Characteristics of Patients With a Complete Response Treated With Dabrafenib Plus Trametinib Combination Therapy: Findings From COMBI-d and COMBI-v 5-Year Analysis

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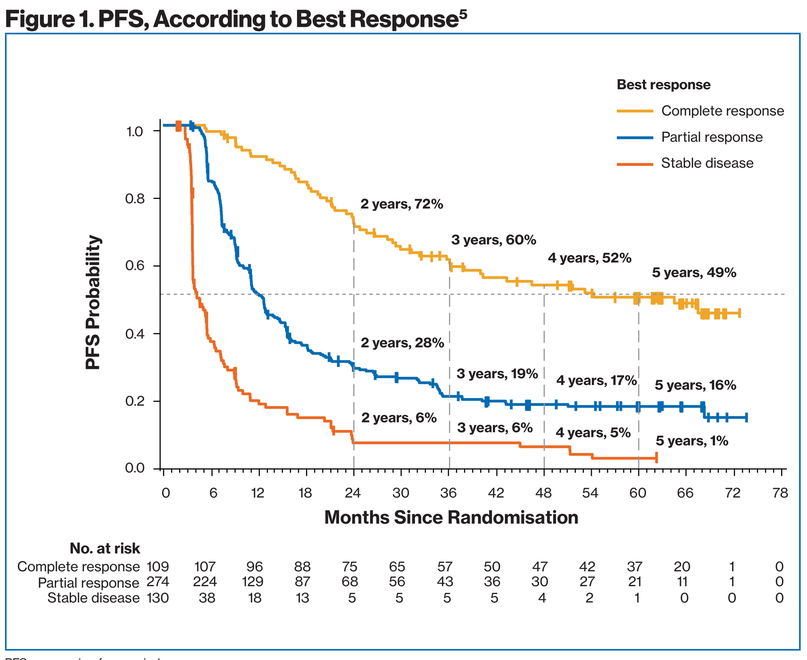
Background

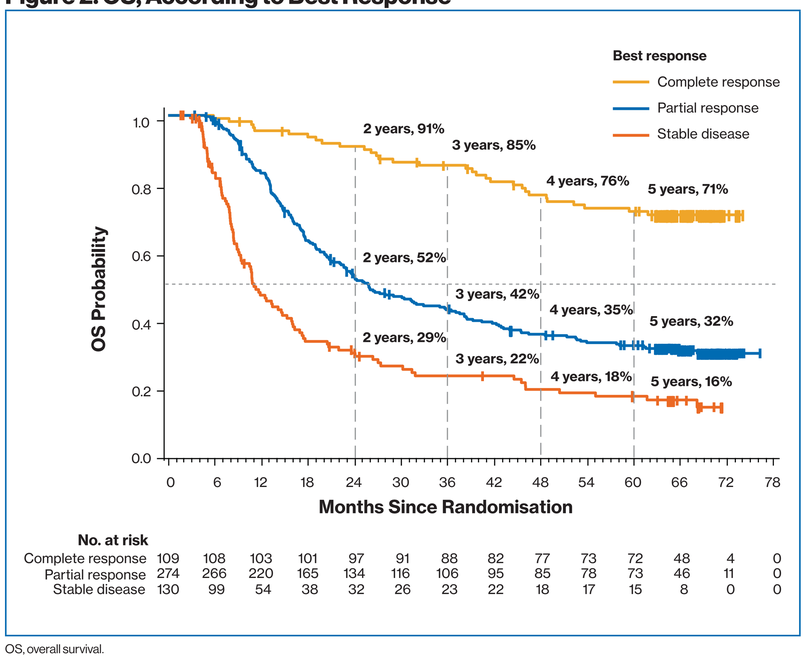
- Dabrafenib (dab) plus trametinib (tram) has been approved in multiple regions for the treatment of patients with *BRAF* V600–mutant unresectable or metastatic melanoma and as adjuvant therapy in patients with resected *BRAF* V600–mutant stage III melanoma[1-4]
- First-line dab + tram led to approximately one-third of patients with *BRAF* V600E/K–mutant unresectable or metastatic melanoma surviving to ≥ 5 years in pooled COMBI-d/v analyses[5,6]
  - Five-year survival rates were higher in patients with normal lactate dehydrogenase (LDH) levels at baseline (43%) and in patients with normal LDH levels and < 3 organ sites with metastases at baseline (55%)
- In pooled analyses, best overall response appeared to be associated with progression-free survival (PFS; **Figure 1**) and overall survival (OS; **Figure 2**), with patients achieving complete response (CR) having the best long-term outcomes[5,7]
  - Median duration of CR was 36.7 months (95% CI, 24.1 months-not reached)[5]
  - Five-year PFS rates were 49% and 19% in patients with CR and the overall population, respectively[5]
  - Five-year OS rates were 71% and 34% in patients with CR and the overall population, respectively[5]
- Increasing evidence, including analyses published by the US Food and Drug Administration at ASCO 2019, suggests that deeper antitumour responses are associated with longer survival[8,9]
- We present additional analyses to characterise outcomes and clinical features of patients who achieved CR in the Phase III randomised COMBI-d/v trials to identify those most likely to derive the greatest clinical benefit from first-line dab + tram therapy

