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Melanoma and Cutaneous Malignancies

Comprehensive Clinical Trial Data Summation for BRAF-MEK Inhibition and Checkpoint Immunotherapy in Metastatic Melanoma

Jason J. Luke

Department of Medicine, Division of Hematology/Oncology, University of Chicago Comprehensive Cancer Center, Chicago, Illinois, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Melanoma • Molecular targeted therapy • BRAF • Immunotherapy

Abstract

Background. Immune checkpoint inhibitors, along with BRAF and MEK inhibitors, have dramatically changed the management of and outlook for patients with metastatic melanoma. Analyses of long-term follow-up data and subanalyses based on disease characteristics may inform clinical decision making.

Methods. Reports of clinical trials in metastatic melanoma published between January 1, 2012, and August 30, 2018, were identified using PubMed (terms: melanoma AND [dabrafenib OR trametinib OR vemurafenib OR cobimetinib OR encorafenib OR ipilimumab OR nivolumab OR pembrolizumab]) and were systematically reviewed. Relevant congress proceedings were also assessed. Efficacy data from key phase III trials were analyzed and trends identified.

Results. Substantial improvements in objective response rates, progression-free survival, and overall survival were documented across 14 identified publications. Subgroup findings supported that patients with lower disease burden derive greater benefit than patients with more advanced disease, limiting the value of disease burden in the clinical decision-making process. However, these agents consistently conferred benefits despite the presence of poor prognostic features. Several clinically relevant questions remain, including how best to sequence immune checkpoint inhibitors and combination targeted therapy.

Conclusion. This research, coupled with ongoing investigations, including those on predictive biomarkers, suggests that the treatment decision-making process is likely to become more nuanced. ***The Oncologist*** 2019;24:e1197–e1211

Implications for Practice: The management of melanoma has been rapidly advancing with new classes of agents, including immune checkpoint and BRAF inhibitors. With long-term follow-up, their impact on response rates and survival outcomes is well documented. Additional findings from subgroup analyses suggest that patients with lower disease burden derive greater benefit, yet both consistently confer benefit in patients with higher disease burden. Currently, there is a paucity of data to guide first-line treatment selection between immunotherapy and BRAF-targeted therapy in clinical practice or to estimate their impact when sequenced. Gaining these insights will facilitate a more nuanced management approach.

Introduction

Since 2011, a number of systemic agents have been approved for the treatment of unresectable or metastatic melanoma. These agents include several checkpoint inhibitors—namely, the anti-cytotoxic T-lymphocyte associated protein-4 (anti-CTLA-4) antibody ipilimumab and the anti-programmed death-1 (anti-PD-1) antibodies nivolumab and pembrolizumab—as well as the BRAF inhibitors vemurafenib and dabrafenib and the mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors trametinib and cobimetinib [1, 2]. Additional agents that have completed phase III clinical trials for advanced melanoma include the BRAF inhibitor encorafenib, the MEK inhibitor binimetinib, and the oncolytic virus talimogene laherparepvec (T-VEC) [3–7].

This systematic review focuses on checkpoint inhibitors and BRAF inhibitors because these agents have long-term data and subanalyses based on disease characteristics, allowing for a comprehensive assessment of their clinical

Correspondence: Jason J. Luke, M.D., Director of the Cancer Immunotherapeutics Center, University of Pittsburgh Medical Center and Hillman Cancer Center, 5150 Centre Ave., Room 564, Pittsburgh, Pennsylvania 15232, USA. Telephone: 412-647-2811; e-mail: lukejj@upmc.edu Received December 12, 2018; accepted for publication March 22, 2019; published Online First on May 7, 2019. http://dx.doi.org/10.1634/theoncologist.2018-0876

impact. Owing to the large number of currently approved agents and the anticipation of forthcoming approvals, the review focuses on exploring outcomes based on clinical and disease characteristics to identify trends that might help inform clinical treatment decisions. Of note, given the volume of available efficacy data, safety data are beyond the scope of this review and not discussed herein.

Materials and Methods

A comprehensive literature search was performed in Medline using PubMed (filters: clinical trial, humans, English, and January 1, 2012, to December 31, 2018) and the following terms: melanoma AND (dabrafenib OR trametinib OR vemurafenib OR cobimetinib OR encorafenib OR ipilimumab OR nivolumab OR pembrolizumab). Additional PubMed searches were performed for the same time frame to identify any publications that had been omitted because of filter use. Publications on prospective phase I/II, II, or III trials involving patients with metastatic cutaneous melanoma were reviewed. However, phase III trials are discussed in the results because their relatively higher patient numbers allowed for interpretation of subgroup analyses. Publications with the following characteristics were excluded: safety, quality of life, or economic focus or data from expanded access or similar patient programs; case reports; single-center or single-institution studies; and combined analyses across trials; of note, this analysis was supplemented with phase II studies of patients with brain metastases, as this is a subset of patients with a significant unmet need. Evaluation included any of the searched agents in combination with other targeted systemic therapies (except for dabrafenib plus trametinib, vemurafenib plus cobimetinib, nivolumab plus ipilimumab, and encorafenib plus binimetinib) or with other treatment modalities (e.g., radiotherapy, surgery, intratumoral therapy, chemotherapy). A few studies identified with these parameters reported primary results before the January 1, 2012 cutoff; in these cases, the primary studies were added to the analysis. Congress proceedings were manually searched, specifically American Society of Clinical Oncology (ASCO) 2012 to 2018 annual meetings, key European Society for Medical Oncology-sponsored congresses (2014, 2016, 2017, and 2018 annual meetings); European Cancer Congress 2013 and 2015, and Society for Melanoma Research 2012 to 2016 annual meetings.

Results

Fourteen randomized phase III trials of immune checkpoint inhibitors, BRAF inhibitors, or MEK inhibitors alone or in combination in previously untreated and/or pretreated melanoma were identified among the studies of all phases (Table 1) [5, 6, 8–30]. Key study design aspects are summarized in Table 1, with key baseline characteristics in Table 2, overall efficacy results in Table 3 (results of phase II trials in brain metastases are found in supplemental online Table 1), and subgroup findings for progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) highlighted in supplemental online Tables 2, 3, and 4, respectively. Selected subgroup findings are summarized and discussed below, with a focus on those based on tumor characteristics of programmed death-ligand 1 (PD-L1) expression and *BRAF* mutation status, as well as clinical characteristics of baseline lactate dehydrogenase (LDH) levels and Eastern Cooperative Oncology Group performance status (ECOG PS).

Checkpoint Inhibitors

Ipilimumab

Previously Treated Patients. MDX010-020 evaluated ipilimumab as second-line or later treatment in stage III/IV melanoma, randomizing patients to receive ipilimumab plus gp100 peptide vaccine, ipilimumab plus gp100-matched placebo, or gp100 plus ipilimumab-matched placebo (supplemental online Table 2). The three arms were well balanced for ECOG PS, stage M1c disease, elevated LDH, and history of brain metastases (Table 2). No difference in the primary endpoint of OS was detected between the two ipilimumab groups, which improved OS relative to gp100 peptide vaccine alone; of the three treatments, ipilimumab monotherapy had the highest rates of ORR and 12-month PFS (Table 3) [8].

Previously Treated or Untreated Patients. The CA184-169 trial evaluated ipilimumab 3 mg/kg versus ipilimumab 10 mg/kg in patients with previously untreated or treated unresectable stage III/IV melanoma (excluding patients treated with BRAF or immune checkpoint inhibitors; Table 1) [9]. Baseline characteristics were generally well balanced between treatment arms (Table 2). Median OS favored ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg (median OS, 15.7 vs. 11.5 months; hazard ratio [HR], 0.84; $p = .04$; Table 3) [9].

