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COMBI-EU: Adverse Event Management of Adjuvant Dabrafenib Plus Trametinib (D+T) in Patients with *BRAF* V600-Mutant Melanoma

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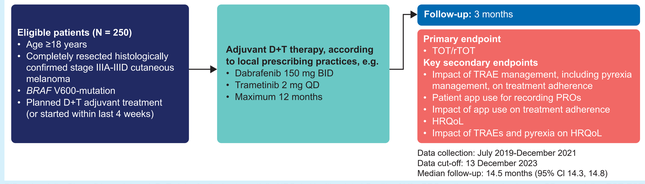
Background and Objectives

- The Phase 3 COMBI-AD study demonstrated that adjuvant therapy with dabrafenib + trametinib (D+T) significantly reduced recurrence risk when given after complete resection in patients with stage III *BRAF* V600-mutant melanoma.[1-3]
  - However, 26% of patients in COMBI-AD discontinued D+T due to adverse events (AEs), including pyrexia.[1]
- Treatment adherence is particularly relevant in the adjuvant setting, where patients often have no evidence of disease and limited tolerance of treatment-related AEs (TRAEs).
- The phase 3b COMBI-APlus trial provided evidence that better management of AEs like pyrexia could improve adherence to adjuvant D+T.[4]
- Digital apps allow patients to track their health and have the potential to enhance care by detecting early changes in symptoms, health-related quality of life (HRQoL), AEs, or treatment adherence that may prompt timely interventions.[5-8]
- In this study, we present the data from the COMBI-EU study, which aims to evaluate the use of adjuvant D+T in clinical practice. In addition, the impact of TRAE management and the use of app-based documentation on treatment adherence are also assessed.

Methods

- COMBI-EU (NCT03944356) is a prospective, non-interventional study conducted by the EUMelaReg consortium from July 2019 to December 2023 at 31 treatment centers in Germany; the data cut-off for this analysis was 13 December 2023.
- Eligible patients were aged ≥18 years with complete surgical resection of histologically confirmed clinical stage IIIA-IIID *BRAF* V600-mutated cutaneous melanoma who had planned treatment with D+T or who had started D+T within 4 weeks of study entry.
- Treatment with D+T was given according to the local prescribing practices (**Figure 1**).
- The primary endpoint was median time on treatment (TOT).
  - The median TOT censored for recurrence (rTOT) was calculated to reflect treatment adherence.
  - Completion rate was defined as the proportion of patients completing 12 months of treatment, censoring for recurrence.
- Selected secondary endpoints include:
  - Impact of TRAE and pyrexia management level on treatment adherence: TRAE management level was based on a self-developed algorithm and pyrexia management level was based on an algorithm adapted from COMBI-APlus[4] (**Table 1**).
  - Voluntary use of a patient app (CANKADO PRO-React, CANKADO Service GmbH), which includes a digital diary to record medication intake and current well-being via patient-reported outcomes, and the impact of app use on treatment adherence.
  - HRQoL, based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), documented in the CANKADO app for app users and on tablets provided by CANKADO during in-person visits for non-users.
  - Efficacy endpoints included recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Figure 1. Design of COMBI-EU, a non-interventional, real-world study



BID, twice daily; CI, confidence interval; D+T, dabrafenib plus trametinib; HRQoL, Health-related Quality of Life; PRO, patient-reported outcome; QD, once daily; rTOT, TOT censored for recurrence (treatment adherence); TOT, time on treatment; TRAE, treatment-related adverse event.

