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Dabrafenib plus trametinib in unselected advanced *BRAF* V600–mut melanoma: a non-interventional, multicenter, prospective trial

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Objective **The efficacy of combined BRAF and MEK inhibition for *BRAF* V600–mutant melanoma in a broad patient population, including subgroups excluded from phase 3 trials, remains unanswered. This noninterventional study (DATUM-NIS) assessed the real-world efficacy, safety and tolerability of dabrafenib plus trametinib in Austrian patients with unresectable/metastatic melanoma.**

Methods **This multicenter, open-label, non-interventional, post-approval, observational study investigated the effectiveness of dabrafenib plus trametinib prescribed in day-to-day clinical practice to patients ($N = 79$) with *BRAF* V600–mutant unresectable/metastatic melanoma with M1c disease (American Joint Committee on Cancer staging manual version 7), ECOG > 1, and elevated serum lactate dehydrogenase (LDH). The primary endpoint was 6-, 12- and 18-month progression-free survival (PFS) rates. Secondary endpoints were median PFS, disease control rate and overall survival (OS).**

Results **The 6-, 12- and 18-month PFS rates were 76%, 30.6% and 16.2%, respectively. Subgroup analysis showed a significant PFS benefit in the absence of lung metastasis. The median PFS and OS were 9.1 (95% CI, 7.1–10.3) months and 17.9 (95% CI, 12.7–27.8) months, respectively. The 12- and 24-month OS rates were 62.7% and 26.8%, respectively. Subgroup analyses showed significant OS benefits in the absence of bone or lung metastasis and the presence of other metastases (excluding bone, lung, brain, liver and lymph nodes). Furthermore, S100 and Eastern Cooperative Oncology Group performance status (ECOG PS) showed a significant impact on survival. No new safety signals were observed.**

Conclusion **Despite an unselected population of melanoma patients with higher M1c disease, ECOG PS > 1 and elevated LDH, this real-world study demonstrated comparable efficacy and safety with the pivotal phase 3 clinical trials for dabrafenib–trametinib. *Melanoma Res* 34: 142–151**

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Keywords: advanced melanoma, *BRAF* V600–mutation, dabrafenib, DATUM, lactate dehydrogenase, metastatic melanoma, non-interventional study, S100, trametinib

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Introduction

The 5-year survival rate of patients diagnosed with distant metastatic melanoma during 2010–2016 was 27% [1], although this may vary depending on the location and magnitude of metastases [2]. According to the GLOBOCAN Global Cancer Statistics 2020 report, melanoma accounted for 21% of skin cancer diagnoses and ranked nineteenth, with 324,635 new cases and 57,043

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deaths worldwide [3]. Excluding nonmelanoma skin cancers, cutaneous melanoma is the fifth most frequent neoplasm in the Austrian population [4].

Advances in targeted therapies and immunotherapies over the last decade have significantly improved survival rates in patients with *BRAF* V600–mutant metastatic melanoma [5–8]. In the recent DREAMSeq and SECOMBIT studies, first-line immunotherapy with anti-CTLA4 and anti-PD-1 improved overall survival (OS) in comparison to BRAF/MEK inhibition in an inoperable metastatic setting. The current treatment landscape often includes previous adjuvant treatment with either BRAF/MEK inhibitors or anti-PD-1, however, data for optimal treatment sequence are still lacking [9].

Five-year pooled analysis from the COMBI-d and COMBI-v phase 3 studies in melanoma patients treated with the first-line dabrafenib–trametinib combination showed progression-free survival (PFS) and OS rates of 19% and 34%, respectively [6]. Elevated serum lactate dehydrogenase (LDH) is the most significant prognostic factor associated with poor response and survival in patients with melanoma [10–13]. In patients with elevated LDH, treated with dabrafenib–trametinib, 5-year PFS was 8% vs. 25% with normal LDH, and 5-year OS was 16% vs. 43%, respectively [6]. Analyses from population-based studies are critical in extending and corroborating the results derived from controlled randomized trials, as baseline and treatment parameters may affect outcomes in cancer patients in real-world settings [14–16].

With the approval of the dabrafenib–trametinib combination in Europe for patients with unresectable/metastatic melanoma, it is now feasible to complement the outcomes from the pivotal COMBI-d and COMBI-v studies [5,6,17–20] with real-world data from noninterventional studies (NIS). Dabrafenib And Trametinib in Unselected advanced *BRAF* V600–mutant Melanoma (DATUM-NIS) specifically aimed to report the efficacy of dabrafenib–trametinib in the Austrian patient population with unresectable/metastatic melanoma, and to evaluate the real-life safety and tolerability of this combination therapy outside the clinical trial setting.

Methods

Study design

This multicenter, open-label, noninterventional, postmarketing, observational study was designed to prospectively investigate the day-to-day clinical routine treatment of patients with unresectable/metastatic melanoma receiving dabrafenib–trametinib by prescription across 12 sites in Austria. Due to the noninterventional nature of the study, treatment visits followed the procedures of the respective treatment site or center.