Subgroup analysis of OS demonstrated a larger benefit with 10 mg/kg versus 3 mg/kg in patients with *BRAF*-mutant tumors (HR, 0.65) than in patients with *BRAF*-wild-type tumors (HR, 0.92). Similarly, greater risk reduction was observed with 10 mg/kg in patients with ECOG PS 0 (HR, 0.80) than in those with ECOG PS 1 (HR, 1.00) and patients with baseline LDH ≤2 × upper limit of normal (ULN; HR, 0.84) than in those with baseline LDH >2 × ULN (HR, 0.97; supplemental online Table 3).

Nivolumab

Previously Treated Patients. Checkmate 037 evaluated nivolumab monotherapy as second-line or later treatment of stage IIIC/IV melanoma (including patients with a BRAF mutation), randomizing patients to receive nivolumab or investigator choice chemotherapy (ICC) with dacarbazine monotherapy or paclitaxel plus carboplatin (Table 1) [11]. The two arms were well balanced for ECOG PS of 0, stage M1c disease, history of brain metastases, and BRAF mutation status; 51% of patients in the nivolumab group versus 35% in the ICC group had elevated LDH levels at baseline (Table 2). Nivolumab conferred significant benefits over ICC in the primary endpoint of ORR [11, 31] and improvement in 2-year PFS rate, but without significant prolongation of median PFS or OS (Table 3) [31].

Across prespecified subgroups (supplemental online Table 4), the ORR with nivolumab was more than twice as high in PD-L1-positive versus PD-L1-negative disease (43.6% vs. 20.3%), whereas response was numerically higher in *BRAF*-wild-type versus *BRAF*-mutant tumors (*BRAF* wild type, 34.0%; *BRAF* mutant, 23.1%) [11].

Table 1. Study designs

Study	Phase	Enrollment, *n*	Randomization	Experimental arm(s)	Prior therapy for metastatic disease	Brain metastases
Ipilimumab						
MDX010-020 [8]	III	676	3:1:1	Ipilimumab + gp100	≥1 prior regimen with dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2	Excluded if active, untreated
CA184-169 [9]	III	727	1:1	Ipilimumab 10 mg/kg	No prior BRAFi or checkpoint inhibitor	Allowed if asymptomatic and not requiring treatment
Hodi [10]	II	245	1:1	Ipilimumab + sargramostim	Untreated or 1 prior therapy	Excluded
CA184-042 [73]	II	72	N/A	Ipilimumab	No prior focused RT or WBRT within 14 days and either no systemic CS in 10 days (cohort A) or corticosteroids for symptoms or edema (cohort B)	Asymptomatic brain metastases required
Nivolumab						
CheckMate 037 [11]	III	631	2:1	Nivolumab	Anti-CTLA-4 if *BRAF* wt; anti-CTLA-4 and BRAFi if *BRAF* V600 positive	Excluded if active
CheckMate 066 [12]	III	518	1:1	Nivolumab + dacarbazine-matched placebo	None	Excluded if active
Weber [13]	I	90	N/A	Nivolumab alone (cohort 6) or with peptide vaccine (cohorts 1–5)	≥1 prior systemic therapy; analysis focused on ipilimumab-refractory patients	Allowed if treated and stable for ≥8 weeks; untreated allowed in cohort 6
Nivolumab/ipilimumab						
CheckMate 067 [14]	III	945	1:1:1	Nivolumab + ipilimumab Nivolumab	None	Excluded if active
CheckMate 069 [15]	II	179	2:1	Nivolumab + ipilimumab	None	Excluded if active
CheckMate 204 [74]	II	94	N/A	Nivolumab + ipilimumab (induction) and Nivolumab (maintenance)	No prior radiation for brain metastases and no systemic glucocorticoids within 10 days	Asymptomatic brain metastases required
Anti-PD1 Brain Collaboration (ABC) trial [64]	II	79	N/A	Nivolumab + ipilimumab or Nivolumab (cohorts A and B) or Nivolumab alone (cohort C)	No prior local brain therapy, except for cohort C (failure of local therapy allowed)	Asymptomatic brain metastases required, except for cohort C (neurological symptoms or leptomeningeal disease allowed)
Pembrolizumab						
KEYNOTE-006 [16]	III	834	1:1:1	Pembrolizumab (2 doses)	≤1 systemic therapy	Excluded if active
KEYNOTE-002 [17, 75]	II	540	1:1:1	Pembrolizumab	Prior ipilimumab and prior BRAFi or MEKi or both (if *BRAF* V600 positive)	Excluded if active
KEYNOTE-001 [18]	I	135	N/A	Pembrolizumab	≤2 prior treatments if ipilimumab naive	Allowed; however, if previously treated, no evidence of CNS progression within 8 weeks was required
Vemurafenib						
BRIM-3 [19]	III	675	1:1	Vemurafenib	None	Excluded if CNS metastases had progressed or required treatment in prior 3 months
MO25653 [76]	II	24	N/A	Vemurafenib	≥1 prior treatment for brain metastases and use of corticosteroids required	Symptomatic brain metastases required
MO25743 [77]	II	146	N/A	Vemurafenib	No prior therapy for brain metastases (cohort A) or SRT, WBRT, or surgery (cohort B)	Symptomatic or asymptomatic brain metastases required

(continued)

Table 1. (continued)

Study	Phase	Enrollment, *n*	Randomization	Experimental arm(s)	Prior therapy for metastatic disease	Brain metastases
Vemurafenib/cobimetinib						
coBRIM [20]	III	495	1:1	Vemurafenib + cobimetinib	None	Allowed if treated and stable for ≥3 weeks
Dabrafenib						
BREAK-3 [21]	III	250	3:1	Dabrafenib	None other than interleukin-2	Excluded unless not active for >3 months after surgery or SRT
BREAK-2 [22]	II	92	N/A	Dabrafenib	Prior therapy allowed (excluding BRAFi/MEKi) but not required	Excluded if history or evidence
BREAK-MB [78]	II	172	N/A	Dabrafenib	No prior local therapy for brain metastases (cohort A) or SRT, WBRT, or surgery (cohort B)	Asymptomatic brain metastases required
Trametinib						
METRIC [23]	III	322	2:1	Trametinib	≤1 systemic therapy (excluding ipilimumab and BRAFi/MEKi)	Allowed if stable
MEK113583 [24]	II	97	N/A	Trametinib	≥1 prior systemic therapy (excluding MEKi)	Allowed if treated with surgery or SRT and stable for ≥8 weeks; cohorts were (a) pretreated with BRAFi or (b) pretreated with chemotherapy and/or immunotherapy but not BRAFi
Dabrafenib/trametinib						
COMBI-v [25]	III	704	1:1	Dabrafenib + trametinib	None	Allowed if treated and stable for ≥12 weeks
COMBI-d [26]	III	423	1:1	Dabrafenib + trametinib	None	Allowed if treated and stable for ≥12 weeks
CombiDT [27]	II	23	N/A	Dabrafenib + trametinib	BRAFi monotherapy	Excluded if active within 4 weeks
COMBI-MB [61]	II	125	N/A	Dabrafenib + trametinib	No prior local brain-directed therapy (cohort A), prior local therapy (cohort B), or with or without local therapy (cohorts C and D)	Asymptomatic $BRAF^{V600E}$ brain metastases (cohorts A and B), asymptomatic $BRAF^{V600D/K/R}$ brain metastases (cohort C), or symptomatic $BRAF^{V600D/E/K/R}$ brain metastases required
Schreuer [28]	II	25	N/A	Dabrafenib + trametinib	BRAFi monotherapy or combination; prior anti-CTLA-4 or anti-PD-1 therapy also required	Allowed, even if progressive or requiring CS
Study 220 [29, 79]	II (Part C of the overall phase I/II study)	162	1:1:1	Dabrafenib + trametinib (2 doses)	≤1 prior chemotherapy regimen; no prior BRAFi or MEKi	Allowed if treated and stable, with no CS and/or enzyme-inducing anticonvulsants for ≥30 days and confirmed stable with 2 consecutive MRI or CT scans ≥90 days apart
Encorafenib/binimetinib						
COLUMBUS Part 1 [4]	III	577	1:1:1	Encorafenib + binimetinib	None or first-line immunotherapy (with progression)	Excluded if CNS lesions were untreated
COLUMBUS Part 2 [4, 5]	III	344	3:1	Encorafenib + binimetinib	None or first-line immunotherapy (with progression)	Excluded if CNS lesions were untreated

