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A randomized, controlled phase III trial of *nab*-Paclitaxel versus dacarbazine in chemotherapy-naïve patients with metastatic melanoma

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Background: The efficacy and safety of *nab*-paclitaxel versus dacarbazine in patients with metastatic melanoma was evaluated in a phase III randomized, controlled trial.

Patients and methods: Chemotherapy-naïve patients with stage IV melanoma received *nab*-paclitaxel 150 mg/m^2 on days 1, 8, and 15 every 4 weeks or dacarbazine 1000 mg/m^2 every 3 weeks. The primary end point was progression-free survival (PFS) by independent radiologic review; the secondary end point was overall survival (OS).

Results: A total of 529 patients were randomized to *nab*-paclitaxel ($n = 264$) or dacarbazine ($n = 265$). Baseline characteristics were well balanced. The majority of patients were men (66%), had an Eastern Cooperative Oncology Group status of 0 (71%), and had M1c stage disease (65%). The median PFS (primary end point) was 4.8 months with *nab*-paclitaxel and 2.5 months with dacarbazine [hazard ratio (HR), 0.792; 95.1% confidence interval (CI) 0.631–0.992; $P = 0.044$]. The median OS was 12.6 months with *nab*-paclitaxel and 10.5 months with dacarbazine (HR, 0.897; 95.1% CI 0.738–1.089; $P = 0.271$). Independently assessed overall response rate was 15% versus 11% ($P = 0.239$), and disease control rate (DCR) was 39% versus 27% ($P = 0.004$) for *nab*-paclitaxel versus dacarbazine, respectively. The most common grade ≥3 treatment-related adverse events were neuropathy (*nab*-paclitaxel, 25% versus dacarbazine, 0%; $P < 0.001$), and neutropenia (*nab*-paclitaxel, 20% versus dacarbazine, 10%; $P = 0.004$). There was no correlation between secreted protein acidic and rich in cysteine (SPARC) status and PFS in either treatment arm.

Conclusions: *nab*-Paclitaxel significantly improved PFS and DCR compared with dacarbazine, with a manageable safety profile.

Key words: BRAF, chemotherapy-naïve, dacarbazine, metastatic melanoma, *nab*-Paclitaxel

introduction

Historically, dacarbazine and high-dose interleukin-2 were the only US Food and Drug Administration (FDA)–approved options for patients with metastatic melanoma [1]. However, several effective new treatment options, including immunotherapy (anti-CTLA-4 and anti PD-1) and targeted therapy (BRAF and MEK inhibitors) for patients with *BRAF*-mutated melanoma have recently been approved by the FDA [2–8]. Despite these therapeutic advances, chemotherapy retains a role in the treatment of patients with metastatic melanoma, including

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those without a targetable mutation [9]. However, neither single agents [10, 11] nor combination chemotherapy regimens [12] have demonstrated a clear advantage over dacarbazine alone, and improved therapeutic options are needed.

Although taxanes have shown limited efficacy in metastatic melanoma [11, 13–17], paclitaxel formulated as albumin-bound nanoparticles [*nab*-paclitaxel (Abraxane); Celgene, Summit, New Jersey] demonstrated a promising response rate (21.6%), median progression-free survival (PFS) of 4.5 months, and median overall survival (OS) of 9.6 months in a phase II study of chemotherapy-naïve patients [18]. Based on the promising utility of *nab*-paclitaxel in metastatic melanoma, this phase III study compared the efficacy and safety of single-agent *nab*-paclitaxel versus dacarbazine in chemotherapy-naïve patients.

patients and methods

This study was approved by the independent ethics committees of the participating medical institutions and was conducted in compliance with the protocol, the World Medical Association Declaration of Helsinki, Good Clinical Practice, and the Guidelines of the International Conference on Harmonization [19]. Written informed consent was obtained from all patients before study initiation.