Adult patients (aged ≥18 years) with *BRAF* V600–mutant, unresectable/metastatic melanoma were included in the study. In addition, patients with the unknown primary site of melanoma, and patients prescribed the dabrafenib–trametinib combination, as indicated in the summary of product characteristics (SmPC) [21,22], for whom treatment had been initiated within 12 weeks of inclusion or immediately after inclusion, were also eligible. Patients were excluded if they were previously treated with trametinib, or any BRAF/MEK inhibitor combination other than dabrafenib–trametinib. Furthermore, patients who initiated treatment with dabrafenib–trametinib >12 weeks before starting the study documentation and/or included before obtaining informed consent; those currently on or planning to participate in any clinical trial (excluding patients in survival follow-up of clinical trials), and those who were on or had planned treatment for any other tumor (except keratoacanthoma and cutaneous squamous/basal cell carcinoma) were also excluded.

BRAF testing was done according to the local standard of the participating centers by validated methods within the hospitals pathology departments. Methods used included Sanger sequencing, pyrosequencing, next-generation sequencing-based panel assays (Ampliseq Focus Panel, truSight Tumor 170; both Illumia, San Diego, California, USA), QIAact Actionable Insights Tumor Panel (Qiagen, Hilden, Germany) and real-time PCR test (cobas 4800 *BRAF* V600 mutation test; Roche, Rotkreuz, Switzerland).

This study was conducted in accordance with the Declaration of Helsinki (1975) and succeeding amendments and was approved by the local ethics committee (28-409 ex 15/16) and by a scientific review board. Informed consent was obtained from all patients prior to the onset of the study.

Primary endpoints were 6-, 12- and 18-month PFS rates. Secondary endpoints included median PFS, disease control rate (DCR), median OS, and 12- and 24-month OS rates. Safety was also assessed.

Statistical methods

No formal statistical hypotheses testing was conducted. All performed inferential statistical tests and calculated confidence intervals (CI) were interpreted in an explorative manner. Subgroup analyses were prepared for all primary and secondary efficacy endpoints. Adverse events (AEs) and serious AEs (SAEs) were calculated after subtracting the progressions. Statistical analysis of the full data set in the study was performed with descriptive statistical methods, using SPSS® v24. The full analysis set comprised all patients who received at least one dose of the study drugs. Historical and demographic data were displayed in a descriptive manner. Event time and survival time analyses were performed using the Kaplan–Meier method.

Results

From August 2016 to August 2018, a total of 79 patients were included in the study. Of the 82 patients screened, three were excluded due to specific pretreatment or participation in another study, and one patient died before the first treatment. Eighteen patients (22.8%) received prior systemic immunotherapy (anti-CTLA4 ± anti-PD-1 agents). Baseline demographics and disease characteristics are presented in Table 1. The median (range) age was 60 years (32–85), and the median (range) duration of treatment was 8.8 months (1.7–36.8); 89% of patients had a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, 78/79 (99%) patients had stage IV disease (per American Joint Committee on Cancer staging manual version 7) [23], and M1c disease was predominant (75%). The observation period was >38 months.

Table 1 Baseline characteristics

Parameters	Patients ($N = 79$)
Age, median (range), years	60 (32–85)
Sex, *n* (%)	
Male	48 (61%)
ECOG PS at baseline, *n* (%)	
0	50 (63%)
1	20 (25%)
2–4	9 (11%)
Disease stage (AJCC 7) at baseline, *n* (%)	
Unresectable IIIC	1 (1%)
IV	78 (99%)
Stage from primary diagnosis to baseline, *n* (%)	
Stage IV at primary diagnosis	17 (22%)
I to IV	22 (28%)
II to IV	13 (16%)
III to IV	23 (29%)
NA[a] to IV	3 (4%)
IB to IIIC	1 (1%)
Metastatic sites at baseline, *n* (%)	
Lymph node	51 (65%)
Lung	44 (56%)
Brain	25 (32%)
Liver	22 (28%)
Bone	20 (25%)
Other metastases (excluding bone, lung, brain, liver and lymph nodes)[b]	36 (46%)
Distant metastases at baseline, *n* (%)	
M0	1 (1%)
M1a	11 (14%)
M1b	8 (10%)
M1c[c]	59 (75%)
LDH at baseline, *n* (%)	
≤Normal	36 (46%)
>1– ≤ 2 × ULN	21 (27%)
>2 × ULN	13 (16%)
Unknown	9 (11%)
CRP at baseline, *n* (%)	
Elevated	41 (52%)
Normal	26 (33%)
Unknown	12 (15%)
S100 at baseline, *n* (%)	
>Cutoff	36 (46%)
≤Cutoff	27 (34%)
Unknown	16 (20%)
BRAF mutation status, *n* (%)	
V600E	72 (91%)
V600K	6 (8%)
V600R	1 (1%)
Line of therapy, *n* (%)	
1	61 (77%)
2–3[d,e]	18 (23%)

AJCC, American Joint Committee on Cancer; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NA, not available; ULN, upper limit of normal.
[a]NA refers to Tx, (Nx or N1b or N1a), M0.
[b]Localization of 'other metastases' are mentioned in Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/MR/A364*.
[c]Metastases to all other visceral sites or distant metastases to any site.
[d]Prior systemic therapies included anti-CTLA4 ± anti-PD-1 agents.
[e]Only one patient received a third line of therapy.

