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

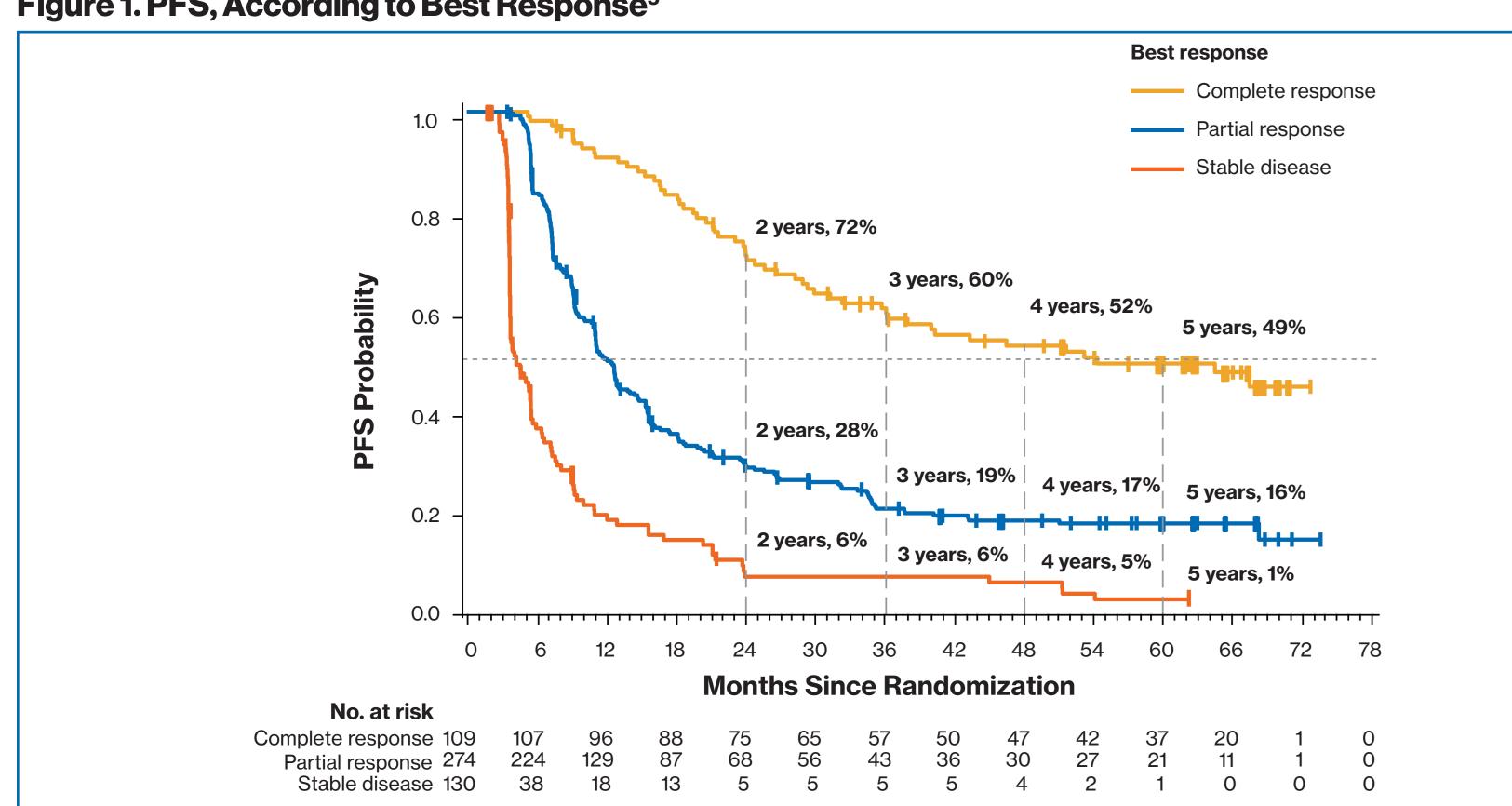
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Background