patients

Adults with histologically/cytologically confirmed stage IV malignant melanoma were eligible if they had received no prior cytotoxic therapy and had ≥1 radiographically measurable lesion, based on Response Evaluation Criteria in Solid Tumor (RECIST) v1.0 [20]. Previous treatments with kinase inhibitors or cytokines were permitted if they were completed 4 weeks before enrollment. Patients with history of *in situ*, basal, or squamous cell skin cancer were eligible. Patients with other malignancies were also eligible if they were cured by surgery and/or radiation and had been continuously disease free for ≥5 years. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a life expectancy of >12 weeks, and lactate dehydrogenase (LDH) levels ≤2× the upper limit of normal (ULN) were eligible. Patients were excluded from the study if they had prior/current brain metastases.

study design

In this open-label, multicenter phase III study, eligible patients were randomized 1 : 1 via a centralized system to *nab*-paclitaxel 150 mg/m^2 administered i.v. on days 1, 8, and 15 every 28 days or dacarbazine 1000 mg/m^2 administered on day 1 every 21 days. Randomization was stratified by disease stage (M1a, M1b, M1c), geographic region (Australia, North America, Western Europe), and baseline LDH levels (<0.8× ULN, 0.8–1.1× ULN, >1.1–2× ULN). Blood counts and chemistries were obtained before each drug administration, and dose modifications were carried out per protocol. Weekly review of patients on treatment was scheduled, irrespective of treatment allocation, to evaluate safety and efficacy. Patients were treated until disease progression, unacceptable toxicity, or patient/physician decision.

assessment of efficacy and safety end points

Patients were evaluated for response and progression using RECIST criteria v1.0. Radiographic evaluation by computed tomography scan was carried out at baseline (within 7 days of starting treatment) and then every 8 weeks in both arms.

Safety and tolerability were monitored through reporting of adverse events (AEs), serious AEs (SAEs), laboratory abnormalities, and incidence of patients experiencing dose modifications and/or premature discontinuation of study drug.

end points and statistical methods

The primary efficacy end point was PFS based on an independent radiological review and the secondary efficacy end point was OS; both were summarized by median time [including 95% confidence interval (CI)] for each treatment arm along with the hazard ratio (HR, including 95.1% CI for PFS and 99.9% CI for OS). The differences in Kaplan–Meier curves were tested using stratified log-rank test. The summary of censoring is described in the CONSORT diagram (supplementary Figure S1, available at *Annals of Oncology* online). All randomized patients were evaluated for efficacy [intent-to-treat (ITT) population]. For PFS, 514 planned patients with 379 events provided ≥80% power to detect a HR of 0.750 (two-sided α, 0.049). The final OS analysis was planned with at least 417 events, which provided ≥80% power to detect an HR of 0.76 (two-sided α, 0.049). Other end points, including overall response rate [ORR, confirmed complete response (CR) or partial response (PR)] and disease control rate [DCR; CR + PR + stable disease (SD) ≥16 weeks], were tested using χ^2 test. The protocol was modified in 2011 for the collection of *BRAF* mutational status, after results showing that *BRAF* mutational status could be related to prognosis and response to other therapies [21]. The statistical plan was amended before database lock to include PFS and OS by *BRAF* status as a prespecified analysis.

All treated patients were evaluated for safety. All AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0, coded using Medical Dictionary for Regulatory Activities v12.1 and summarized by System Organ Class and Preferred Term. Statistical testing of AE differences between *nab*-paclitaxel and dacarbazine were compared using the Fisher's exact test (overall) and the Cochran–Mantel–Haenszel test (by grade). The NCI CTCAE grades for hematology and chemistry laboratory results were summarized by the most severe grade.

exploratory biomarker analyses

SPARC immunohistochemistry (IHC) was carried out and scored as previously described (see supplementary Materials, available at *Annals of Oncology* online) [22]. H&E stained slides were scored for tumor-infiltrating lymphocytes and the score was correlated with survival outcomes (see supplementary Materials, available at *Annals of Oncology* online).

results

patients

A total of 529 patients were randomized between April 2009 and June 2011, 264 to *nab*-paclitaxel and 265 to dacarbazine (ITT population; see CONSORT diagram in supplementary Figure S1, available at *Annals of Oncology* online). The two treatment arms were generally well balanced for relevant baseline characteristics (Table 1). Only 8% of patients received prior therapy for metastatic disease, such as immunostimulants (6%) and antineoplastic agents (2%), including kinase inhibitors.