Efficacy

After 6 months, 57 patients (76%) had not experienced progression or died, which decreased to 22 (30.6%) after 12 months and 11 (16.2%) after 18 months. Due to lack of information on progression status, four patients were censored before the 6-month analysis. Median PFS for the overall population was 9.1 months (95% CI, 7.1–10.3; Table 2, Fig. 1a). In a subgroup analysis, median PFS in patients without lung metastasis was 9.5 months (95% CI, 9.14–21.76) vs. 7.1 months (95% CI, 6.02–23.9) with lung metastasis ($P = 0.003$; Fig. 1b). All other localizations showed no statistically significant differences.

The median OS was 17.93 months (95% CI, 12.7–27.8; Table 2, Fig. 2a) with a survival rate of 62.7% and 26.8% after 12 and 24 months, respectively. Median OS in patients with or without bone metastasis was 9.7 months (95% CI, 6.84–14.18) and 27.8 months (95% CI, 14.34–27.8) ($P = 0.009$). Median OS in patients with or without lung metastasis was 13.2 months (95% CI, 8.26–18.26 and not reached (NR) ($P = 0.013$). Likewise, median OS with or without other metastases (excluding bone, lung, brain, liver and lymph nodes) was 27.8 months (95% CI, 14.18–27.8) vs. 13.1 months (95% CI, 8.42–19.24) ($P = 0.028$). Median OS in patients with ECOG PS < 1 or 2–4 was 13.1 months (95% CI, 7.93–27.8) vs. 7 months (95% CI, 1.78–13.49) ($P = 0.010$) (Table 2, Fig. 2b).

In patients with or without pyrexia, median PFS was 9.5 vs. 9.0 months ($P = 0.228$), and median OS was 27.8 vs. 15 months ($P = 0.206$), respectively. Median PFS in patients receiving dabrafenib–trametinib as first-line vs. second- or third-line treatment was 9.1 vs. 10.9 months ($P = 0.616$), and median OS was 17.9 vs. 14.3 months ($P = 0.732$), respectively (Table 2).

Based on the investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [24], 13.9% of patients achieved complete response (CR), 63.3% partial response (PR) and 13.9% had stable disease (SD), leading to a DCR of 91.2%. Only 8.9% of patients had progressive disease (PD) as their best response. ORR analysis of patients alive at 12 and 24 months showed 10% CR, 45% PR, 10% SD and 35% PD after 12 months, and 36% CR, 27% PR, 18% SD and 18% PD after 24 months, respectively (Table 2).

Table 2 **Impact of baseline characteristics on median progression-free survival and median overall population**

