Eisai, Ipsen, Merck, and Pfizer.

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Dr. Paolo A. Ascierto has/had a consultant/advisory role for Bristol Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre-Fabre, AstraZeneca, Sun Pharma, Sanofi, Sandoz, Immunocore, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, Oncosec, Nouscom, Lunaphore, Seagen, iTeos, Medicenna, Bio-Al Health, ValoTX, Replimmune, Bayer, Erasca. He also received research funding from Bristol Myers Squibb, Roche-Genentech, Pfizer, Sanofi. Travel support by Pfizer, Bio-Al Health, Replimmune.

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The rest of the authors have no declaration of interests.

Appendix A. Supplementary data

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