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

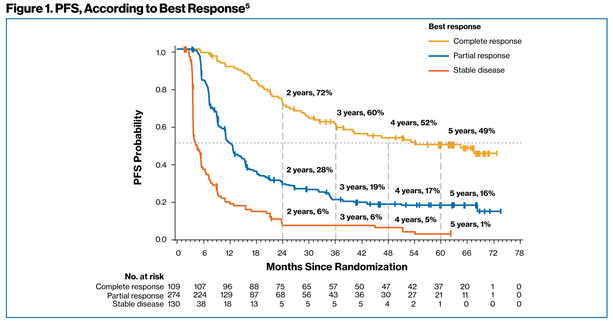
Caroline Robert,[1] Jean Jacques Grob,[2] Daniil Stroyakovskiy,[3] Boguslawa Karaszewska,[4] Axel Hauschild,[5] Evgeny Levchenko,[6] Vanna Chiarion Sileni,[7] Jacob Schachter,[8] Claus Garbe,[9] Igor Bondarenko,[10] Paul Nathan,[11] Antoni Ribas,[12] Michael A. Davies,[13] Keith Flaherty,[14] Paul Burgess,[15] Monique Tan,[16] Eduard Gasal,[16] Dirk Schadendorf,[17] Georgina V. Long[18]

[1]Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; [2]Aix-Marseille University, Marseille, France; [3]Moscow City Oncology Hospital, Moscow, Russia; [4]Przychodnia Lekarska KOMED, Konin, Poland; [5]University Hospital Schleswig-Holstein, Kiel, Germany; [6]Petrov Research Institute of Oncology, St Petersburg, Russia; [7]Melanoma Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy; [8]Ella Lemelbaum Institute for Immuno-Oncology and Melanoma, Sheba Medical Center, Tel Hashomer, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [9]Department of Dermatology, University of Tübingen, Tübingen, Germany; [10]Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine; [11]Mount Vernon Cancer Centre, Northwood, UK; [12]University of California, Los Angeles, CA; [13]The University of Texas MD Anderson Cancer Center, Houston, TX; [14]Dana-Farber Cancer Institute/Harvard Medical School and Massachusetts General Hospital, Boston, MA; [15]Novartis Pharma AG, Basel, Switzerland; [16]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [17]University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; [18]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Background

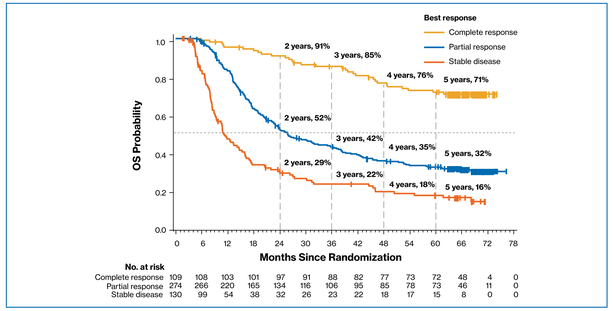
- Dabrafenib (D) + trametinib (T) has been approved in multiple regions for the treatment of patients with *BRAF* V600–mutant unresectable or metastatic melanoma and as adjuvant therapy in patients with resected *BRAF* V600–mutant stage III melanoma[1-4]
- First-line D+T led to approximately one-third of patients with *BRAF* V600E/K–mutant unresectable or metastatic melanoma surviving to ≥ 5 years in pooled COMBI-d/v analysis[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 [NR])[5]
  - Five-year PFS rates were 49% and 19% in patients with CR and the overall population, respectively[6]
  - Five-year OS rates were 71% and 34% in patients with CR and the overall population, respectively[5]
- Increasing evidence, including recent analyses published by the US Food and Drug Administration at ASCO 2019, suggests that deeper antitumor responses are associated with longer survival[8,9]
- We present additional analyses to characterize outcomes and clinical features of patients who achieved CR in Phase III randomized COMBI-d/v trials to identify those most likely to derive the greatest clinical benefit from first-line D+T 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 randomized to D+T 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 analysis (COMBI-d, December 10, 2018; COMBI-v, October 8, 2018)
- An overview of patients included in the pooled analysis is presented in **Table 1**

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

Study – D+T 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; D, dabrafenib; ITT, intention to treat; T, trametinib.
[a]Includes patients who achieved a confirmed CR and who may or may not have subsequently remained in CR at the data cutoff date.