		N	PFS median (95% CI)	*P*	OS median (95% CI)	*P*
Overall		79	9.14 (7.10–10.32)		17.93 (12.70–27.80)	
Brain metastases	No	54	9.14 (7.04–10.88)	0.799	17.93 (12.70–27.80)	0.947
	Yes	25	8.74 (6.18–11.84)		19.24 (8.49–19.24)	
Bone metastases	No	59	9.47 (8.51–11.84)	0.096	27.8 (14.34–27.80)	0.009
	Yes	20	6.02 (2.96–9.14)		9.70 (6.84–14.18)	
Liver metastases	No	57	9.40 (8.48–11.34)	0.489	19.24 (13.09–27.80)	0.188
	Yes	22	7.10 (5.10–10.88)		13.16 (7.04–15.07)	
Lung metastases	No	35	9.50 (9.14–21.76)	0.003	NR	0.013
	Yes	44	7.10 (6.02–23.9)		13.16 (8.26–18.26)	
Lymph node metastases	No	28	9.40 (6.18–14.66)	0.448	17.93 (8.75–19.24)	0.949
	Yes	51	9.11 (6.97–10.52)		18.26 (12.60–27.80)	
Other metastases[a]	No	43	9.01 (6.18–14.66)	0.944	13.09 (8.42–19.24)	0.028
	Yes	36	9.40 (7.10–10.52)		27.80 (14.18–27.80)	
LDH	≤Normal	36	9.14 (6.97–10.52)	0.108	17.93 (13.16–19.24)	0.055
	>1– ≤ 2 × ULN	21	11.84 (6.15–21.76)		19.41 (7.89–27.80)	
	>2 × ULN	13	6.67 (2.07–18.94)		8.22 (3.85–14.34)	
	Unknown	9	9.50 (7.66–20.94)		NR	
S100	≤Cutoff	27	10.88 (9.14–16.37)	0.027	NR	0.002
	>Cutoff	36	6.41 (5.10–8.48)		10.89 (7.86–15.07)	
CRP	Elevated	41	8.48 (6.18–11.34)	0.727	13.16 (8.49–27.80)	0.175
	Normal	26	9.40 (7.66–10.88)		19.41 (13.49–19.41)	
	Unknown	12	9.01 (3.71–11.84)		15.07 (6.35–15.07)	
ECOG PS	0	50	9.47 (7.30–12.13)	0.044	19.41 (14.34–19.41)	0.010
	1	20	9.01 (6.02–23.90)		13.09 (7.93–27.80)	
	2–4	9	6.97 (1.12–14.66)		6.97 (1.78–13.49)	
Adjuvant treatment	No	63	9.14 (7.10–10.32)	0.953	18.26 (11.55–27.80)	0.848
	Yes	16	9.14 (4.24–17.92)		15.07 (8.42–17.93)	
Systemic pretreatment type[b]	IO	18	10.88 (6.15–23.90)	0.676	14.34 (7.73–27.80)	0.732
	No IO	61	9.11 (6.97–9.96)		17.93 (12.60–19.41)	
FU-treatment type[c]	NO FU/IMI/ RTX/DTIC	44	9.96 (7.04–18.94)	0.017	14.34 (8.22–19.41)	0.497
	IO/TT/T–VEC	35	8.52 (6.15–23.90)		18.26 (12.70–27.80)	
Pyrexia	No	49	9.01 (6.41–9.96)	0.228	14.97 (10.43–19.41)	0.206
	Yes	30	9.50 (7.04–16.37)		27.80 (12.60–27.80)	
Dose interrupted	No	23	8.75 (6.02–9.47)	0.610	13.16 (7.93–14.18)	0.587
	Yes	56	9.40 (7.1–11.84)		18.26 (13.09–27.80)	
Dose reduced	No	45	9.14 (6.97–11.34)	0.831	14.97 (10.89–18.26)	0.887
	Yes	34	9.14 (6.41–10.52)		17.93 (10.86–27.80)	
Co-morbidities	No	19	9.47 (5.98–21.76)	0.707	27.80 (9.70–27.80)	0.480
	Yes	60	9.14 (7.04–10.52)		17.93 (11.55–19.41)	
Best response	CR	11	23.90 (4.96–23.90)	<0.0001	NR	<0.0001
	PR	50	9.14 (7.3–21.76)		15.07 (12.60–19.24)	
	SD	11	6.97 (5.16–17.92)		17.93 (6.84–19.41)	
	DP	7	2.40 (1.12–2.93)		5.16 (1.78–13.09)	

CI, confidence interval; CR, complete response; CRP, C-reactive protein; DP, disease progression; DTIC, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow-up; IMI, imiquimod; IO, immunotherapy; LDH, lactate dehydrogenase; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response; RTX, radiotherapy; SD, stable disease; TT, targeted therapy; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

[a]Localization of 'metastases other' (excluding bone, lung, brain, liver and lymph nodes) are mentioned in the Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/MR/A364*.

[b]Excluding adjuvant treatment.

[c]Group 1: Patients with either no follow-up treatment (NO FU, $n = 41$), with radiotherapy (RTX, $n = 1$) or palliative treatment with imiquimod (IMI, $n = 1$), or DTIC ($n = 1$); Group 2: Systemic follow-up treatment with checkpoint inhibitors (IO, $n = 29$), targeted therapy (TT, $n = 5$) or talimogene laherparepvec (T-VEC, $n = 1$). Kaplan–Meier curves corresponding to each subgroup are shown in the Supplementary Figures 1 and 2, Supplemental digital content 2, *http://links.lww.com/MR/A365*.