Abbreviations: BRAFi, BRAF inhibitor; CNS, central nervous system; CS, corticosteroids; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte associated protein-4; MEKi, MEK inhibitor; MRI, magnetic resonance imaging; PD-1, programmed death-1; RT, radiation therapy; SRT, stereotactic radiation therapy; WBRT, whole-brain radiation therapy; wt, wild type.

Previously Untreated Patients. CheckMate 066 evaluated nivolumab monotherapy in previously untreated stage III/IV melanoma (excluding patients with a *BRAF* mutation), randomizing patients to receive nivolumab plus dacarbazine-matched placebo or dacarbazine plus nivolumab-matched placebo (Table 1) [12]. The proportion of patients with ECOG PS 0 was higher in

the nivolumab arm (70% vs. 58% with dacarbazine), with the groups well matched for baseline stage M1c disease, elevated LDH, and history of brain metastases (Table 2). Nivolumab conferred significant benefits over dacarbazine in the primary endpoint of 1-year OS and secondary efficacy outcomes of median PFS and ORR (Table 3) [12].

In the analyses of prespecified subgroups (supplemental online Table 3), median OS was not reached with nivolumab, irrespective of PD-L1 status or baseline LDH level, and it was not reached in patients with a history of brain metastases (of note, there were too few patients with brain metastases to calculate) or in those with ECOG PS 0. In the subset with ECOG PS 1, median OS was 12.7 months, translating into a 36% reduction in the risk of death with nivolumab versus dacarbazine versus a 68% reduction in the ECOG PS 0 subset. For ORR (supplemental online Table 4), subgroup data were available for PD-L1 status, with rates of 52.7% in PD-L1-positive disease versus 33.1% in PD-L1-negative or indeterminate disease [12].

Nivolumab/Ipilimumab

CheckMate 067 evaluated nivolumab plus ipilimumab in previously untreated stage III/IV melanoma (excluding patients with unknown *BRAF* mutation status), randomizing patients to receive the combination, nivolumab monotherapy, or ipilimumab monotherapy (Table 1). The three arms were well balanced for ECOG PS, stage M1c disease, elevated LDH levels, history of brain metastases, and *BRAF* mutation status (Table 2). Both the combination and nivolumab monotherapy were significantly more effective than ipilimumab monotherapy in the two coprimary endpoints of PFS and OS and in ORR (Table 3) [14, 32–35].

Three- and 4-year results are available for the prespecified subgroups in CheckMate 067 (supplemental online Tables 2–4), demonstrating numerically higher PFS and OS rates with the combination versus nivolumab monotherapy across most subgroups, with survival outcomes favoring nivolumab-containing therapies versus ipilimumab monotherapy in all subgroups [32, 34, 35]. For PFS, certain subgroups fared better with the combination than with nivolumab monotherapy, particularly those with a PD-L1 level ≥10% (4-year PFS rate, 48% with combination vs. 37% with nivolumab; HR, 0.67) and *BRAF* mutation-positive disease (39% vs. 23%; HR, 0.62; supplemental online Table 2). Four-year PFS rate in combination-treated patients was similar between *BRAF*-mutant (39%) and *BRAF*-wild-type (35%) disease. The combination was associated with PFS rates of 42% to 45% in patients with the most favorable LDH levels (ULN or lower), disease burden (Q1 or lower [31 mm]), and lesion site (limited to one) categories, with corresponding rates that were slightly lower with nivolumab monotherapy (35%–37%) but markedly lower with ipilimumab monotherapy (11%–14%). The more mature OS data suggest that nivolumab plus ipilimumab may confer improved outcomes over nivolumab alone in patients with low PD-L1-expressing tumors (HR 0.68 with the combination vs. nivolumab in patients with PD-L1 expression <1%), whereas the two regimens were associated with similar OS in patients with PD-L1 expression ≥1% (HR, 0.98; supplemental online Table 3). OS results by *BRAF* subgroup were consistent with the PFS results, with a notable reduction in the risk of death in patients with *BRAF*-mutant disease (HR 0.70 vs. 0.92 in *BRAF*-wild-type disease with the combination vs. nivolumab alone, although the trial was not powered for this comparison) [35]. In addition, results by region and *BRAF* mutation status showed that 2-year OS in each arm in EU patients with *BRAF*-wild-type disease was lower than in EU patients with *BRAF*-mutant disease and U.S. patients with *BRAF*-wild-type disease (possibly reflecting differences in the extent of advanced disease) [36].

Pembrolizumab

KEYNOTE-006 evaluated pembrolizumab monotherapy in previously treated or untreated (one or fewer prior systemic therapy for advanced disease) stage III/IV melanoma, randomizing patients to receive pembrolizumab every 2 weeks, pembrolizumab every 3 weeks, or ipilimumab every 3 weeks (Table 1). The three arms were well balanced (Table 2). In this study, pembrolizumab in both arms was superior to ipilimumab in the coprimary endpoints of PFS and OS and the secondary efficacy outcome of ORR [16], with higher 2- and 3-year OS and PFS rates per updated results (Table 3) [37, 38].

In KEYNOTE-006, PFS benefits in either pembrolizumab arm versus the ipilimumab arm were seen across subgroups based on *BRAF* mutation status, baseline ECOG PS, and PD-L1 status (supplemental online Table 2) [16]. Risk reductions for progression and death were similar between the various categories within a subgroup. The risk reductions for death with pembrolizumab were similar irrespective of *BRAF* status and ECOG PS but were more favorable in patients with PD-L1-positive versus -negative disease (supplemental online Table 3) [16].

Summary of Key Findings: Checkpoint Inhibitors

- Single-agent checkpoint inhibitors show a clear benefit over chemotherapy for patients with metastatic melanoma, and these benefits appear to be consistent across patient subgroups.
- Anti-PD-1 monotherapies (nivolumab and pembrolizumab) demonstrate an efficacy benefit over ipilimumab monotherapy that appears consistent over the several subgroups analyzed. Benefit for anti-PD-1 therapy appears greater for patients with elevated PD-L1 expression; however, the relevance of this finding is debatable in consideration of standard practice.

Single-agent checkpoint inhibitors show a clear benefit over chemotherapy for patients with metastatic melanoma, and these benefits appear to be consistent across patient subgroups.

- The combination of nivolumab plus ipilimumab is significantly more effective in improving ORR, PFS, and OS relative to ipilimumab monotherapy in the first-line setting, with benefit maintained at 4 years. Certain patient subgroups may derive greater benefit from the combination of nivolumab plus ipilimumab versus nivolumab monotherapy, particularly those who have low expression of PD-L1.

