T-WIN: Patterns of response to/progression after first-line treatment with dabrafenib and trametinib in patients with unresectable/metastatic *BRAF* V600-mutant melanoma

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BACKGROUND

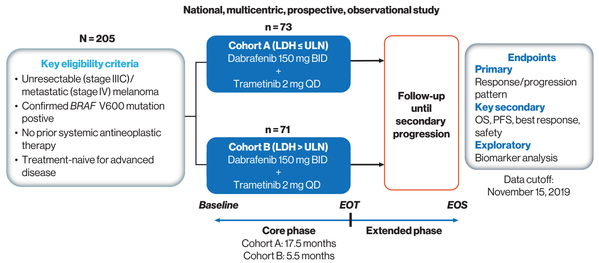
- Dabrafenib (dab; BRAF inhibitor) and trametinib (tram; MEK inhibitor) combination is approved for the treatment of *BRAF* V600 mutation–positive unresectable/metastatic melanoma and other *BRAF* V600-mutated solid tumors[1,2]
- The efficacy of dab + tram combination was established based on the results from two global trials—COMBI-d (median progression-free survival [PFS], 11 months) and COMBI-v (median PFS, 11.4 months)[3,4]
  - These trials included a heterogeneous patient population distinct only through the stratification for lactate dehydrogenase (LDH) levels (> upper limit of normal [ULN] vs ≤ ULN) and *BRAF* V600E/K mutation
- Dab + tram combination therapy is widely used as treatment not only for patients with a high tumor burden but also for the indolent disease
- Limited data are available on the patterns of disease progression and the impact of the dab + tram combination on the clinical outcomes of subsequent treatment lines in a real-world setting
- This observational study aimed to assess the patterns of response to/progression after first-line (1L) treatment with dab + tram combination in patients with *BRAF* V600E/K or other *BRAF*-activating mutation–positive cutaneous melanoma with limited (LDH ≤ ULN) or bulky (LDH > ULN) disease burden in clinical practice
  - Here, we report the interim analysis results from the study, including the efficacy and safety outcomes of 1L dab + tram treatment for patients with unresectable/metastatic *BRAF* V600-mutant melanoma

METHODS

Study Design

- This is a national, multicentric, prospective, observational study
- The primary and co-primary objectives of this study were to describe the patterns of 1L treatment response/progression with dab + tram combination in *BRAF*-mutant patients with bulky or limited tumor burden, respectively
- The key secondary objectives were to
  - Evaluate the impact of patterns of progression during 1L treatment on treatment outcomes in patients receiving second-line (2L) treatment
  - Assess the clinical benefit of 1L and 2L treatments and treatment duration
  - Confirm the safety and tolerability profile of the combination
- The study also aimed to identify the clinical biomarkers potentially related to tumor response or disease progression, following 1L and 2L treatments
- Patients naive to treatment for advanced/metastatic disease at enrollment with a confirmed diagnosis of *BRAF* V600E/K or other *BRAF*-mutant advanced/metastatic melanoma assigned to 1L treatment with labeled use of dab + tram combination were divided into two cohorts (**Figure 1**)
  - Cohort A: patients with limited disease burden (LDH ≤ ULN)
  - Cohort B: patients with bulky disease (LDH > ULN)
- Patients were analyzed for patterns of 1L treatment response/progression at the time of the median PFS reported in the registration trial COMBI-v, i.e. 17.5 months for cohort A and 5.5 months for cohort B
  - Data about patterns of response/progression to 1L treatment with the combination and their influence on 2L treatment outcomes were collected prospectively for both cohorts, from initial visit until progression to 2L treatment
  - Patterns of response/progression were described according to the number of metastases per organ, median time to develop new metastases from the treatment start, and Eastern Cooperative Oncology Group (ECOG) performance status (PS)
- The patients who discontinued treatment due to progression and assigned a 2L treatment were followed up for 12 months after starting the 2L treatment or until second progression (whichever comes first) to investigate how dab + tram 1L treatment may influence subsequent treatment outcomes

Figure 1. Study Design



BID, twice daily; EOS, end of study; EOT, end of treatment; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; QD, once daily; ULN, upper limit of normal.