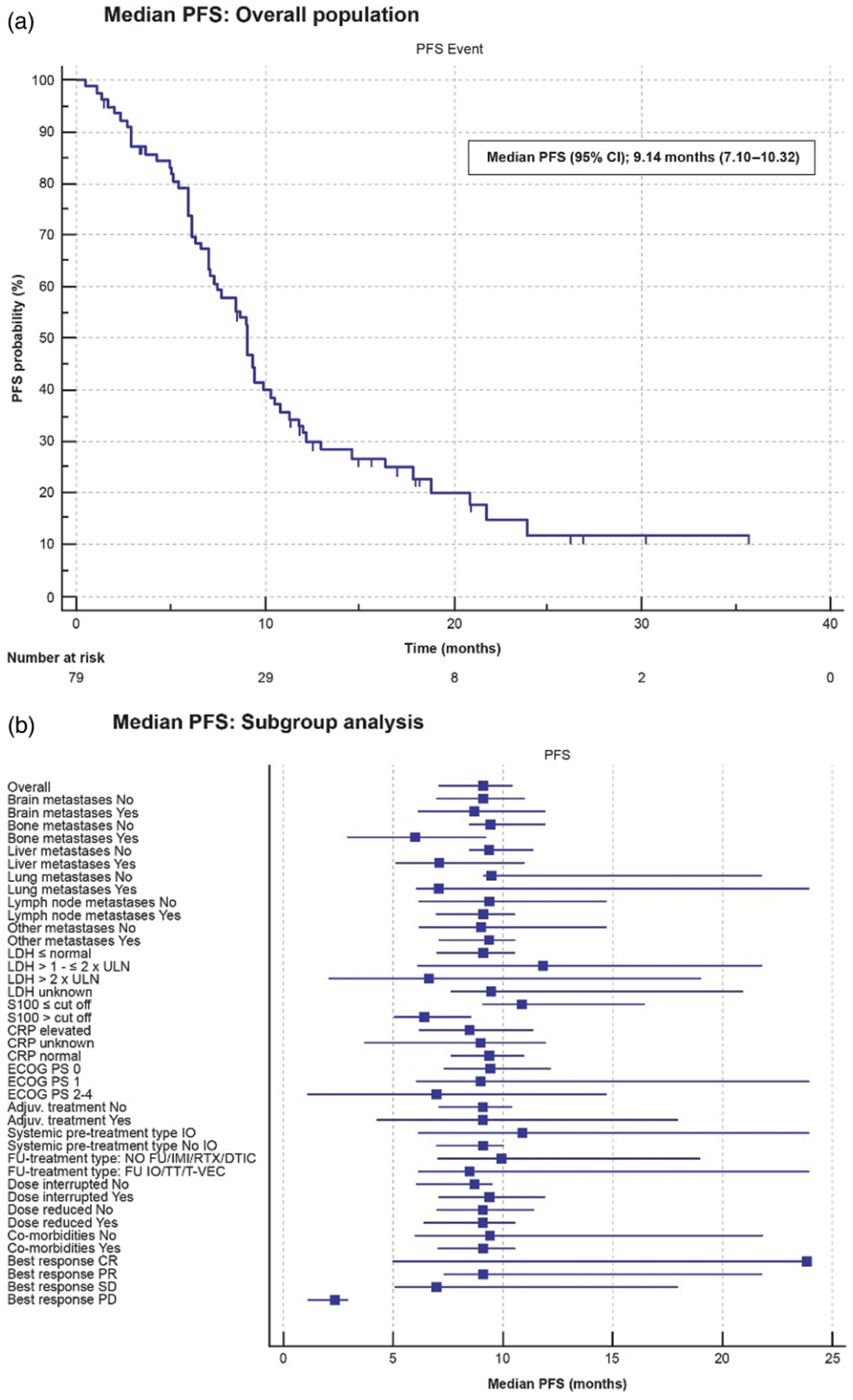
Correlations of clinical benefit with biomarkers

C-reactive protein, lactate dehydrogenase and S100

In a subgroup of patients with normal C-reactive protein (CRP), 80.7% of patients showed PR + CR, 15.4% SD and 3.8% PD (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/MR/A364*); median PFS was 9.4 months and median OS was 19.4 months (Table 2). The PR + CR in patients with elevated CRP was 70.7%, and SD or PD was 14.6% each; median PFS was 8.5 months and median OS was 13.16 months.