Figure 1. PFS, According to Best Response[5]



PFS, progression-free survival.

Figure 2. OS, According to Best Response[5]



OS, overall survival.

Methods

- This analysis included treatment-naive patients randomised to receive dab + tram in COMBI-d and COMBI-v who achieved a confirmed CR and who may or may not have subsequently remained in CR at the data cutoff for the 5-year pooled analyses (COMBI-d, 10 December 2018; COMBI-v, 8 October 2018)
- An overview of patients included in the pooled analyses is presented in **Table 1**

Table 1. Overview of Overall Population and Patients With CR Included in COMBI-d/v 5-Year Analyses

Study: Dab + Tram Arm	ITT Population, n	Patients With CR, n[a]	Median Follow-Up for Patients With CR (range), mo
COMBI-d (NCT01584648)	211	39	68.0 (5.0-73.0)
COMBI-v (NCT01597908)	352	70	64.0 (7.0-74.0)
Pooled	**563**	**109**	**64.0 (5.0-74.0)**

CR, complete response; dab, dabrafenib; ITT, intention to treat; tram, trametinib.
[a]Includes patients who achieved a confirmed CR and who may or may not have subsequently remained in CR at the data cutoff.

Results

Duration of Response

- Median duration of response (DOR) was longer in patients with CR than in patients with partial response (PR; **Table 2**)
  - In patients with CR, median DOR was estimated to be > 60 months in COMBI-d and was 49.7 months in COMBI-v (**Table 2**)

Table 2. DOR in Patients Treated With Dab + Tram With CR or PR

	Patients With CR	Patients With PR
COMBI-d		
Patients, n	39	107
DOR, median (95% CI), mo	NR (34.5-NR)	9.2 (7.2-10.5)
COMBI-v		
Patients, n	70	167
DOR, median (95% CI), mo	49.7 (27.6-NR)	10.8 (8.5-11.3)

CR, complete response; dab, dabrafenib; DOR, duration of response; NR, not reached; PR, partial response; tram, trametinib.

Baseline Characteristics in Patients With and Without CR

- A higher proportion of patients who achieved CR had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, normal LDH levels, and < 3 organ sites with metastases at baseline compared with patients who did not have a CR (**Table 3**)

Table 3. Baseline Characteristics in Patients With and Without CR

	Patients With CR[a] (n = 109)	Patients Without CR (n = 454)
Age, median (range), years	57 (26-80)	55 (18-91)
Male, n (%)	50 (46)	269 (59)
Stage IV M1c, n (%)	42 (39)	318 (70)
ECOG PS, n (%)		
0	94 (86)	309 (68)
≥ 1	14 (13)	141 (31)
Missing	1 (< 1)	4 (< 1)
LDH level, n (%)		
≤ ULN	98 (90)	267 (59)
> ULN	11 (10)	183 (40)
Missing	0	4 (< 1)
≥ 3 Disease sites, n (%)	17 (16)	258 (57)
Sum of lesion diameters, median, mm	34.0	69.0

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a]Includes patients who achieved CR and who may or may not have subsequently remained in CR at the data cutoff, including those who were subsequently withdrawn from study or lost to follow-up prior to documented progression.