efficacy results

progression-free survival. In the final PFS analysis, 152 patients (58%) in the *nab*-paclitaxel and 170 patients (64%) in the dacarbazine arm had progressed or died. Median PFS was 4.8 and 2.5 months, respectively (HR, 0.792; 95.1% CI 0.631–0.992; $P = 0.044$; Figure 1A; Table 2). The PFS estimate at 6 months was 37% with *nab*-paclitaxel versus 30% with dacarbazine. The robustness of the PFS analysis was supported with various sensitivity analyses related to off-schedule response assessments

Table 1. Baseline patient demographics and characteristics

Variable	*nab*-Paclitaxel (*N* = 264)	Dacarbazine (*N* = 265)	All patients (*N* = 529)
Age			
Median years (min, max)	62 (21, 85)	64 (28, 87)	63 (21, 87)
<65, *n* (%)	154 (58)	135 (51)	289 (55)
Sex			
Male, *n* (%)	173 (66)	174 (66)	347 (66)
Region			
North America, *n* (%)	115 (44)	116 (44)	231 (44)
Western Europe, *n* (%)	114 (43)	114 (43)	228 (43)
Australia, *n* (%)	35 (13)	35 (13)	70 (13)
Ethnicity			
White, *n* (%)	251 (95)	252 (95)	503 (95)
Latino, *n* (%)	12 (5)	12 (5)	24 (95)
Asian, *n* (%)	1 (<1)	1 (<1)	2 (<1)
ECOG PS			
0, *n* (%)	195 (74)	181 (68)	367 (71)
1, *n* (%)	68 (26)	82 (31)	150 (28)
2, *n* (%)	1 (<1)	2 (<1)	3 (<1)
Metastatic stage			
M1a, *n* (%)	27 (10)	21 (8)	48 (9)
M1b, *n* (%)	66 (25)	69 (26)	135 (26)
M1c, *n* (%)	171 (65)	175 (66)	346 (65)
LDH category			
<0.8× ULN, *n* (%)	138 (52)	139 (52)	277 (52)
0.8–1.1× ULN, *n* (%)	72 (27)	69 (26)	141 (27)
>1.1–2× ULN, *n* (%)	51 (19)	56 (21)	107 (20)
>2× ULN, *n* (%)	3 (1)	1 (<1)	4 (<1)
BRAF status			
Known, *n* (%)	181 (69)	175 (66)	356 (67)
Mutant	65 (36)	67 (38)	132 (37)
Wild type	116 (64)	108 (62)	224 (63)
Unknown, *n* (%)	83 (31)	90 (34)	173 (33)
Prior therapy			
Metastatic, *n* (%)	18 (7)	24 (9)	42 (8)

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal.

or missed study visits (supplementary Table S1, available at *Annals of Oncology* online). Investigator-assessed median PFS was 3.7 months with *nab*-paclitaxel and 2.1 months with dacarbazine (HR, 0.845; 95.1% CI 0.696–1.025; $P = 0.086$; supplementary Figure S2, available at *Annals of Oncology* online).

overall survival. At the time of the final OS analysis (data cutoff 20 September 2013), 427 patients (81%) died [215 (81%) in the *nab*-paclitaxel and 212 (80%) in the dacarbazine arms]. Median OS was 12.6 months with *nab*-paclitaxel and 10.5 months with dacarbazine (HR, 0.897; 95.1% CI 0.738–1.089; $P = 0.271$; Figure 1B; Table 2).

Most (75%) patients received subsequent therapies (77% *nab*-paclitaxel; 73% dacarbazine): 13% and 10% of patients received a BRAF inhibitor, and 31% and 32% received ipilimumab, in the *nab*-paclitaxel and dacarbazine arms, respectively. Additionally, 15% and 11% of patients received other immunotherapy or targeted therapy, 18% and 23% of patients received subsequent chemotherapy (other than *nab*-paclitaxel-based therapy), and 25% and 22% of patients received radiotherapy in the *nab*-paclitaxel and dacarbazine arms, respectively. The median time to the start of poststudy therapy was 26 and 21 days, respectively.