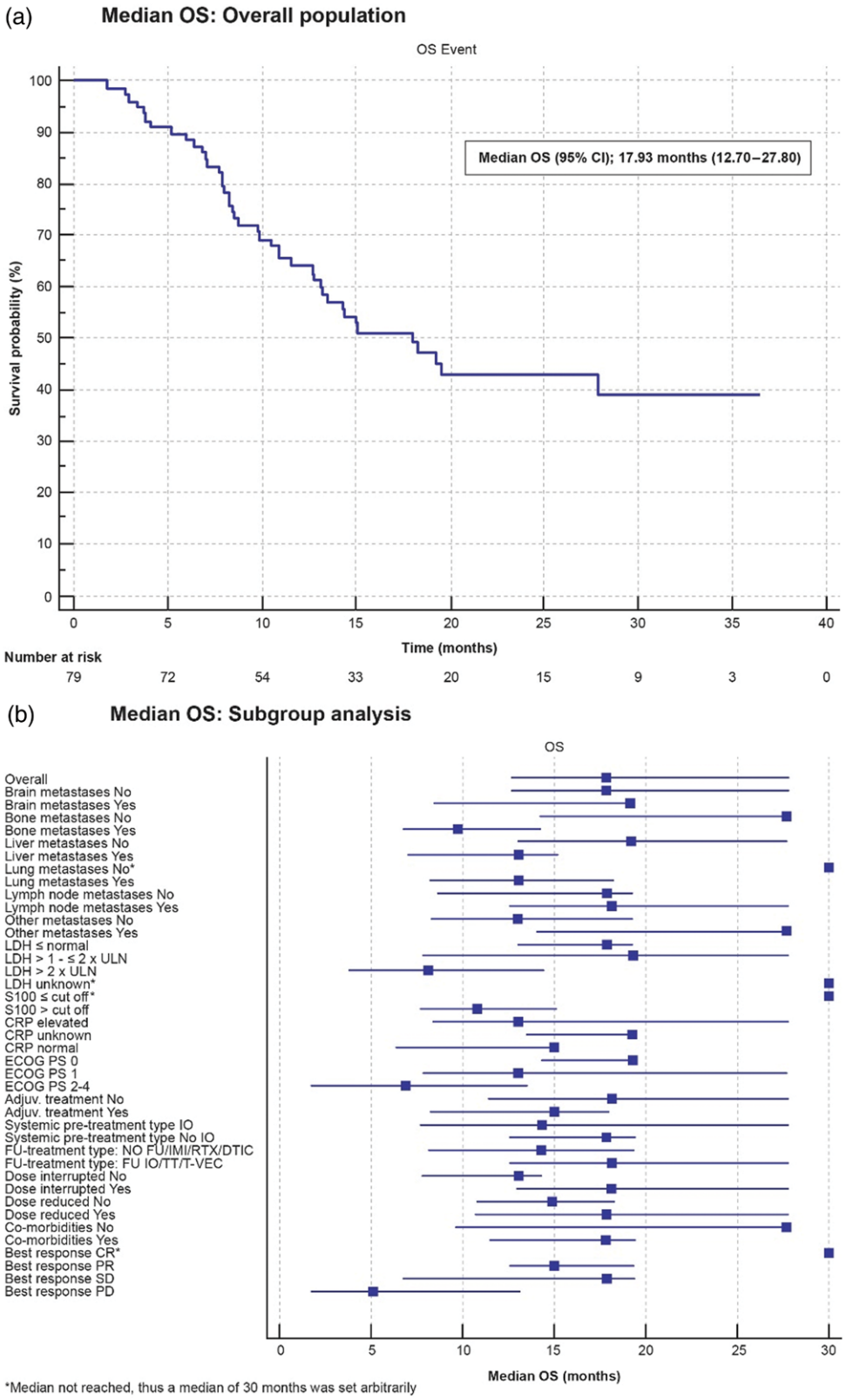
Best response in patients with normal vs. modestly increased (>1–≤ 2 × ULN) LDH was CR 11.1% vs. 19%; PR 72.2% vs. 57.1%; SD 11.1% vs. 14.3%; and PD 5.6% vs. 9.5%. Best response in patients with >2 × ULN LDH was 0.0% CR, 61.5% PR, 15.4% SD and 23.1% PD (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/MR/A364*). Median PFS was 9.1, 11.8 and 6.7 months, whereas median OS was 17.9, 19.4 and 8.2 months in patients with normal, >1–≤2 × ULN and >2 × ULN LDH, respectively. Best response in patients with normal vs. elevated S100 was CR + PR: 85.2% vs. 75.0%; SD 14.8% vs. 8.3%; and no PD vs. 16.7% (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/MR/A364*). The S100 levels significantly impacted the disease progression (DP) and survival as median PFS was 10.9 vs. 6.4 months, while median OS was NR vs. 10.9 months (95% CI, 7.86–15.07) in normal and elevated S100, respectively ($P = 0.002$) (Table 2).

Fig. 1



Median PFS of overall population and in subgroups. (a) Median PFS: overall population. (b) Median PFS: subgroup analysis. CI, confidence interval; CR, complete response; CRP, C-reactive protein; DP, disease progression; DTIC, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow-up; IMI, imiquimod; IO, immunotherapy; LDH, lactate dehydrogenase; PFS, progression-free survival; PR, partial response; RTX, radiotherapy; SD, stable disease; TT, targeted therapy; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

Fig. 2



Median OS of overall population and in subgroups. (a) Median OS: overall population. (b) Median OS: subgroup analysis. *Median not reached, thus a median of 30 months was set arbitrarily. CI, confidence interval; CR, complete response; CRP, C-reactive protein; DP, disease progression; DTIC, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow-up; IMI, imiquimod; IO, immunotherapy; LDH, lactate dehydrogenase; OS, overall survival; PR, partial response; RTX, radiotherapy; SD, stable disease; TT, targeted therapy; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