Table 2. Baseline characteristics for phase III trials

Study	*n*	Treatment	ECOG PS 0, %	Stage IV/ M1c disease, %	LDH elevated or >ULN, %	Brain/CNS metastases, %	Disease sites ≥3, %	*BRAF* mutation positive, %
Ipilimumab								
MDX010-020 [8]	403	Ipilimumab + gp100	58	99/71	37	11	NR	NR
	137	Ipilimumab + placebo	53	99/73	39	11	NR	NR
	136	gp100 + placebo	51	97/72	38	15	NR	NR
CA184-169 [9]	365	Ipilimumab 10 mg/kg	72	90/63	36	18	NR	22
	362	Ipilimumab 3 mg/kg	70	90/61	38	17	NR	22
Nivolumab								
CheckMate 037 [11]	272	Nivolumab	60	96/75	51	19	NR	22
	133	Dacarbazine or carboplatin + paclitaxel (ICC)	63	98/77	35	14	NR	22
CheckMate 066 [12]	210	Nivolumab + placebo	70	NR/61	38	3	NR	0
	208	Dacarbazine + placebo	58	NR/61	36	4	NR	0
Nivolumab/ipilimumab								
CheckMate 067 [14]	314	Nivolumab + ipilimumab	73	NR/58	36	4	NR	32
	316	Nivolumab	75	NR/58	35	3	NR	32
	315	Ipilimumab	71	NR/58	37	5	NR	31
Pembrolizumab								
KEYNOTE-006 [16]	279	Pembrolizumab q2w	70	97/64	NR	8	NR	35
	277	Pembrolizumab q3w	68	97/68	NR	10	NR	35
	278	Ipilimumab	68	95/64	NR	10	NR	38
Vemurafenib								
BRIM-3 [19]	337	Vemurafenib	68	94/66	42	NR	NR	100
	338	Dacarbazine	68	96/65	42	NR	NR	100
Cobimetinib/vemurafenib								
coBRIM [40]	247	Cobimetinib + vemurafenib	76	91/59	46	<1	NR	100
	248	Placebo + vemurafenib	67	95/62	43	1	NR	100
Dabrafenib								
BREAK-3 [21]	187	Dabrafenib	66	97/66	36	NR	NR	100
	63	Dacarbazine	70	98/63	30	NR	NR	100
Trametinib								
METRIC [23]	214	Trametinib	64	95/67	36	4	57	100
	108	Dacarbazine or paclitaxel (ICC)	64	93/58	39	2	52	100
Dabrafenib/trametinib								
COMBI-v [25]	352	Dabrafenib + trametinib	71	96/63	34	NR	50	100
	352	Vemurafenib	70	93/59	32	NR	43	100
COMBI-d [26]	211	Dabrafenib + trametinib	74	98/67	37	NR	48	100
	212	Dabrafenib + placebo	71	95/65	34	NR	44	100
Encorafenib/binimetinib								
COLUMBUS Part 1 [4, 47]	192	Encorafenib + binimetinib	71	95/64	29	NR	45	100
	194	Encorafenib	72	97/62	24	NR	44	100
	191	Vemurafenib	73	94/65	27	NR	46	100
COLUMBUS Part 2 [5]	258	Encorafenib + binimetinib	73	NR/67	31	NR	44	100
	280 (parts 1 and 2)	Encorafenib	72	NR/64	28	NR	45	100
	86 (part 2)	Encorafenib	72	NR/67	37	NR	48	100

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ICC, investigator choice chemotherapy; LDH, lactate dehydrogenase; NR, not reported; q2w, every 2 weeks; q3w, every 3 weeks; ULN, upper limit of normal.

Targeted Agents

Vemurafenib

BRIM-3 evaluated vemurafenib in previously untreated stage IIIC/IV melanoma harboring a *BRAF* V600 mutation, randomizing patients to receive vemurafenib or dacarbazine (Table 1). The two arms were well balanced for ECOG PS, stage M1c disease, and elevated LDH levels (Table 2). Vemurafenib conferred significant benefit over dacarbazine in the coprimary endpoints of PFS

and OS and the secondary efficacy outcome of ORR [19], with the OS benefit maintained in the recently published final analysis (Table 3) [39].

Analysis of OS based on ECOG PS showed a median OS in the vemurafenib arm of 16.8 months in patients with ECOG PS 0 and 10.0 months in patients with ECOG PS 1 (supplemental online Table 3). Median OS in the vemurafenib arm was 18.1 months in patients with normal baseline LDH and 9.6 months in patients with elevated LDH [39].

Vemurafenib/Cobimetinib

coBRIM evaluated vemurafenib plus cobimetinib in previously untreated stage IIIC/IV melanoma harboring a *BRAF* V600 mutation, randomizing patients to receive the combination or vemurafenib with placebo (Table 1). The two arms were well balanced for ECOG PS, stage M1c disease, elevated LDH, and history of brain metastases (Table 2). Vemurafenib plus cobimetinib plus conferred significant benefit over vemurafenib alone in the primary endpoint of PFS and the secondary outcomes of OS and ORR (Table 3) [40, 41].

For PFS and OS, HRs favored the combination in the prespecified subgroups, which included *BRAF* mutation type, baseline LDH, and ECOG PS (supplemental online Tables 2 and 3). HRs for PFS were similar based on *BRAF* mutation type, ECOG PS, and baseline LDH levels. For median OS, the most pronounced risk reductions were seen in the patients with ECOG PS 1 (47% reduction) or normal baseline LDH (41% reduction) (supplemental online Table 2) [40].

Dabrafenib

BREAK-3 evaluated dabrafenib monotherapy in previously untreated stage III/IV melanoma harboring a *BRAF* V600E mutation, randomizing patients to receive dabrafenib or dacarbazine (Table 1). The two arms were well balanced for ECOG PS, stage M1c disease, and elevated LDH (Table 2). Dabrafenib conferred significant benefit over dacarbazine in the primary endpoint of PFS [21], with updated results presented at the ASCO 2017 annual meeting reporting 5-year outcomes, at which time PFS was 12% with dabrafenib and 0% with dacarbazine (Table 3) [42].

PFS was analyzed by baseline LDH levels (supplemental online Table 2) [42]. The results have been consistent over ongoing follow-up, with PFS of 21% and 6% in patients with LDH levels at the ULN or lower and greater than the ULN, respectively, at 3 years; 17% and 4%, respectively, at 4 years; and 16% and 4%, respectively, at 5 years [42].

Trametinib

METRIC evaluated trametinib monotherapy in previously treated or untreated (one or fewer prior chemotherapy regimen for advanced or metastatic disease) stage IIIC/IV melanoma harboring a *BRAF* V600E or V600K mutation, randomizing patients to receive trametinib or ICC with dacarbazine or paclitaxel (Table 1). The two arms were well balanced for baseline characteristics and disease history (Table 2). Trametinib conferred significant benefit over ICC in the primary endpoint of PFS and the secondary outcome of 6-month OS [23]; a recently published update reported OS after 5-year follow-up, at which time the median was 15.6 months with trametinib versus 11.3 months with ICC and OS rates were 13% versus 17%, with a high rate of crossover from chemotherapy to trametinib and some differences in postprogression therapies between the arms (Table 3) [43]. PFS benefit with trametinib over ICC was observed in subgroups based on ECOG PS and LDH (supplemental online Table 2) [23].

Dabrafenib/Trametinib

COMBI-v evaluated dabrafenib plus trametinib in previously untreated stage IIIC/IV melanoma harboring a *BRAF* V600E or V600K mutation, randomizing patients to receive the combination or vemurafenib monotherapy (Table 1). The two arms were well balanced for ECOG PS, stage M1c disease, elevated LDH levels, and at least three disease sites (Table 2) [25]. At the published interim analysis [25] and subsequently presented update [44], dabrafenib plus trametinib conferred significant benefit over vemurafenib in the primary endpoint of OS and secondary outcomes of median PFS and ORR (Table 3).