overall response and disease control rates. Independently assessed ORR was 15% versus 11% (response rate ratio, 1.305; 95% CI 0.837–2.035; $P = 0.239$) with *nab*-paclitaxel versus dacarbazine (Table 2). For patients who had a confirmed CR or PR, the median time to response was 2.2 versus 3.6 months, respectively ($P = 0.44$). Treatment with *nab*-paclitaxel versus dacarbazine resulted in a significant improvement in DCR ($P = 0.004$) and best ORR ($P = 0.002$; Table 2). Significantly less progressive disease was observed with *nab*-paclitaxel (35%) versus dacarbazine (48%), $P = 0.005$.

analyses by subgroups. In general, most subgroup analyses indicated an improvement in favor of the *nab*-paclitaxel arm (Figure 2). Improvement in PFS with *nab*-paclitaxel occurred in all patients regardless of age, region, baseline LDH, *BRAF* mutation status, and patients with M1c/poor prognosis. Of note, *nab*-paclitaxel produced longer PFS (HR, 0.734; 95% CI 0.558–0.965; $P = 0.028$) compared with dacarbazine for patients with the most advanced melanoma (M1c). Trends toward longer PFS favoring *nab*-paclitaxel were observed in all *BRAF* subgroups (Table 2).

treatment exposure and dose reductions

The median treatment duration was 11.1 weeks for *nab*-paclitaxel and 6.4 weeks for dacarbazine. The median number of cycles was 3 in each arm. Median percentage of protocol dose was 98% (min, max: 50%, 105%) and 100% (min, max: 48%, 105%) in the *nab*-paclitaxel and dacarbazine arms, respectively. Median dose intensity was 146.5 and 333.3 mg/m^2/week, respectively, noting that dacarbazine was given every 3 weeks. More dose reductions occurred with *nab*-paclitaxel (32%) versus dacarbazine (20%), all of which were due to AEs, mainly neuropathy.

safety results

Both agents produced expected AE profiles (Table 3). Specifically, 50% versus 27% of patients had ≥1 treatment-related AE (TRAE) and 9% versus 7% patients had ≥1 treatment-related SAE in the *nab*-paclitaxel arm versus dacarbazine arm, respectively. The most common grade ≥3 TRAEs were neuropathy (25% versus 0%), neutropenia (20% versus 10%), and leukopenia (12% versus 7%) in the *nab*-paclitaxel versus dacarbazine arm, respectively (Table 3). No patients experienced grade ≥3 thrombocytopenia during treatment with *nab*-paclitaxel compared with 6% of patients receiving dacarbazine. Of the grade ≥3 treatment-related peripheral neuropathy events, all occurred in the *nab*-paclitaxel arm; 2 events were grade 4. The median onset of grade ≥3 peripheral neuropathy was 101 days (95% CI 85–113) after start of treatment. After treatment modification, median times for grade ≥3 peripheral neuropathy to improve by ≥1 grade and to reduce to grade ≤1 were 28 and 67 days, respectively. Thirty-two percent of patients never developed treatment-related neuropathy in the *nab*-paclitaxel arm.