Table 3 Most frequent (>5%) adverse events

AE	Regardless of treatment			Treatment-related		
System organ class/ preferred term	Number of AEs, all grade	Number of AEs, grade 3/4	Patients with AEs, *n* (%)	Number of AEs, all grade	Number of AEs, grade 3/4	Patients with AEs, *n* (%)
Pyrexia	64	1	30 (39%)	52	1	24 (31%)
Fatigue	23	0	18 (23%)	10	0	9 (12%)
Diarrhea	21	0	17 (22%)	10	0	9 (12%)
Nausea	23	0	15 (19%)	7	0	6 (8%)
Headache	14	0	12 (16%)	–	–	–
Rash	12	1	11 (14%)	6	1	5 (6%)
Blood CPK increased	12	0	8 (10%)	8	0	7 (9%)
Decreased appetite	10	0	7 (9%)	6	0	6 (8%)
Chills	9	0	7 (9%)	6	0	6 (8%)
Pain in extremity	8	0	6 (8%)	–	–	–
Edema peripheral	7	0	6 (8%)	5	0	5 (6%)
Hepatic enzyme increased	6	2	6 (8%)	4	2	4 (5%)
Weight decreased	7	0	5 (6%)	–	–	–
Neoplasm progression	5	1	5 (6%)	–	–	–
Eczema	5	1	5 (6%)	–	–	–
Pruritus	5	1	5 (6%)	–	–	–
Peripheral swelling	5	0	5 (6%)	–	–	–
RTI	5	0	5 (6%)	–	–	–
Arthralgia	5	0	4 (5%)	4	1	4 (5%)
Blood creatinine increased	4	1	4 (5%)	–	–	–
Back pain	4	1	4 (5%)	–	–	–
Hyperlipidemia	4	0	4 (5%)	–	–	–
Sleep disorder	4	0	4 (5%)	–	–	–
Dyspnea	4	0	4 (5%)	–	–	–
Hypertension	4	0	4 (5%)	–	–	–

AE, adverse event; CPK, creatine phosphokinase; RTI, respiratory tract infection.

Safety and tolerability

A total of 533 AEs were reported throughout the observation period (>38 months) and 77 patients (97.5%) experienced at least one AE. Most AEs were mild or moderate (66.8% and 25.3%). Median time-to-first AE in the overall population was 26 days, while for first- and second-line patients it was 26 and 21 days, respectively (Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/MR/A364*). At least one dabrafenib-related or one trametinib-related AE was reported in 50 (63.3%) and 42 patients (53.2%), respectively. The most frequent AEs regardless of study drug(s) were pyrexia, fatigue, diarrhea, nausea, headache and rash; most of them were low-grade (Table 3). Fifty-six patients (70.9%) interrupted the treatment, and 34 patients (43.0%) reduced one or both study drugs at least once. The median duration of dose interruption was 7 days for both drugs. Neither dose interruption nor dose reduction had a significant impact on efficacy (Table 2). Of the 21 patients (26.6%) who permanently stopped the therapy due to an AE, six AEs (7.6%) were suspected to be treatment-related.

A total of 124 SAEs were reported in 55 patients (69.6%); of these, 31 patients (56.4%) recovered. In first-line treatment, 25% of SAEs were related to dabrafenib and 25% to trametinib, whereas in second-line treatment, 20% of SAEs were related to dabrafenib and 26.7% to trametinib. Number of patients with AEs by treatment line and grade, and by treatment line, relatedness and severity are provided in Supplementary Tables 4 and 5, Supplemental digital content 1, *http://links.lww.com/MR/A364*, respectively. Forty-two patients (53.2%) died during the study period; in 32 of the reported deaths, the AE outcome per protocol was DP, neoplasm progression and tumor hemorrhage. No deaths were directly related to dabrafenib or trametinib.

Most AEs occurred within the first 3 months of therapy (90.9%) and decreased over the observation period to 26.7% (>24 months). The frequency of drug-related AEs decreased from 59.7% (months 1–3) to 6.7% (13–24 months and later; Table 4). Median time to AE resolution was 13 days.

Discussion

DATUM-NIS confirms the efficacy and safety of dabrafenib–trametinib under real-world conditions in unselected patients with *BRAF* V600–mutant unresectable/metastatic melanoma and sheds light on the impact of prognostic factors (e.g. LDH, location of metastases, CRP and S100) on efficacy and safety. Biomarkers S100 and CRP were analyzed for their correlation with clinical benefit [25,26]. The primary endpoints of 6-, 12- and 18-month PFS rates were 76.0%, 30.6% and 16.2%, respectively, and the secondary endpoint of median PFS was 9.1 months. In selected patient populations, dabrafenib–trametinib extended the PFS rates in the long-term (3-year) survival and safety analysis of COMBI-d, and subsequent pooled 5-year analysis of COMBI-d and COMBI-v, reporting a 5-year PFS rate of 19% [6,19]. Median PFS in this study was approximately 2 months shorter, and the median OS

Table 4 Adverse event frequency by time of adverse event onset and therapy

			Study drug-related		Not related to study drug	
AE onset after start of treatment (months)[a]	AEs	Patients on observation *n* (%)	AEs (*n*)	Patients on observation *n* (%)	AEs (*n*)	Patients on observation *n* (%)
0–3	231	70 (90.9%)	115	46 (59.7%)	116	54 (70.1%)
4–6	120	43 (58.1%)	42	29 (39.2%)	78	31 (41.9%)
7–12	115	41 (60.3%)	16	11 (16.2%)	99	41 (60.3%)
13–24	48	18 (40.0%)	9	4 (8.9%)	39	18 (40.0%)
>24	15	4 (26.7%)	2	1 (6.7%)	13	4 (26.7%)
Total AEs	529		184		345	

AE, adverse events.
[a]The time of onset was not specified for additional four AEs.

of 17.9 months was comparable with the 17.2 months reported in the pivotal COMBI-v study [5]. The 12- and 24-month OS rates were 62.7% and 26.8%, respectively, which were lower than those reported in the COMBI-v study [20].