Table 1. Algorithm-based approach to assess the impact of AE management on treatment adherence

Event	Management level	Definition
TRAE	High	TRAE managed by dose reduction, or any TRAE that did not lead to treatment discontinuation
	Low	Grade 1-2 TRAE or any pyrexia event managed by treatment interruption
	NA	No AE, grade 1 TRAE not affecting treatment delivery, or grade ≥3 TRAE requiring treatment discontinuation
Pyrexia*	High	Pyrexia managed by dose interruption, after which full-dose treatment resumed
	Low	Pyrexia managed by 1) no change in treatment or 2) treatment discontinuation
	Partly managed	Pyrexia managed by dose reduction or treatment interruption, after which treatment resumed at a lower dose level
	NA	No pyrexia

*Pyrexia was defined as ≥1 episode of fever, chills, flu-like symptoms, or any combination of these events. NA, not applicable; TRAE, treatment-related adverse event.

Statistical analysis

- TOT and other time-to-event parameters were calculated by Kaplan-Meier analysis; all other parameters were assessed in an exploratory and descriptive manner.
- Statistical significance between variables was assessed by chi-squared text, while numerical differences were calculated by Wilcoxon rank sum test (2 groups) or Kruskal-Wallis test (>2 groups).
- Correlations were analyzed using Spearman and linear regression models.

Results

Patients and treatment adherence

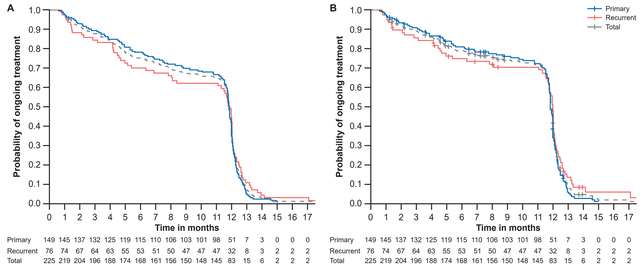
- A total of 225 patients were enrolled (149 primary, 76 recurrent) (**Table 2**).
- 138 (61%) completed a 12-month course of adjuvant D+T and 37 (16%) discontinued treatment due to TRAEs.
- With a median follow-up time of 14.5 months (95% confidence interval [CI]: 14.3, 14.8), most patients (151; 67%) received > 9 months of study treatment, including 83 (37%) who had 12 months of treatment; only 28 (12%) had <3 months of treatment.
- The most common reasons for early discontinuation were AEs (16%), disease progression (11%), and patient preference (6%).
- TOT and rTOT (treatment adherence) are shown in **Figure 2**. The overall completion rate, censoring for recurrence, was 72%.