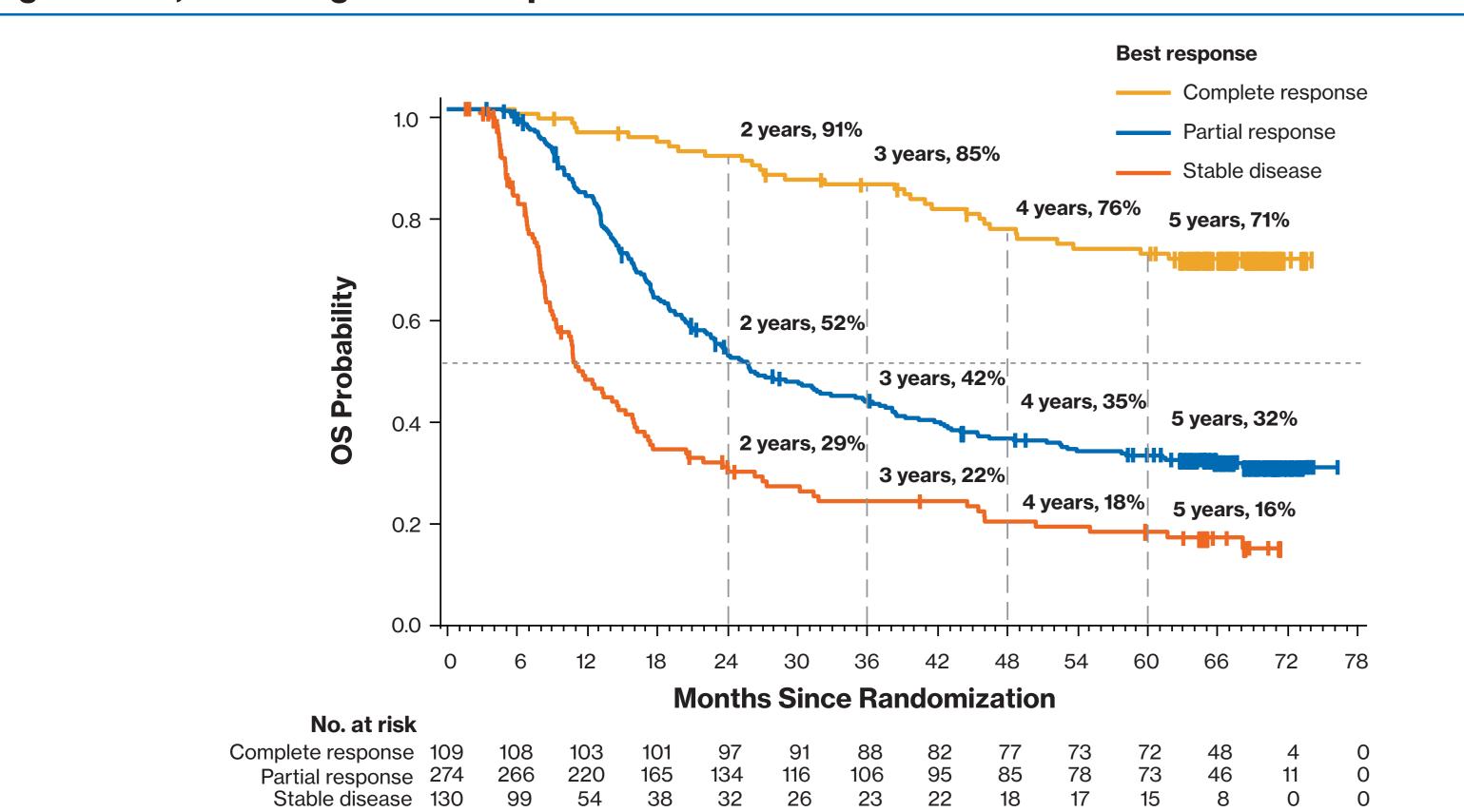
- Dabrafenib (D) + trametinib (T) has been approved in multiple regions for the treatment of patients with BRAF V600-mutant unresectable or metastatic melanoma and as adjuvant therapy in patients with resected BRAF V600-mutant stage III melanoma¹⁻⁴
- First-line D+T led to approximately one-third of patients 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, respectively⁵
- Five-year OS rates were 71% and 34% in patients with CR and the overall population, respectively⁵
- 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 Response⁵



PFS, progression-free survival

Figure 2. OS, According to Best Response⁵



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. DOR in Patients Treated With D+T With CR or PR