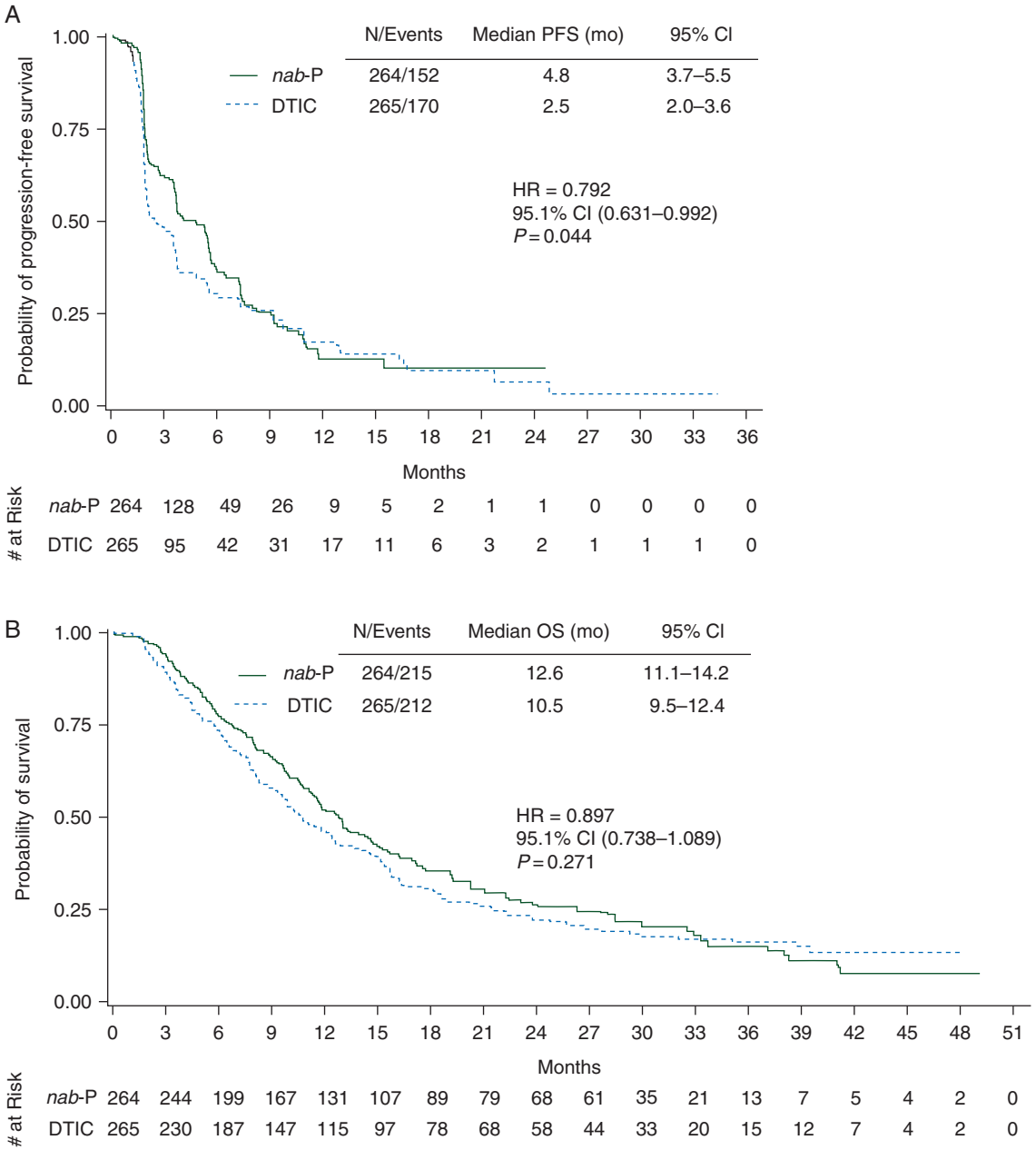

Figure 1. Independent radiologist-assessed progression-free survival (A) and final overall survival (B) Kaplan–Meier curves for the intent-to-treat population.

exploratory biomarker analyses

SPARC IHC data were evaluable in 194 patient tumor samples (100 for *nab*-paclitaxel and 94 for dacarbazine). Baseline characteristics for this patient subset were similar to the ITT population. Patients were classified into high SPARC ($n = 53$ for *nab*-paclitaxel; $n = 50$ for dacarbazine) or low SPARC ($n = 47$ for *nab*-paclitaxel; $n = 44$ for dacarbazine). Independently assessed PFS was similar between patients with high SPARC and low SPARC scores who were in the *nab*-paclitaxel (median PFS 3.71 versus 3.94 months; $P = 0.783$) or dacarbazine (median PFS 3.71 versus 1.91 months; $P = 0.182$) arms.