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 D+T With CR or PR

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

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

Baseline Characteristics in Patients With and Without CR

- A higher proportion of patients who achieved CR had Eastern Cooperative Oncology Group performance status (ECOG PS) 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 (%)		
Normal	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 date, 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 D+T or had entered follow-up (**Table 4**)
- Of 109 patients with CR, 55 (50%) had ongoing CR at the data cutoff date

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 D and/or T
- The most common reason for discontinuation of D or T was disease progression (**Table 5**)
  - A higher proportion of patients who had a PR discontinued D or T due to disease progression (≈ 72%) compared with patients who achieved a CR (≈ 42%)

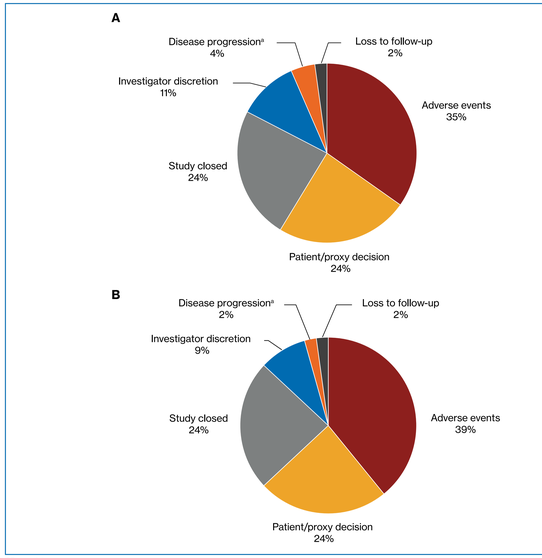
Table 5. Overview of Reasons for Discontinuation of D or T in Patients Who Achieved CR

n (%)	D (n = 88)	T (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; D, dabrafenib; T, trametinib.

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

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



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

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**)

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

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, n (%)		
Normal	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.

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%), and anti–cytotoxic T-lymphocyte–associated antigen 4 immunotherapies (16%) (**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 D+T 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 ECOG PS 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 D+T 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 D+T with the anti–PD-1 inhibitor spartalizumab in patients with metastatic *BRAF* V600–mutant melanoma (NCT02967692) is ongoing

Acknowledgments

The authors thank the patients and their families for their participation. We also thank all investigators and site staff for their contributions.

Statistical support needed to conduct this post hoc analysis was provided by Novartis Pharmaceuticals Corporation. We also thank Maurizio Voi, MD (Novartis Pharmaceuticals Corporation), for guidance and critical review and Jorge J. Moreno-Cantu, MSc, PhD (Novartis Pharmaceuticals Corporation), for editorial assistance. We thank Zareen Khan, PhD, from ArticulateScience LLC, for medical editorial assistance with this presentation, which was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, in accordance with Good Publication Practice (GPP3) (https://www.ismpp.org/gpp3) guidelines and International Committee of Medical Journal Editors recommendations.

This study was sponsored by GlaxoSmithKline; dabrafenib and trametinib are assets of Novartis AG as of March 2, 2015.

References

1. Tafinlar (dabrafenib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.
2. Mekinist (trametinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.
3. Tafinlar (dabrafenib) [summary of product characteristics]. Camberley, UK: Novartis Pharmaceuticals UK Ltd; 2020. https://www.ema.europa.eu/en/documents/product-information/tafinlar-epar-product-information_en.pdf. Accessed July 31, 2020.
4. Mekinist (trametinib) [summary of product characteristics]. Camberley, UK: Novartis Pharmaceuticals UK Ltd; 2020. https://www.ema.europa.eu/en/documents/product-information/mekinist-epar-product-information_en.pdf. Accessed July 31, 2020.
5. Robert C, et al. *N Engl J Med*. 2019;381:626-636.
6. Nathan P, et al. *J Clin Oncol*. 2019;37:abstract 9507.
7. Long GV, et al. *Lancet Oncol*. 2016;17:1743-1754.
8. Osgood C, et al. *J Clin Oncol*. 2019;37:abstract 9508.
9. McCoach CE, et al. *Ann Oncol*. 2017;28:2707-2714.

Poster presentation at the Maui Derm Connect Virtual Dermatology CME Conference; September 23-26, 2020.

This was previously presented at the 2019 International Congress of the Society for Melanoma Research.

Text: Q59edb
To 81404 (86682) US only
+18324604729 North, Central and South Americas, Caribbean; China
+447860024038 UK, Europe, and Russia
+46737494608 Sweden and Europe

Visit the web at:
http://novartis.medicalcongressposters.com/Default.aspx?doc=59edb

Scan this QR code to download a copy of the poster