RESULTS

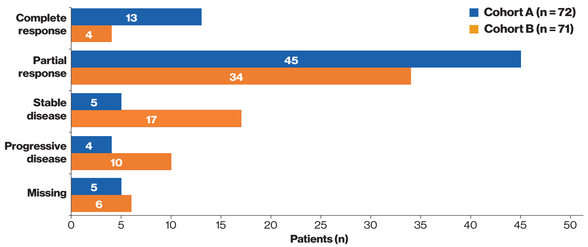
- Of the 205 patients treatment-naive for advanced/metastatic disease enrolled at 33 sites, only 144 patients (cohort A, n = 73; cohort B, n = 71) with clean data were considered for the interim analysis (data cutoff: November 15, 2019)
  - Of these, 143 patients (cohort A, n = 72; cohort B, n = 71) were analyzed for patterns of 1L treatment response/progression
- More patients in cohort A (81%) had ECOG PS 0 than cohort B (63%)
  - Patient demographics and baseline characteristics are shown in **Table 1**
- Best response to 1L treatment with dab + tram is shown in **Figure 2**

Table 1. Patient Demographics and Baseline Characteristics

Demographic Variable	Cohort A n = 73	Cohort B n = 71	Overall N = 144
Age, median (range), years	61 (20–85)	66 (33–86)	63 (20–86)
18 to < 65 years, n (%)	43 (59)	34 (48)	77 (53)
65 to < 85 years, n (%)	28 (38)	33 (46)	61 (42)
≥ 85 years, n (%)	1 (1)	3 (4)	4 (3)
Missing, n (%)	1 (1)	1 (1)	2 (1)
Sex, n (%)			
Male	48 (66)	43 (61)	91 (63)
Female	25 (34)	28 (39)	53 (37)
ECOG performance status, n (%)			
0	59 (81)	45 (63)	104 (72)
1	9 (12)	18 (25)	27 (19)
2	2 (3)	4 (6)	6 (4)
Missing	3 (4)	4 (6)	7 (5)
Prior antineoplastic therapy, n (%)	64 (88)	64 (90)	128 (89)
Chemotherapy	8 (11)	17 (24)	25 (17)
Surgery	63 (86)	60 (85)	123 (85)
Radiotherapy	5 (7)	8 (11)	13 (9)

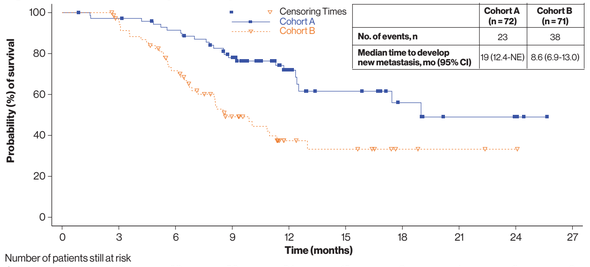
ECOG, Eastern Cooperative Oncology Group.

Figure 2. Best Overall Response to 1L Treatment With Dab + Tram



- The median time to develop subsequent new metastases was longer in cohort A (19 months) than in cohort B (8.6 months) (**Figure 3**)

Figure 3. Time to Develop Subsequent New Metastasis in 1L Treatment



	Cohort A (n = 72)	Cohort B (n = 71)
No. of events, n	23	38
Median time to develop new metastasis, mo (95% CI)	19 (12.4-NE)	8.6 (6.9-13.0)

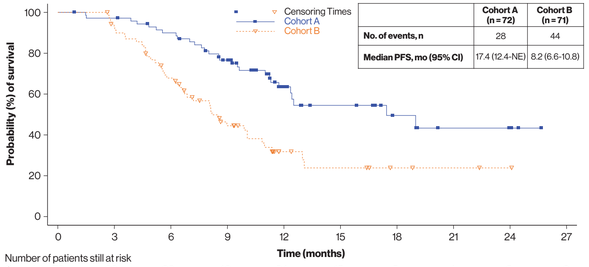
Number of patients still at risk

Cohort A	72	69	63	50	24	15	8	4	3	0
Cohort B	71	65	46	24	10	8	3	2	1	0

Note: The curves represent dab therapy only. For tram therapy the number of patients at risk differed by a patient at month 24 (cohort A).