Results from a *post hoc* analysis of TILs are reported in the supplementary Materials, available at *Annals of Oncology* online.

discussion

nab-Paclitaxel demonstrated clinically meaningful superiority compared with dacarbazine, with a near doubling of median PFS and a 44% improvement in DCR (includes patients with SD for ≥16 weeks) in chemotherapy-naïve patients with metastatic melanoma. Compared with dacarbazine, *nab*-paclitaxel reduced the risk of disease progression or death by >20%. The results observed for dacarbazine in this study were consistent with recent phase III trials [3–5, 8, 10, 11]. Early separation of the survival curves at 3 months provided evidence of early treatment effect, which was maintained for more than 30 months. Although a significant difference in PFS was observed with *nab*-paclitaxel versus dacarbazine, a significant treatment effect of *nab*-paclitaxel on

Table 2. Response rates, progression-free survival, and overall survival for the intent-to-treat population based on independent radiological assessment

Blinded radiology assessment	*nab*-Paclitaxel ($N = 264$)	Dacarbazine ($N = 265$)	Response rate ratio[a] ($P_{nab\text{-}P}/P_{DTIC}$)	P[b]
ORR, *n* (%)	39 (15)	30 (11)	1.305 (0.837–2.035)	0.239
95% CI	10.5–19.1	7.5–15.1		
DCR,[c] *n* (%)	102 (39)	71 (27)	1.442 (1.123–1.852)	0.004
95% CI	32.8–44.5	21.5–32.1		
PR, *n* (%)	39 (15)	30 (11)		
SD ≥16 weeks, *n* (%)	63 (24)	41 (15)		
Best response, *n* (%)				0.0017[d]
PR	39 (15)	30 (11)		
SD	67 (25)	41 (16)		
PD	93 (35)	128 (48)		
Not evaluable[e]	65 (25)	65 (25)		0.005[f]
			HR ($HR_{nab\text{-}P/DTIC}$)	
PFS, median (95% CI) based on independent radiology review (months)	4.8 (3.7–5.5)	2.5 (2.0–3.6)	0.792 (0.631–0.992)[g]	0.044
BRAF mutant	5.3 (3.5–7.5)	3.5 (1.9–5.5)	0.883 (0.515–1.513)	0.656
BRAF wild type	5.4 (3.5–5.7)	2.5 (1.9–3.7)	0.715 (0.492–1.040)	0.088
BRAF unknown	3.7 (2.8–5.6)	2.2 (1.9–3.6)	0.684 (0.457–1.024)	0.066
PFS, median (95% CI) based on investigator review (months)	3.7 (3.1–3.9)	2.1 (1.9–2.5)	0.845 (0.696–1.025)	0.086
OS, median (95% CI) (months)	12.6 (11.1–14.2)	10.5 (9.5–12.4)	0.897 (0.738–1.089)[h]	0.271

[a]The 95% CI for response rate ratios is calculated according to the asymptotic 95% CI of the relative risk of *nab*-paclitaxel to dacarbazine.
[b]The P values are based on the χ^2 test.
[c]DCR includes CR + PR + stable disease (SD) ≥16 weeks.
[d]Includes confirmed PR, SD, and PD.
[e]Nonassessable patients had (i) scans that were not done, (ii) scans that were done but not fully evaluable, or (iii) scans that were done and evaluable but a single response of CR, PR, or SD was not confirmed at a later assessment.
[f]Comparison of PD rate between arms.
[g]95.1% CI is provided given that two-sided type I error of 0.049 was allocated for final PFS analysis.
[h]95.1% CI is provided given that two-sided type I error of 0.049 was allocated for final OS analysis.
DCR, disease control rate; DTIC, dacarbazine; HR, hazard ratio; *nab*-P, *nab*-paclitaxel; ORR, objective response rate; OS, overall survival; P, proportion of improved patients; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