In COMBI-v, HRs for OS favored the combination in the prespecified subgroups (which included *BRAF* mutation subtype, baseline LDH levels, number of disease sites, and ECOG PS), except in the ECOG PS 1 subgroup (supplemental online Table 3). HRs for OS were 1.03 for patients with an ECOG PS of 1 and 0.53 for patients with ECOG PS of 0 [25]. With dabrafenib plus trametinib, median OS was not reached in patients with LDH levels at the ULN or lower but was 10.8 months in those with LDH levels higher than the ULN [44]. HRs for PFS all favored the combination in the prespecified subgroups; the HRs were similar to the risk reductions for OS (except, in contrast to the OS results, a 25% reduction in the risk of progression or death was seen in patients with an ECOG PS of 1; supplemental online Table 2) [25].

COMBI-d evaluated dabrafenib plus trametinib in previously untreated stage IIIC/IV melanoma harboring a *BRAF* V600E or V600K mutation, randomizing patients (1:1) to receive the combination or dabrafenib with placebo (Table 1). The two arms were well balanced for ECOG PS of 0, stage M1c disease, elevated LDH levels, and at least three disease sites (Table 2). Dabrafenib plus trametinib conferred significant benefit over dabrafenib alone in the primary endpoint of PFS [45] and secondary outcomes of OS and ORR; 3-year updated PFS and OS rates were published in 2017 (Table 3) [46].

Subgroup findings for COMBI-d shared some similarities with those from COMBI-v; however, in COMBI-d, the benefit of the combination was similar irrespective of baseline ECOG PS (supplemental online Table 2). Whereas HRs for PFS favored the combination in most prespecified subgroups, the HR for dabrafenib plus trametinib versus dabrafenib alone was 1.02 for no more than two disease sites versus 0.60 for at least three disease sites in the initially reported data [26]. However, with longer follow-up, 3-year PFS and OS rates were highest with the combination in patients with both LDH levels ≤ULN or lower and fewer than three disease sites (PFS, 38% with combination vs. 16% with dabrafenib; OS, 62% vs. 45%; supplemental online Tables 2 and 3) [26, 46].

Encorafenib/Binimetinib

COLUMBUS is a 2-part study of encorafenib plus binimetinib in previously treated (with first-line immunotherapy) or untreated

Table 3. Key efficacy findings from phase III trials

Study	Citation	*n*	Treatment	Median follow-up, mo	ORR, %	Time to response, mo	Median duration of response, mo	Median PFS, mo	PFS rate, %			Median OS, mo	OS rate, %		
									12 mo	24 mo	36 mo		12 mo	24 mo	36 mo
MDX010-020	Hodi 2010 [8]	403	Ipilimumab + gp100	21.0	5.7	3.32	11.5	2.76	NR 49.1 (12-wk)	NR	NR	10.0	43.6	21.6	NR
		137	Ipilimumab + placebo	27.8	10.9	3.18	Not reached	2.86	NR 57.7 (12-wk)	NR	NR	10.1	45.6	23.5	NR
		136	gp100 + placebo	17.2	1.5	2.74	Not reached	2.76	NR 48.5 (12-wk)	NR	NR	6.4	25.3	13.7	NR
CA184-169	Ascierto 2017 [9]	365	Ipilimumab 10 mg/kg	14.5	15.3	NR	16.3	2.8	NR	NR	NR	15.7	54.3	38.5	31.2
		362	Ipilimumab 3 mg/kg	11.2	12.2	NR	15.9	2.8	NR	NR	NR	11.5	47.6	31.0	23.2
CheckMate 037	Weber 2015 [11]	272	Nivolumab	8.4	31.7 (per-protocol)	2.1	Not reached	4.7	NR 48 (6-mo)	NR	NR	NR	NR	NR	NR
		133	Dacarbazine or carboplatin + paclitaxel (ICC)		8.3 (per-protocol)	3.5	3.5	4.2	NR 34 (6-mo)	NR	NR	NR	NR	NR	NR
	Weber 2016 [31]	272	Nivolumab	NR (minimum of 2 y)	27	2.2	31.9	3.1	NR	20	NR	15.7	NR	39	NR
		133	Dacarbazine or carboplatin + paclitaxel (ICC)		10	2.1	12.8	3.7	NR	4	NR	14.4	NR	34	NR
CheckMate 066	Robert 2015 [12]	210	Nivolumab + placebo	8.9	40.0	2.1	Not reached	5.1	NR	NR	NR	NR	72.9	NR	NR
		208	Dacarbazine + placebo	6.8	13.9	2.1	6.0	2.2	NR	NR	NR	10.8	42.1	NR	NR
CheckMate 067	Larkin 2015 [14]	314	Nivolumab + ipilimumab	12.2–12.5 across the groups	57.6	2.76	Not reached	11.5	NR	NR	NR	NR	NR	NR	NR
		316	Nivolumab		43.7	2.78	Not reached	6.9	NR	NR	NR	NR	NR	NR	NR
		315	Ipilimumab		19.0	2.79	Not reached	2.9	NR	NR	NR	NR	NR	NR	NR
	Wolchok 2016 [32]	314	Nivolumab + ipilimumab	20.7	57.6	NR	Not reached	11.5	49	46	NR	NR	NR	NR	NR
		316	Nivolumab		43.7	NR	22.3	6.9	42	39	NR	NR	NR	NR	NR
		315	Ipilimumab		19.0	NR	14.4	2.9	18	14	NR	NR	NR	NR	NR
	Larkin 2017 [33]	314	Nivolumab + ipilimumab	≈30	58.9	NR	Not reached	11.7	50	43	NR	Not reached	73	64	NR
		316	Nivolumab		44.6	NR	31.1	6.9	43	37	NR	Not reached	74	59	NR
		315	Ipilimumab	≥28	19.0	NR	18.2	2.9	18	12	NR	20.0	67	45	NR
	Wolchok 2017 [34]	314	Nivolumab + ipilimumab	38.0	58	NR	Not reached	11.5	NR	NR	39	Not reached	NR	64	58
		316	Nivolumab	35.7	44	NR	Not reached	6.9	NR	NR	32	37.6	NR	59	52
		315	Ipilimumab	18.6	19	NR	19.3	2.9	NR	NR	10	19.9	NR	45	34
	Hodi 2018 [35]	314	Nivolumab + ipilimumab	46.9	NR	NR	NR	11.5	NR	NR	37 (4-y)	Not reached	NR	NR	53 (4-y)
		316	Nivolumab	36.0	NR	NR	NR	6.9	NR	NR	31 (4-y)	36.9	NR	NR	46 (4-y)
		315	Ipilimumab	18.6	NR	NR	NR	2.9	NR	NR	9 (4-y)	19.9	NR	NR	30 (4-y)
KEYNOTE-006	Robert 2015 [16]	279	Pembrolizumab q2w	7.9	33.7	86 days	Not reached	5.5	NR 47.3 (6-mo)	NR	NR	Not reached	74.1	NR	NR
		277	Pembrolizumab q3w		32.9	85 days	Not reached	4.1	NR 46.4 (6-mo)	NR	NR	Not reached	68.4	NR	NR
		278	Ipilimumab		11.9	87 days	Not reached	2.8	NR 26.5 (6-mo)	NR	NR	Not reached	58.2	NR	NR
	Schachter 2016 [37]	279	Pembrolizumab q2w	23	36.9	NR	Not reached	5.6	39	31	NR	Not reached	74	55	NR
		277	Pembrolizumab q3w		36.1	NR	Not reached	4.1	38	28	NR	Not reached	68	55	NR
		278	Ipilimumab		13.3	NR	Not reached	2.8	19	14	NR	16.0	59	43	NR
	Long 2018 [38]	556	Pembrolizumab q2w or q3w	45.9	42	NR	Not reached	8.3	NR	33.6	31.1	32.7	NR	55.2	48.1 41.7 (4-y)
		278	Ipilimumab		17	NR	Not reached	3.3	NR	14.8	13.3	15.9	NR	42.4	37.8 34.1 (4-y)
BRIM-3	McArthur 2014 [19]	337	Vemurafenib	12.5	57	NR	NR	6.9	NR 14 (18-mo)	NR	NR	13.6	56	NR 39 (18-mo)	NR
		338	Dacarbazine	9.5	9	NR	NR	1.6	NR 6 (18-mo)	NR	NR	9.7	44	NR 34 (18-mo)	NR
	Chapman 2017 [39]	337	Vemurafenib	13.4	NR	NR	NR	NR	NR	NR	NR	13.6	56	30	21 17 (4-y)
		338	Dacarbazine	9.2	NR	NR	NR	NR	NR	NR	NR	9.7	46	25	19 16 (4-y)
coBRIM	Ascierto 2016 [40]	247	Cobimetinib + vemurafenib	14.2 (PFS); 18.5 (OS)	70	NR (most responses seen by first assessment at 8 wk)	13.0	12.3	NR	NR	NR	22.3	74.5	48.3	NR
		248	Placebo + vemurafenib		50		9.2	7.2	NR	NR	NR	17.4	63.8	38.0	NR
	Dréno 2018 [41]	247	Cobimetinib + vemurafenib	21.2	NR	NR	NR	NR	NR	NR	NR	22.5	74.5	49.0	38.5 34.7 (4-y)
		248	Placebo + vemurafenib	16.8	NR	NR	NR	NR	NR	NR	NR	17.4	63.8	39.0	31.1 29.2 (4-y)