Based on investigator assessment of response per RECIST 1.1, the DCR was 91.2%. Even in this real-world patient population, including an increased proportion of patients with brain metastasis, elevated LDH, M1c disease and worse ECOG PS than in pivotal studies, only 8.9% of patients had PD as their best response. Assessment of response based on patients alive at 12 and 24 months showed a better response; this shift towards patients with better response confirms previous analyses from pivotal studies demonstrating that patients with a CR or PR have a higher likelihood of prolonged survival [6,27].

Subgroup analysis showed a significant PFS benefit in the absence of lung metastases, and significant OS benefits in the absence of bone or lung metastases and in the presence of 'other metastases' (excluding bone, lung, brain, liver and lymph nodes). The PFS benefit in patients without lung metastases is in contrast to previous data on treatment with BRAF/MEK inhibitors, for example, a multivariate analysis of baseline factors in a pooled analysis of dabrafenib and trametinib trials [28], where patients with M1b disease show a better PFS outcome as patients with M1c disease. The most likely explanation for our observation is, rather than a biological reason, that this is a statistical outlier due to the smaller patient cohort in our study. Subgroup analysis also showed an improved prognosis for patients with LDH, S100 (below cutoff), CRP within normal range and ECOG PS of 0, similarly to other studies [25,26]. All these results are consistent with the pivotal trials of dabrafenib–trametinib in unresectable/metastatic melanoma [17,18]. Median PFS in patients treated with first-line dabrafenib–trametinib was numerically lower than in those treated in second + third-line; conversely, median OS in first-line patients was numerically higher. However, these differences in PFS or OS were not statistically significant. A relatively larger proportion of patients treated in later lines may have corroborated the current findings with more clarity. Compared to the phase 2 COMBI-MB study [22], DATUM-NIS showed superior PFS [median PFS 4.2–7.2 months (COMBI-MB)] and comparable OS [median OS 11–24.3 months (COMBI-MB)]. The OS in this real-world study is higher than in a recent retrospective study (7.8 months) [29] in the subgroup of patients with brain metastases; albeit with a relatively lower proportion of patients.

The safety profile was similar to that reported in previous studies, as pyrexia remained the most frequent AE followed by fatigue, diarrhea, nausea and headache, which are the most common AEs associated with dabrafenib–trametinib treatment [17,18,27]. No new safety signals were identified. Most AEs were mild or moderate, occurred early in treatment and decreased with time; most were resolved by either dose reduction or interruption, which is supported by a recent study showing the successful management of pyrexia with dose interruption [30]. Dose interruption or reduction did not appear to significantly impact efficacy.

Despite an unselected patient population with a higher percentage of patients with M1c disease, ECOG PS > 1 and elevated LDH (>2 × ULN), the DATUM-NIS study demonstrated comparable efficacy and safety with the pivotal COMBI-d/v clinical trials for dabrafenib–trametinib [5,6,17–20]. The COMBI-d/v phase 3 studies did not represent the entire melanoma population, as patients with unfavorable ECOG PS (≥2), certain tumor locations or symptomatic brain metastases, which represent negative prognostic factors for patient survival, were not included in these investigations [5,17,20,27].

Limitations

Patients were only included if dabrafenib–trametinib was prescribed as indicated in the SmPC and if they met the eligibility criteria. Due to the open, noninterventional and observational nature of the study (without any randomization/stratification or comparison group in the same treatment line and without study hypothesis), a non-comparative bias is expected. Finally, small numbers of patients in subgroups made detailed subgroup analysis difficult. A larger cohort study would add further clarity and may corroborate the findings.

Conclusions

DATUM-NIS confirms the efficacy of dabrafenib–trametinib in patients with melanoma in daily clinical

practice in the real-world setting. It describes the impact of prognostic factors (LDH levels and site of metastases), and AE-related therapy management on the treatment outcomes. In comparison to pivotal randomized clinical trials, this study demonstrates highly comparable efficacy and safety outcomes in an unselected patient population, especially in patient groups with poor prognosis. Further studies are warranted to confirm the described findings in a larger patient population.

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Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. We confirm that the data generated by our research supports our current article. Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients. The authors confirm they had no special access or privileges that other researchers would not have.

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Conflicts of interest

There are no conflicts of interest.

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