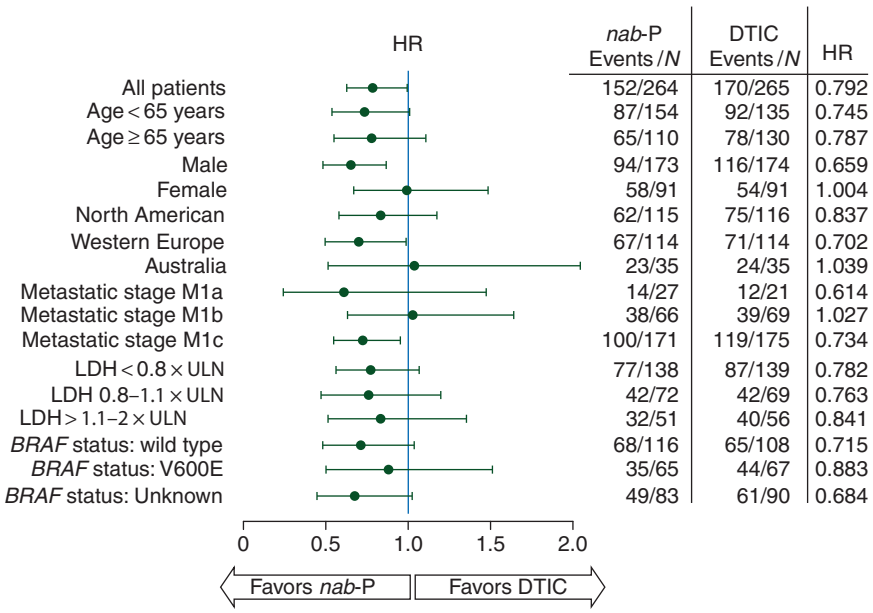

Figure 2. Subgroup analyses of progression-free survival by independent review.

Table 3. Most common treatment-related grade ≥2 adverse events reported in ≥5% patients

Preferred terms	*nab*-Paclitaxel ($N = 257$)			Dacarbazine ($N = 258$)		
Treatment-related death	2 (<1)			1 (<1)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Hematologic AEs, *n* (%)[a]						
Neutropenia	67 (26)	42 (17)	8 (3)	34 (14)	14 (6)	11 (4)
Leukopenia	93 (37)	30 (12)	1 (<1)	48 (20)	14 (6)	3 (1)
Lymphocytopenia	63 (25)	18 (7)	1 (<1)	71 (29)	23 (9)	4 (2)
Thrombocytopenia	0	0	0	14 (6)	9 (4)	6 (2)
Anemia	52 (21)	4 (2)	0	31 (13)	12 (5)	0
Nonhematologic AEs, *n* (%)[a]						
Alopecia	101 (39)	12 (5)	0	0	0	0
Peripheral neuropathy[b]	42 (16)	62 (24)	2 (<1)	1 (<1)	0	0
Fatigue	47 (18)	21 (8)	0	33 (13)	4 (2)	0
Diarrhea	24 (9)	3 (1)	0	11 (4)	1 (<1)	0
Nausea	22 (9)	1 (<1)	0	20 (8)	3 (1)	0
Rash	23 (9)	1 (<1)	0	1 (<1)	0	0
Nail disorder	21 (8)	3 (1)	0	0	0	0

[a]Based on central laboratory values. Except for lymphocytopenia, all events across all grades (Cochran–Mantel–Haenszel test) and for grade 3 and 4 (Fisher's exact test) $P < 0$ .05.
[b]Peripheral neuropathy was classified based on Standardized MedDRA Queries (SMQ) (broad scope).
AE, adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

OS may have been limited by the equivalent and high rate (75%) of use of poststudy therapy, including newer agents, such as BRAF inhibitors and ipilimumab, by patients in both treatment arms.

SPARC, an albumin-binding protein, has both protumorigenic and antitumorigenic properties [23]. SPARC expression may be associated with positive clinical outcomes in patients receiving *nab*-paclitaxel, as it may help to enrich *nab*-paclitaxel in the tumor and/or tumor microenvironment (reviewed in Yardley) [24]. However, no correlation was found between tumor SPARC expression and PFS with *nab*-paclitaxel treatment in this trial. A recent analysis of a large phase III trial of metastatic pancreatic cancer similarly found no correlation between SPARC expression, *nab*-paclitaxel treatment, and clinical outcome [25].

All AEs were manageable, and no new or unexpected AEs were noted for *nab*-paclitaxel in patients with metastatic melanoma [26–28]. Grade ≥3 treatment-related peripheral neuropathy was seen only in patients receiving *nab*-paclitaxel and was consistent with the incidence observed in patients receiving the agent for the approved indications [26–28]. Peripheral neuropathy was the primary reason for the higher rate of treatment discontinuation in the *nab*-paclitaxel arm than in the dacarbazine arm. Despite the high rate of grade ≥3 peripheral neuropathy, a number of patients were able to resume treatment with *nab*-paclitaxel following dose modification procedures that improved peripheral neuropathy by at least 1 grade in half the patients within 1 month. Thus, neuropathy management with treatment modifications remains important for patients to be able to receive the maximum benefit from *nab*-paclitaxel. Other strategies may include using drugs such as pregabalin or duloxetine, which may ameliorate chemotherapy-induced peripheral neuropathy [29].