	Patients With CR	Patients With PR
COMBI-d Patients, n Median DOR (95% CI), mo	39 NR (34.5-NR)	107 9.2 (7.2-10.5)
COMBI-v Patients, n Median DOR (95% CI), mo	70 49.7 (27.6-NR)	167 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 ≥1 Missing	94 (86) 14 (13) 1 (< 1)	309 (68) 141 (31) 4 (< 1)
LDH level, n (%) Normal > ULN Missing	98 (90) 11 (10) 0	267 (59) 183 (40) 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

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

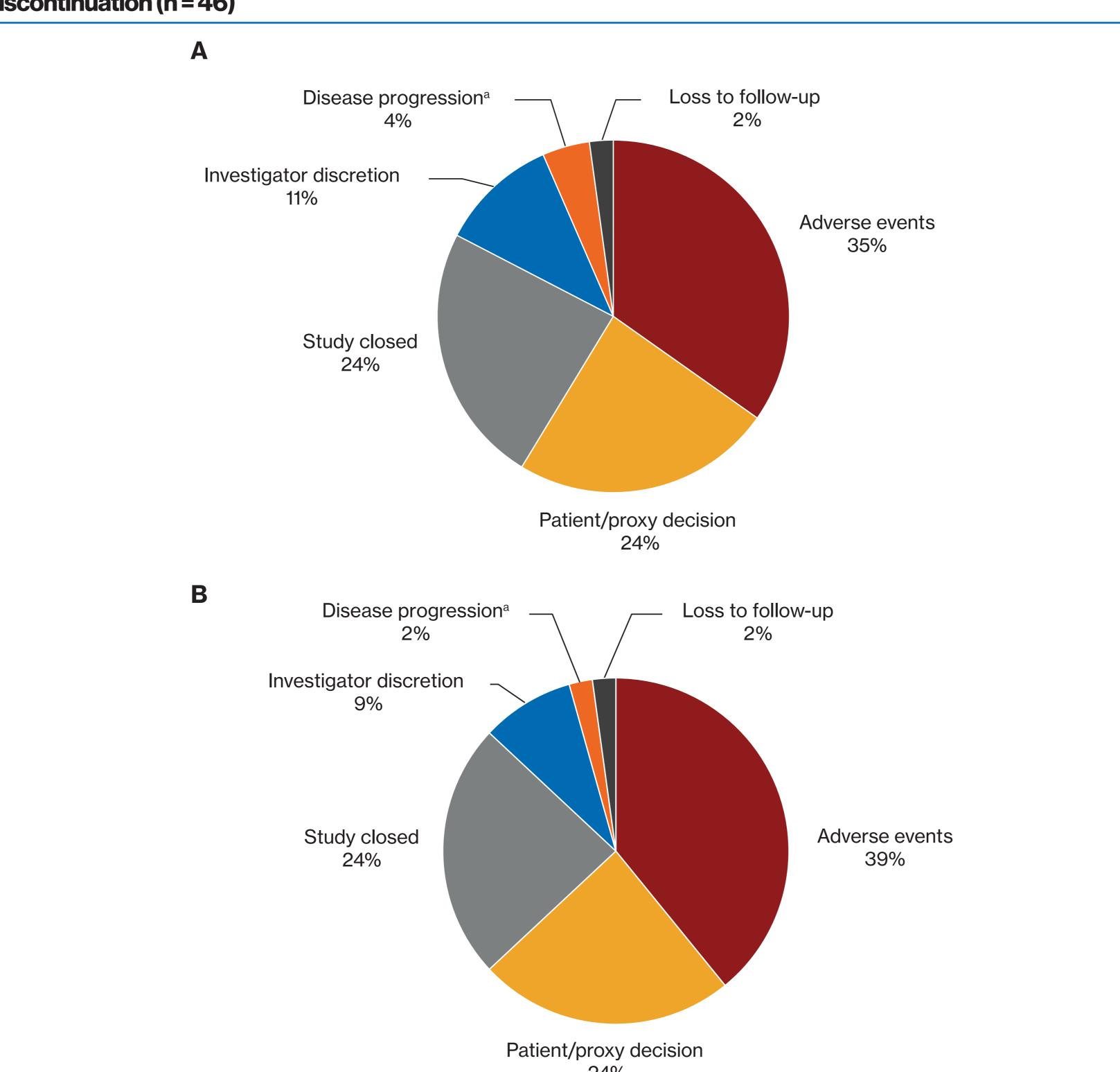
- Median time to CR was 5.6 months (95% CI, 4.0-7.3 months)
- Of 109 patients who achieved a CR, 88 (81%) discontinued D and/or T
- The most common reason for discontinuation of D or T was disease progression (Table 5)
- A higher proportion of patients who had a PR discontinued D or T due to disease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