Patient Disposition

- At the time of this analysis, 41% of patients with CR were still receiving dab + tram or had entered follow-up (**Table 4**)
- Of 109 patients with CR, 55 (50%) had ongoing CR at the data cutoff

Table 4. Disposition of Patients With CR

n (%)	Patients With CR (n = 109)
Died	31 (28)
Ongoing	45 (41)
On treatment	21 (19)
In follow-up	24 (22)
Withdrawn from study	33 (30)
Study closed	23 (21)
Consent withdrawn	5 (5)
Loss to follow-up	3 (3)
Investigator discretion	2 (2)

CR, complete response.

Treatment Status in Patients Who Achieved CR

- Median time to CR was 5.6 months (95% CI, 4.0-7.3 months)
- Of 109 patients who achieved a CR, 88 (81%) discontinued dab and/or tram
- The most common reason for discontinuation of dab or tram was disease progression (**Table 5**)
  - A higher proportion of patients who had a PR discontinued dab or tram due to disease progression (≈ 72%) compared with patients who achieved a CR (≈ 42%)

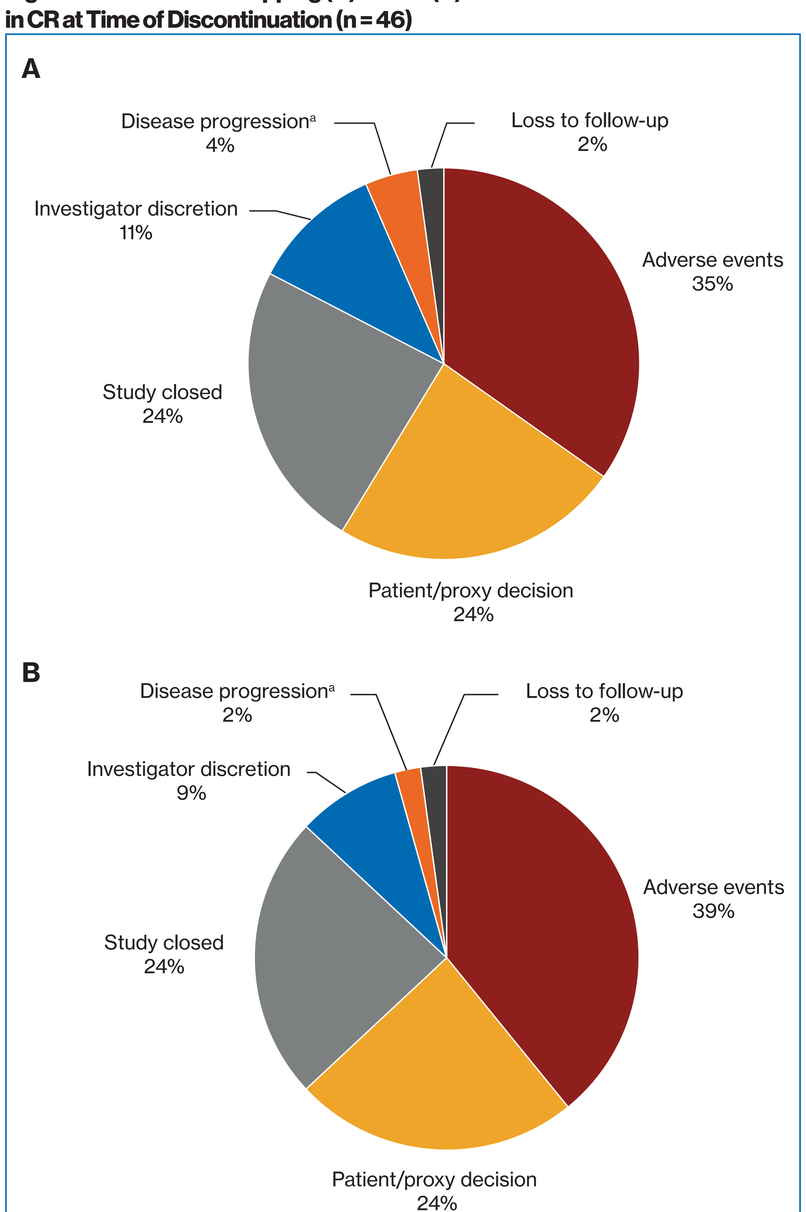
Table 5. Reasons for Discontinuation of Dab or Tram in Patients Who Achieved CR

n (%)	Dab (n = 88)	Tram (n = 88)
Disease progression	38 (43)	36 (41)
Adverse events	20 (23)	23 (26)
Patient/proxy decision	13 (15)	12 (14)
Study closed	11 (13)	12 (14)
Investigator discretion	5 (6)	4 (5)
Loss to follow-up	1 (1)	1 (1)

CR, complete response; dab, dabrafenib; tram, trametinib.