One limitation of this study was that patients with >2× ULN of LDH were excluded; however, attempts were made to mirror the general population within the LDH categories. It has been established that exceedingly high levels of LDH may also make melanoma cells resistant to certain treatments [30]. Collection of quality-of-life data may have helped to more fully assess the clinical benefit of *nab*-paclitaxel in this patient population.

The higher efficacy observed for *nab*-paclitaxel versus historical trials of sb-paclitaxel in metastatic melanoma [15–17] may be explained by the intrinsic benefit of albumin-based *nab* technology and its distinct pharmacokinetic profile versus sb-paclitaxel [31]. The lack of solvent, which alone contributes to neuropathy [32] and hypersensitivity reactions [33], may contribute to an improved tolerability profile and allow for higher dose delivery and intensity of *nab*-paclitaxel compared with sb-paclitaxel [26, 27]. Efficacy results with single-agent *nab*-paclitaxel in our study compared favorably with the commonly used regimen of sb-paclitaxel plus carboplatin reported in a phase III study of patients with metastatic melanoma, producing similar efficacy outcomes (18% ORR; median PFS and OS of 4.2 and 11.3 months, respectively) [34]. Neutropenia, leukopenia, and sensory neuropathy were the most common grade ≥3 TRAEs observed with sb-paclitaxel plus carboplatin in that study. In a recent phase II study, *nab*-paclitaxel plus bevacizumab as first-line therapy in patients with metastatic melanoma produced a 36% ORR and a median PFS and OS of 7.6 and 16.8 months, respectively [35], suggesting that *nab*-paclitaxel may synergize with other therapeutics, including immunotherapy, and should be further explored in clinical trials. A phase II trial is underway to study *nab*-paclitaxel in combination with ipilimumab (NCT01827111) in patients with advanced or metastatic melanoma [36].

Chemotherapy remains an important treatment option for patients with *BRAF* wild-type melanoma who are not candidates for ipilimumab and patients with *BRAF* mutant disease resistant to BRAF inhibitors [9]. In the present trial, *nab*-paclitaxel benefited patients regardless of *BRAF* mutation status. Additionally, in a *post hoc* analysis of this trial, *nab*-paclitaxel was shown to benefit a subgroup of patients with low or absent TILs (see supplementary Materials, available at *Annals of Oncology* online), a poor prognostic factor in melanoma [37].

In conclusion, *nab*-paclitaxel demonstrated a clinical benefit versus dacarbazine and produced a manageable safety profile. Thus, *nab*-paclitaxel can be considered in the treatment armamentarium for chemotherapy-naïve patients with metastatic melanoma. The National Comprehensive Cancer Network guidelines recommend *nab*-paclitaxel as a single agent for the treatment of advanced or metastatic melanoma (category 2A) [38]. Results of ongoing trials of *nab*-paclitaxel in combination with targeted therapies or novel immunotherapies may help expand this recommendation in the future, as *nab*-paclitaxel may provide a good backbone regimen to build upon given its safety profile.

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disclosure

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Randomized phase III trial of treatment duration for oral uracil and tegafur plus leucovorin as adjuvant chemotherapy for patients with stage IIB/III colon cancer: final results of JFMC33-0502

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Background: While adjuvant chemotherapy is preferable for high-risk colon cancer, treatment duration is controversial. Oral uracil and tegafur (UFT)/leucovorin (LV) is widely used as a standard adjuvant chemotherapy for colon cancer in Japan. We conducted a phase III trial to investigate the optimal duration of adjuvant chemotherapy for stage IIB/III colon cancer.

Patients and methods: Patients with curatively resected stage IIB/III colon cancer were eligible for enrollment in this trial. Patients were registered within 6 weeks after surgery and were randomly assigned to receive UFT/LV for 28 of 35 days for 6 months in the control group or for 5 consecutive days per week for 18 months in the study group. The primary end point was the disease-free survival (DFS), and the secondary end points were overall survival (OS) and safety.

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