(continued)

Table 3. (continued)

Study	Citation	*n*	Treatment	Median follow-up, mo	ORR, %	Time to response, mo	Median duration of response, mo	Median PFS, mo	PFS rate, %			Median OS, mo	OS rate, %		
									12 mo	24 mo	36 mo		12 mo	24 mo	36 mo
BREAK-3	Hauschild 2012 [21]	187	Dabrafenib	4.9	50	6.3 wk	5.5	5.1	NR	NR	NR	NR	NR	NR	NR
		63	Dacarbazine		6	NR	Not reached	2.7	NR	NR	NR	NR	NR	NR	NR
	Chapman 2017 [42]	187	Dabrafenib	17.0	NR	NR	NR	NR	NR	NR	16 13 (4-y) 12 (5-y)	NR	NR	NR	31 27 (4-y) 24 (5-y)
		63	Dacarbazine	11.8	NR	NR	NR	NR	NR	NR	3 0 (4-y) 0 (5-y)	NR	NR	NR	28 22 (4-y) 22 (5-y)
METRIC	Flaherty 2012 [23]	214	Trametinib	NR	22	NR	5.5	4.8	NR	NR	NR	Not reached	NR 81 (6-mo)	NR	NR
		108	Dacarbazine or paclitaxel (ICC)	NR	8	NR	Not reached	1.5	NR	NR	NR	NR	NR 67 (6-mo)	NR	NR
	Schadendorf 2013 [80]	214	Trametinib	14.7	NR	NR	NR	NR	NR	NR	NR	15.6	NR	NR	NR
		108	Dacarbazine or paclitaxel (ICC)	8.7	NR	NR	NR	NR	NR	NR	NR	11.3	NR	NR	NR
	Robert2019 [43]	214	Trametinib	14.7	29	NR	5.3	4.9	NR	NR	NR	15.6	61	32	21 13 (5-y)
		108	Dacarbazine or paclitaxel (ICC)	8.7	9	NR	8.1	1.5	NR	NR	NR	11.3	50	29	23 17 (5-y)
COMBI-v	Robert 2015 [25]	352	Dabrafenib + trametinib	11	64	NR	13.8	11.4	NR	NR	NR	Not reached	72	NR	NR
		352	Vemurafenib	10	51	NR	7.5	7.3	NR	NR	NR	17.2	65	NR	NR
	Robert 2016 [44]	352	Dabrafenib + trametinib	23	67	NR	13.8	12.1	NR	30	24	26.1	NR	53	45
		352	Vemurafenib		53	NR	7.9	7.3	NR	16	10	17.8	NR	39	31
COMBI-d	Long 2015 [45]	211	Dabrafenib + trametinib	20	69	NR	12.9	11.0	NR	NR	NR	25.1	74	51	NR
		212	Dabrafenib + placebo	16	53	NR	10.6	8.8	NR	NR	NR	18.7	68	42	NR
	Long 2017 [46]	211	Dabrafenib + trametinib	NR	68	NR	12.0	NR	NR	30	22	NR	NR	52	44
		212	Dabrafenib + placebo	NR	55	NR	10.6	NR	NR	16	12	NR	NR	43	32
COLUMBUS Part 1 (per central review)	Dummer 2016 [48]	192	Encorafenib 450 mg + binimetinib 45 mg	NR	63	NR	16.6	14.9	NR	NR	NR	NR	NR	NR	NR
		194	Encorafenib 300 mg	NR	51	NR	14.9	9.6	NR	NR	NR	NR	NR	NR	NR
		191	Vemurafenib	NR	40	NR	12.5	7.3	NR	NR	NR	NR	NR	NR	NR
	Dummer 2018 [4, 81]	192	Encorafenib 450 mg + binimetinib 45 mg	32.1 (PFS) 36.8 (OS)	64	NR	18.6	14.9	56	37	28	33.6	76	58	47
		194	Encorafenib 300 mg		52	NR	15.2	9.6	NR	NR	NR	23.5	75	49	NR
		191	Vemurafenib		41	NR	12.3	7.3	33	20	13	16.9	63	43	32
COLUMBUS Part 2 (per central review)	Dummer 2017 [5]	258	Encorafenib 300 mg+ binimetinib 45 mg	NR	66	NR	12.7	12.9	NR	NR	NR	NR	NR	NR	NR
		280	Encorafenib 300 mg (Parts 1 and 2)	NR	50	NR	12.9	9.2	NR	NR	NR	NR	NR	NR	NR
		86	Encorafenib 300 mg (Part 2)	NR	50	NR	7.5	7.4	NR	NR	NR	NR	NR	NR	NR

Abbreviations: ICC, investigator choice chemotherapy; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks.

stage III/IV melanoma harboring a *BRAF* V600 mutation. In part 1, patients were randomized to receive binimetinib with encorafenib 450 mg/day (COMBO450), encorafenib 300 mg/day, or vemurafenib; in part 2, patients were randomized to receive binimetinib with encorafenib 300 mg/day (COMBO300) or encorafenib 300 mg/day (Table 1). In both parts, the arms were well balanced (Table 2). In part 1, COMBO450 significantly improved PFS and OS over vemurafenib (but not encorafenib monotherapy) [4]; in part 2, COMBO300 demonstrated significantly improved PFS and ORR versus encorafenib monotherapy (therefore showing that binimetinib directly contributes to the efficacy of the combination; Table 3) [4, 5, 47].

Subgroup data are available from part 1 of COLUMBUS, showing reductions in the risk of progression or death for encorafenib plus binimetinib versus vemurafenib of 53% and 27% for those with LDH levels lower than the ULN and at the ULN or higher, respectively (supplemental online Table 2) [48]. Updated subgroup data showed reductions in the risk of death for COMBO450 versus vemurafenib of 49% and 5% for those with LDH levels at the ULN or lower and higher than the ULN, respectively (supplemental online Table 3) [4, 47].