- Of 109 patients who achieved a CR, 46 (42%) discontinued dab and/or tram while in response
  - Adverse events were the most common reason for discontinuation of dab (35%) or tram (39%) in patients still in CR (**Figure 3**)

Figure 3. Reasons for Stopping (A) Dab or (B) Tram in Patients Who Remained in CR at Time of Discontinuation (n = 46)



CR, complete response; dab, dabrafenib; tram, trametinib.
[a]Treatment discontinued before the date of disease progression, but disease progression occurred prior to the data cutoff.

Baseline Characteristics in Patients Whose Disease Did or Did Not Progress After CR

- Baseline characteristics were similar overall in patients whose disease did or did not progress after they achieved a CR (**Table 6**)

Table 6. Baseline Characteristics in Patients With CR Whose Disease Did or Did Not Progress

	Patients With CR Whose Disease Progressed (n = 54)	Patients With CR Whose Disease Did Not Progress (n = 55)
Age, median (range), years	56 (26-80)	57 (31-77)
Male, n (%)	26 (48)	24 (44)
Stage IV M1c, n (%)	20 (37)	22 (40)
ECOG PS, n (%)		
0	47 (87)	47 (85)
≥ 1	7 (13)	7 (13)
Missing	0	1 (2)
LDH level, n (%)		
≤ ULN	47 (87)	51 (93)
> ULN	7 (13)	4 (7)
≥ 3 Disease sites, n (%)	10 (19)	7 (13)
Sum of lesion diameters, median, mm	35.0	33.0

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

Patterns of Progression

- Of 109 patients with CR, 54 (50%) had disease progression and 48 had new lesions
  - Common sites of new lesions included the central nervous system (CNS; 54%), lung (17%), lymph nodes (17%), and skin/subcutaneous tissue (13%)
- In patients with CR whose disease progressed, the patterns of progression were similar to those observed in the overall population (n = 359)
  - In the overall population, common sites of progression included the CNS (40%), lung (21%), lymph nodes (21%), and liver (14%)
  - The CNS was the only site of new lesions in 19 of 26 patients (73%) with CR and 104 of 144 patients (72%) in the overall population

Subsequent Therapy

- Common posttreatment anticancer therapy for patients who achieved a CR included targeted therapy (23%) and anti–programmed death receptor 1 (PD-1; 19%) or anti–cytotoxic T-lymphocyte–associated antigen 4 (16%) immunotherapies (**Table 7**)

Table 7. Summary of Posttreatment Anticancer Therapy

n (%)	Patients With CR (n = 109)
Any subsequent therapy	43 (39)
Radiotherapy	21 (19)
Surgery	5 (5)
Targeted therapy	25 (23)
Dabrafenib	20 (18)
Trametinib	14 (13)
Vemurafenib	6 (6)
Cobimetinib	4 (4)
Binimetinib	2 (2)
Encorafenib	2 (2)
Immunotherapy	28 (26)
Ipilimumab	17 (16)
Pembrolizumab	13 (12)
Nivolumab	8 (7)
Chemotherapy	10 (9)

CR, complete response.

Conclusions

- Pooled analysis of the COMBI-d/v studies showed that patients who were treated with dab + tram and achieved CR (19%) demonstrated improved survival outcomes compared with the overall population
  - CRs showed durability, with a median duration of 36.7 months and 55 patients (50%) still in CR as of the last disease assessment
  - Median DOR was longer in patients with CR than in patients with PR
- A higher proportion of patients who achieved CR had an ECOG PS of 0, normal LDH levels, and < 3 organ sites with metastases at baseline compared with patients without CR
- Select baseline factors may be useful for identifying patients with advanced *BRAF* V600E/K–mutant melanoma who may derive the greatest clinical benefit from first-line dab + tram combination therapy, although additional analyses are needed for validation
- Increasing evidence suggests that CR is associated with long-term benefit.[8,9] To further improve outcomes, a trial combining the PD-1 inhibitor spartalizumab with dab + tram in patients with metastatic *BRAF* V600–mutant melanoma (NCT02967692) is ongoing

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