^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

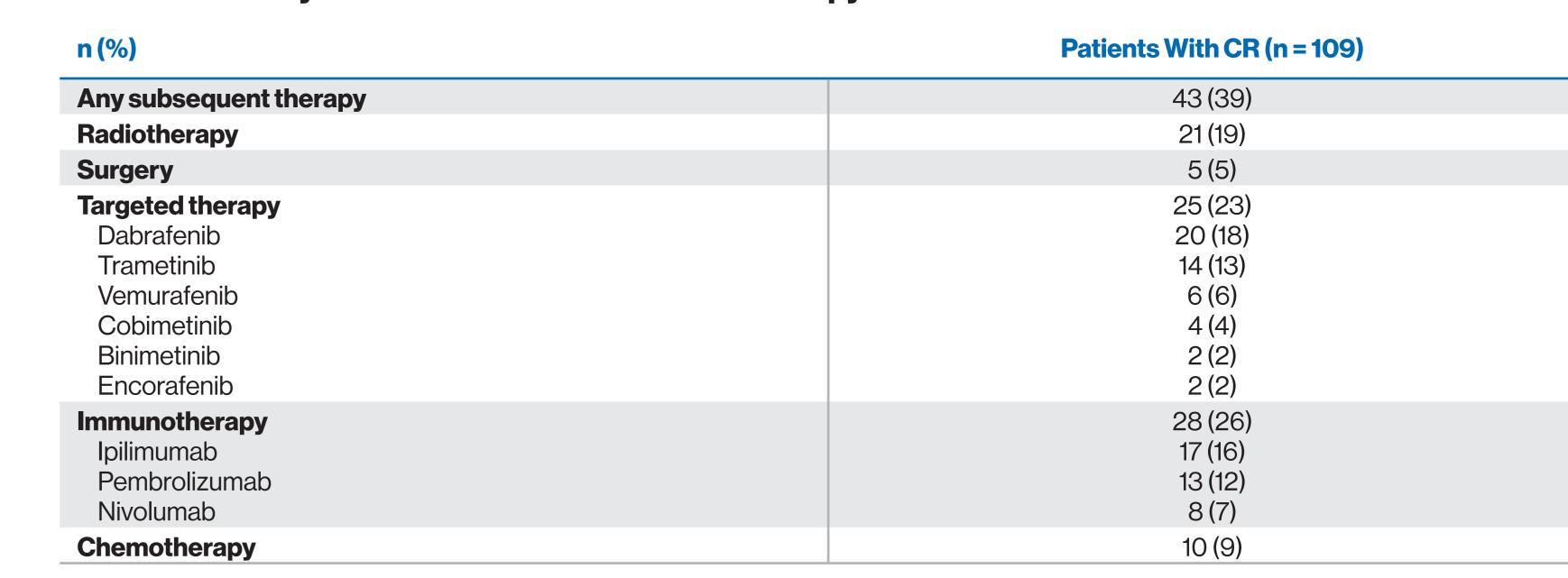
	Patients With CR Whose Disease Progressed (n = 54)	Patients With CR Whose Disease Did Not Progress (n = 55)
Age, median (range), years	56 (26-80)	57 (31-77)
Male, n (%)	26 (48)	24 (44)
Stage IV M1c, n (%)	20 (37)	22 (40)
ECOG PS, n (%) 0 ≥1 Missing	47 (87) 7 (13) 0	47 (85) 7 (13) 1 (2)
LDH, n (%) Normal > ULN	47 (87) 7 (13)	51 (93) 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



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
- 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
- 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

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