Summary of Key Findings: Targeted Therapy

- Single-agent vemurafenib, dabrafenib, and trametinib are significantly more effective than single-agent dacarbazine in *BRAF* V600-mutant advanced melanoma.
- The combination of BRAF and MEK inhibitors has been shown to improve ORR, PFS, and OS versus targeted monotherapy in patients with *BRAF* V600-mutant advanced melanoma. Benefit is consistent across all subgroups.

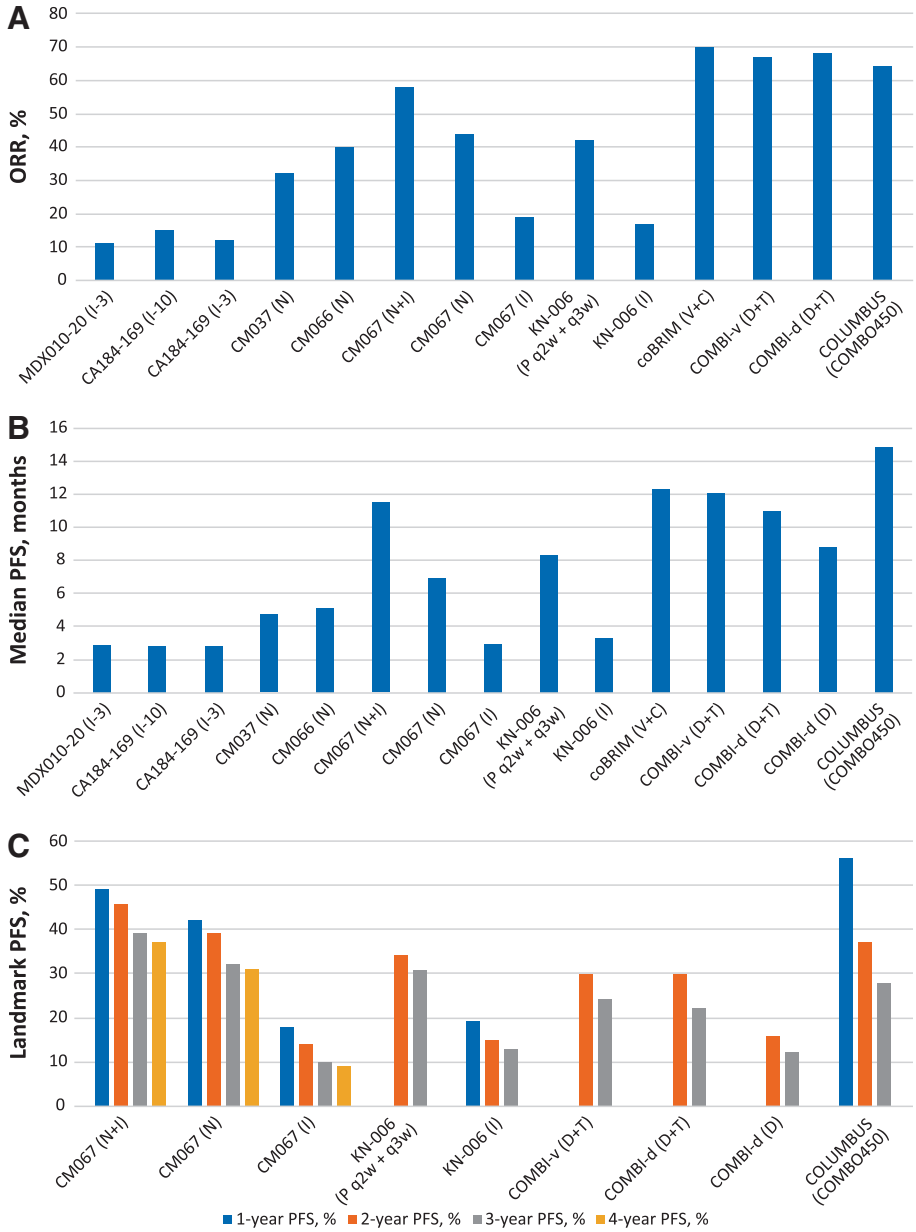

Figure 1. Key efficacy data for BRAF-MEK combination therapy and checkpoint immunotherapy in metastatic melanoma.
Abbreviations: C, cobimetinib; COMBO450, encorafenib 450 mg daily plus binimetinib 45 mg twice daily; D, dabrafenib; I, ipilimumab; I-3, ipilimumab 3 mg/kg; I-10, ipilimumab 10 mg/kg; N, nivolumab; ORR, overall response rate; OS, overall survival; P, pembrolizumab; PFS, progression-free survival; Pt, part; q2w, every 2 weeks; q3w, every 3 weeks; T, trametinib; V, vemurafenib.

- Benefit for combination targeted therapy appears greatest among patients with favorable prognostic factors, such as normal LDH levels, ECOG status, and fewer than three sites of metastasis.

Discussion and Future Directions

The field of systemic therapeutics has advanced rapidly over the past 7 years, from a time when chemotherapy and interleukin-2 were the only treatment options to the current status, with several BRAF-directed and checkpoint immunotherapies available. The impact of these treatments is clear, with increasing ORR, PFS, and OS over time, with key results specific to BRAF-MEK combination therapy and checkpoint immunotherapy in Figure 1. Despite the growing list of effective therapies, data from their trials do not address a number of important questions about the clinical management of patients with advanced melanoma, including but not limited to how best to (1) choose first-line therapy, (2) rechallenge with the same drug in later lines of therapy, and (3) manage populations with rare types of melanoma. Beyond these caveats, the field is developing rapidly with further combinations of these agents and the integration of novel therapeutics.

Multiple regimens are now approved as first-line therapy for melanoma; however, there is a paucity of randomized data to guide treatment selection between immunotherapy and BRAF-targeted therapy. The only data surrounding frontline therapy suggest that BRAF/MEK combination therapy is superior to and

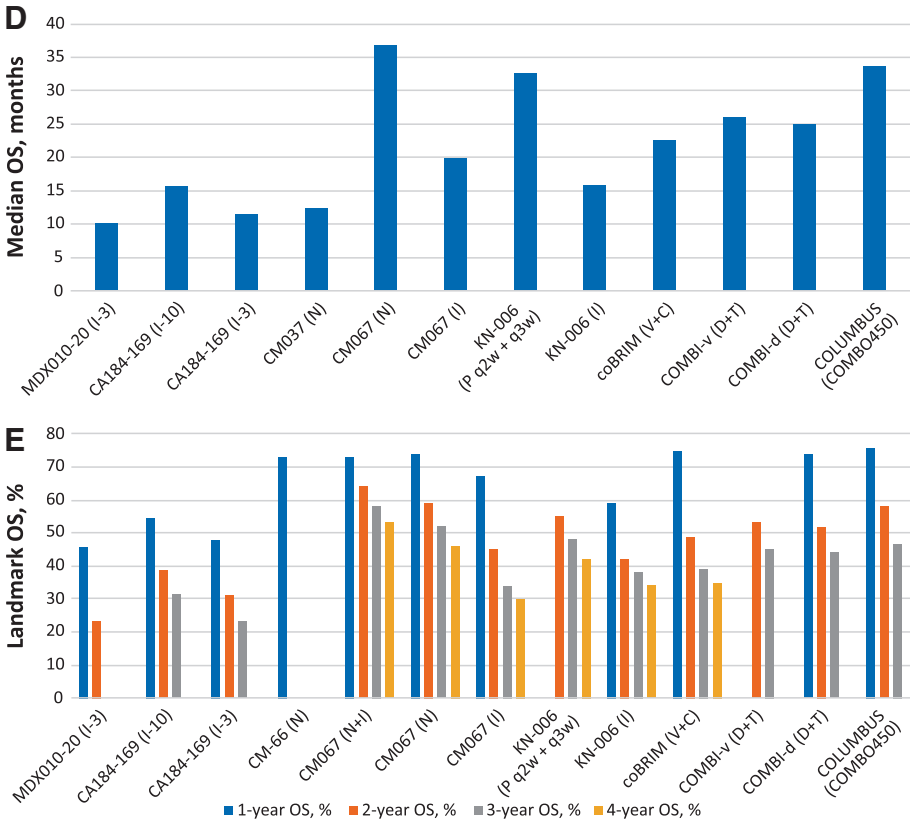

Figure 1. (Continued).