Table 2. Patient baseline characteristics

Characteristics	Primary stage III disease (n = 149)	Recurrent stage III disease (n = 76)	*P* value	Overall (N = 225)
Female sex, n (%)	62 (41.6)	34 (44.7)	0.76	96 (42.7)
Median age (range), years	57 (24–83)	60.5 (20–87)	0.073	58 (20–87)
ECOG PS score, n (%)				
0	133 (89.3)	72 (94.7)	0.394	205 (91.1)
1	12 (8.1)	3 (3.9)		15 (6.7)
≥ 2	4 (2.7)	1 (1.3)		5 (2.2)
Melanoma subtype, n (%)				
Superficial spreading melanoma	45 (30.2)	29 (38.2)	0.0412	74 (32.9)
Nodular melanoma	61 (40.9)	21 (27.6)		82 (36.4)
Acral lentiginous melanoma	3 (2.0)	6 (7.9)		9 (4.0)
Not classifiable melanoma	2 (1.3)	3 (3.9)		5 (2.2)
Cutaneous melanoma, unspecified	19 (12.8)	12 (15.8)		31 (13.8)
Melanoma of unknown primary	11 (7.4)	1 (1.3)		12 (5.3)
Other cutaneous subtype	8 (5.4)	4 (5.3)		12 (5.3)
Ulceration of primary tumor, n (%)				
Yes	69 (46.3)	31 (40.8)	0.0162	100 (44.4)
No	69 (46.3)	41 (53.9)		110 (48.9)
Unknown	0 (0)	3 (3.9)		3 (1.3)
Not applicable*	11 (7.4)	1 (1.3)		12 (5.3)
AJCC stage (8th edition)				
IIIA	28 (18.8)	0 (0)	<0.001	28 (12.4)
IIIB	46 (30.9)	25 (32.9)		71 (31.6)
IIIC	70 (47.0)	48 (63.2)		118 (52.4)
IIID	5 (3.4)	3 (3.9)		8 (3.6)
Type of lymph node involvement				
Microscopic	112 (75.2)	0 (0)	<0.001	112 (49.8)
Macroscopic	28 (18.8)	43 (56.6)		71 (31.6)
Number of lymph nodes involved				
1	100 (67.1)	24 (31.6)	0.217	124 (55.1)
2	25 (16.8)	9 (11.8)		34 (15.1)
3	3 (2.0)	2 (2.6)		5 (2.2)
≥ 4	10 (6.7)	7 (9.2)		17 (7.6)
Unknown	3 (2.0)	2 (2.6)		5 (2.2)
Size of largest sentinel lymph node, mm				
<1	31 (20.8)	0 (0)	<0.001	31 (13.8)
≥ 1	70 (47.0)	0 (0)		70 (31.1)
Unknown	14 (9.4)	0 (0)		14 (6.2)
In-transit disease				
Yes	9 (6.0)	32 (42.1)	<0.001	41 (18.2)
Yes + microscopic	4 (2.7)	0 (0)		4 (1.8)
Yes + macroscopic	2 (1.3)	11 (14.5)		13 (5.8)
No	134 (89.9)	33 (43.4)		167 (74.2)
***BRAF* mutation**				
V600E	126 (84.6)	58 (76.3)	0.657	184 (81.8)
V600K	12 (8.1)	10 (13.2)		22 (9.8)
V600D	2 (1.3)	1 (1.3)		3 (1.3)
V600R	2 (1.3)	1 (1.3)		3 (1.3)
Other variant	6 (4.0)	5 (6.6)		11 (4.9)

*Patients with melanoma of unknown primary origin. AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Figure 2. Estimated time on treatment (A) and treatment adherence (time on treatment censored for recurrence; B) in patients with primary or recurrent stage III disease at baseline



Treatment adherence assessed by TRAE management

- TRAEs occurred in 181 patients (80%); the most common TRAEs (>25%, grades 1-2) were increased liver enzymes (40%), fever (30%), and fatigue (27%) (**Table 3**).
- A total of 98 patients received high-level TRAE management and 32 had low-level management; all remaining patients were included in the 'Not applicable' group.
- High-level TRAE management was associated with improved treatment adherence compared with low-level AE management (hazard ratio [HR]: 0.74; 95% CI: 0.49, 1.14; **Figure 3A**).
- Among patients with relevant and manageable TRAEs, the completion rate was 69% with high-level management and 49% with low-level management.

Table 3. TRAEs occurring in >5% of patients (grades 1-2) or in ≥1 patient (grades 3-4)

	N = 225	
TRAEs, n (%)	**Any grade**	**Grades 3-4**
Patients with ≥1 TRAEs	181 (80.4)	NR
General disorders		
Fever	68 (30.2)	3 (1.3)
Chills	47 (20.9)	0
Fatigue	61 (27.1)	0
General disorders – other	16 (7.1)	3 (1.3)
Gastrointestinal disorders		
Nausea	43 (19.1)	0
Vomiting	14 (6.2)	1 (0.4)
Diarrhea	28 (12.4)	2 (0.9)
Investigations		
Liver enzymes increased	91 (40.4)	11 (4.9)
Creatine phosphokinase increased	53 (23.6)	6 (2.7)
Musculoskeletal disorders		
Muscle cramp	14 (6.2)	0
Nervous system disorders		
Headache	30 (13.3)	1 (0.4)
Skin disorders	28 (12.4)	0
Eye disorders		
Retinal detachment	2 (0.9)	2 (0.9)
Vascular disorders		
Hypertension	5 (2.2)	5 (2.2)

Subcategories may be overlapping. NR, not reported; TRAE, treatment-related adverse event.