- The median PFS in 1L treatment was 17.4 and 8.2 months in cohorts A and B, respectively (**Figure 4**)

Figure 4. Progression-free Survival in 1L Treatment



	Cohort A (n = 72)	Cohort B (n = 71)
No. of events, n	28	44
Median PFS, mo (95% CI)	17.4 (12.4-NE)	8.2 (6.6-10.8)

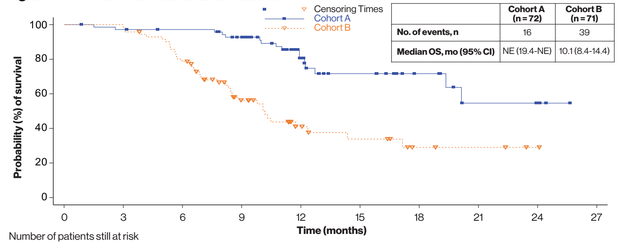
Number of patients still at risk

Cohort A	72	69	62	49	24	15	8	4	3	0
Cohort B	71	64	45	24	9	6	3	2	1	0

Note: The curves represent dab therapy only. For tram therapy the number of patients at risk differed by a patient at months 3 and 24 (cohort A).

- The median overall survival (OS) was not estimable (NE) in cohort A and 10 months in cohort B (**Figure 5**)

Figure 5. Overall Survival in 1L Treatment



	Cohort A (n = 72)	Cohort B (n = 71)
No. of events, n	16	39
Median OS, mo (95% CI)	NE (19.4-NE)	10.1 (8.4-14.4)

Number of patients still at risk

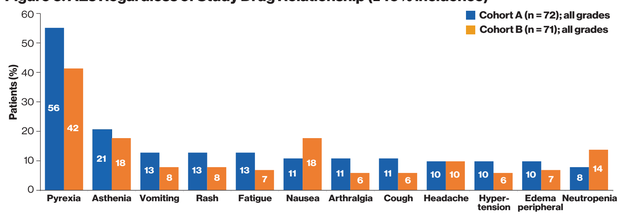
Cohort A	72	69	67	59	30	19	11	5	4	0
Cohort B	71	70	55	30	13	9	4	3	1	0

Note: The curves represent dab therapy only. For tram therapy the number of patients at risk differed by a patient at month 24 (cohort A).

Safety

- At least one any-grade adverse event (AE) was observed in 93% and 87% of patients in cohorts A and B, respectively
  - The most common AE was pyrexia in both cohorts (cohort A, 56%; cohort B, 42%), but it was typically low grade (**Figure 6**)
  - Grade ≥ 3 AEs were higher in cohort B (52%) compared with cohort A (33%)
- The most common treatment-related AEs were pyrexia (cohort A, 44%; cohort B, 32%), asthenia (cohort A, 13%; cohort B, 11%), and neutropenia (cohort A, 8%; cohort B, 13%)

Figure 6. AEs Regardless of Study Drug Relationship (≥ 10% incidence)



Conclusions

- This observational study describes the impact of the prognostic factor, LDH level, on the efficacy and safety of dab + tram combination in a real-world setting
- The preliminary findings from this interim analysis confirm that the safety and effectiveness of the dab + tram combination in *BRAF*-mutant melanoma patients were similar to the previously conducted clinical phase 3 trials[3,4], particularly those with a low disease burden (LDH ≤ ULN)and supports the use of dab + tram combination in routine clinical practice, where the patient population is more heterogeneous

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