Treatment adherence assessed by pyrexia management

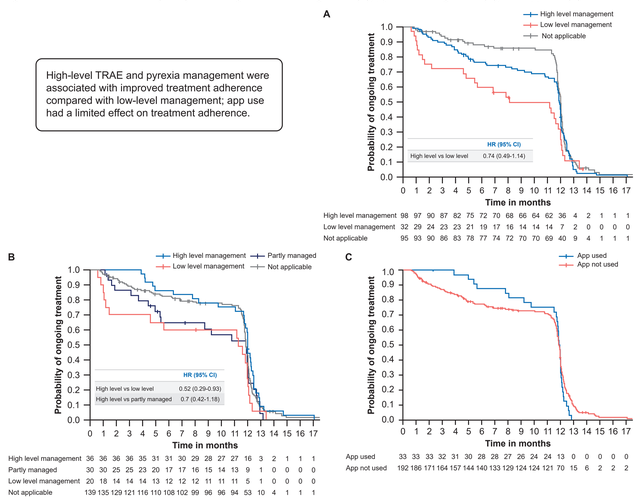
- Occurrence of at least 1 pyrexia event was reported in 86 (38%) patients.
- A total of 36 patients received high-level pyrexia management, 30 were partly managed, and 20 received low-level management; all remaining patients were included in the 'Not applicable' group.
- High-level pyrexia management was associated with improved treatment adherence compared with low-level pyrexia management (HR 0.52; 95% CI: 0.29, 0.93; **Figure 3B**).
- Completion rates for patients receiving high-level, low-level, and partial management were 75%, 60%, and 57%, respectively.

App use

- Only 79 patients (35%) indicated they intended to use the electronic app and 33 (15%) used the app.
- Baseline characteristics were similar between app users and non-users, except that users were significantly younger than non-users (median age: 55 years [range: 20-75] vs 59 years [range: 24-87]).
- The completion rate was 75% in app users and 71% in non-users (**Figure 3C**).

Figure 3. Treatment adherence (rTOT) according to TRAE management (A), pyrexia management (B), and app use (C)

High-level TRAE and pyrexia management were associated with improved treatment adherence compared with low-level management; app use had a limited effect on treatment adherence.

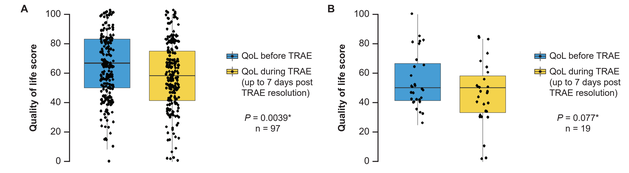


CI, confidence interval; HR, hazard ratio; TRAE, treatment-related adverse event.

HRQoL

- Experiencing a TRAE was associated with significant worsening in EORTC-QLQ-C30 summary score (*P*=0.0039; **Figure 4A**).
- There was no significant association of pyrexia and HRQoL (*P*=0.077; **Figure 4B**).

Figure 4. Effect of experiencing a TRAE (A) or pyrexia (B) on HRQoL scores (EORTC-QLQ-C30)



Each data point represents 1 TRAE/pyrexia/recurrence episode. *Wilcoxon matched pairs test. EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL, health-related quality of life; QoL, quality of life; TRAE, treatment-related adverse event.

Efficacy outcomes

- Median RFS, DMFS, and OS were not reached at the time of the analysis.
- A planned analysis to evaluate the relationship between treatment adherence and efficacy outcomes could not be conducted due to limitations of the data structure.

CONCLUSIONS

- High-level AE management, particularly for pyrexia, was associated with improved adherence to adjuvant D+T following complete resection for stage III *BRAF* V600-mutant melanoma.
- Optional use of an app did not affect treatment adherence.
- Further research is needed to understand the impact of treatment adherence on the effectiveness of adjuvant therapy.

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