less toxic than BRAF inhibitor monotherapy [5] and, somewhat similarly, that anti-PD-1 monotherapy has higher efficacy and less toxicity than anti-CTLA-4 monotherapy [16, 37], whereas a combination of an anti-PD-1 and an anti-CTLA-4 is more efficacious than either checkpoint inhibitor alone but has greater toxicity [14, 32–34]. No prospective clinical trial data have addressed the question of BRAF-directed therapy versus immunotherapy in the frontline setting, although an ongoing randomized trial is attempting to address it (NCT02224781), and there are several relevant retrospective analyses. Using regression tree analyses to assess hierarchical effect on treatment outcomes with dabrafenib and trametinib, Long et al. [46, 49] demonstrated that the clinical factors most highly associated with long-term benefit with BRAF-MEK inhibition included normal LDH levels (consistent with the 3-year OS results from COMBI-d [Fig. 2]), fewer than three sites of metastatic melanoma, and ECOG PS of 0. This is potentially in contrast to the most common clinical use of BRAF-MEK inhibition: targeted therapy for large disease volume or rapidly progressive disease. At the same time, however, OS data from CheckMate 067 (Fig. 2 and supplemental online Table 3) [34, 35] and the findings of other studies of immunotherapies have also suggested that greater benefit is associated with lower disease burden, making this a less useful clinical discriminator [50, 51]. Instead, treatment choice should likely be dictated by other factors, such as route of administration (intravenous vs. oral), schedule of treatments and assessments, and toxicity profile (and health care provider comfort level in managing adverse events).

The only data surrounding frontline therapy suggest that BRAF/MEK combination therapy is superior to and less toxic than BRAF inhibitor monotherapy and, somewhat similarly, that anti-PD-1 monotherapy has higher efficacy and less toxicity than anti-CTLA-4 monotherapy, whereas a combination of an anti-PD-1 and an anti-CTLA-4 is more efficacious than either checkpoint inhibitor alone but has greater toxicity.

To assess the efficacy of sequencing BRAF inhibitors before or after immunotherapy treatments, only retrospective data are available. Such observations have predominately suggested that there may be a detriment to the ORR with immunotherapy (specifically ipilimumab) if it is administered after BRAF inhibition, but the reverse sequence does not influence the ORR with BRAF inhibition [52, 53]. Recently, however, a retrospective series of 78 patients with *BRAF* V600-mutant melanoma receiving a BRAF-MEK combination after PD-1-based therapy showed an 83% rate of BRAF-MEK dose modification, 31% rate of adverse event-related hospitalization, and median BRAF-MEK therapy and OS durations of 5.8 and 15.6 months, respectively [54]. Overall, the available retrospective data sets are small, and their findings should be considered on a less urgent level relative to patient-specific factors and preferences. In addition,

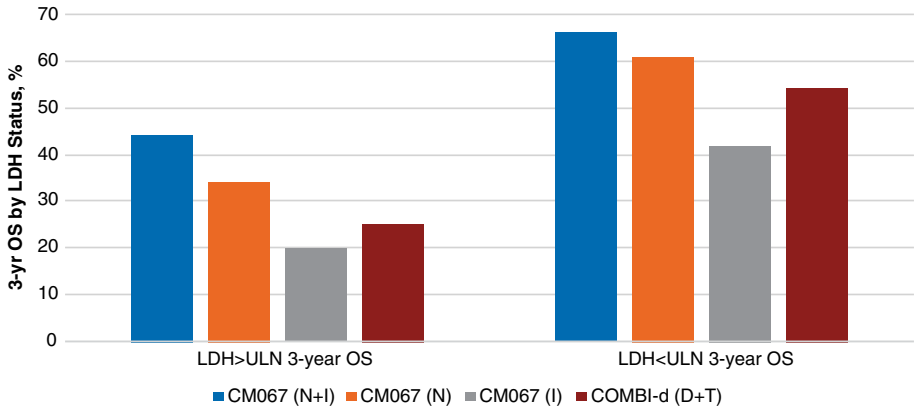

Figure 2. Three-year overall survival by LDH status with BRAF-MEK combination therapy and checkpoint immunotherapy in metastatic melanoma.
Abbreviations: D, dabrafenib; I, ipilimumab; LDH, lactate dehydrogenase; N, nivolumab; OS, overall survival; P, pembrolizumab; T, trametinib; ULN, upper limit of normal.

translational investigations have suggested potential overlap in resistance mechanisms between BRAF-targeted agents and immunotherapies [55–58]. Some have suggested this as a rationale for sequencing immunotherapy before BRAF-directed treatment or, alternatively, for the use of triplet BRAF-MEK-PD-1 combinations. Specific to immunotherapy, prospective phase II [59] and phase III data [14, 32–34] strongly suggest that treatment with an anti-PD-1 antibody should be universally prioritized over an anti-CTLA-4 antibody.

An intriguing consideration related to treatment sequencing is the possibility of rechallenge with previously used systemic therapies. The mechanisms of resistance to BRAF inhibitors, as understood from accumulating basic and preclinical research, suggest that resistance to BRAF inhibitors indicates a reactivation of the mitogen-activated protein kinase pathway (independent of BRAF) or activation of alternative pathways and may be reversible after withholding and then reinitiating therapy [28]. In a phase II study by Schreuer et al. [28], 32% of patients (8/25) with BRAF inhibitor-resistant stage IIIC/IV melanoma achieved a partial response when treated with dabrafenib plus trametinib. An analysis of the MDX010-20 trial also supports the potential benefit of retreatment with ipilimumab, with the investigators reporting post-retreatment ORRs of 13% with ipilimumab plus gp100 and 38% with ipilimumab plus placebo [60].

Although patients with brain metastases or uncontrolled brain metastases were typically excluded from the included studies, recent phase II data showing the intracranial activity of BRAF-MEK and combination checkpoint inhibition in such patients are noteworthy and are changing the approach to managing brain metastases in clinical practice (supplemental online Table 1) [61–64]. For example, in the COMBI-MB trial of dabrafenib plus trametinib in *BRAF*-mutant melanoma brain metastases, investigator-determined intracranial response rates were 44% to 59% across the four patient cohorts (which differed in mutation type, prior local brain therapy, and symptoms), with median durations of 4.5 to 8.3 months [61]. In the context of increasing numbers of reports of long-term adverse events following radiation, such as radionecrosis [65], these data raise the possibility that some patients may be better served by proceeding with systemic therapy (either targeted or immunotherapy) before considering radiation [66].

The complex mechanisms involved in primary and acquired resistance to molecularly and immune-targeted therapies for metastatic melanoma are only beginning to be understood [56, 67–70]. Recent findings with anti-PD-1 checkpoint inhibitors implicate the involvement of pathways associated with interferon receptor signaling (as evidenced by identification of loss-of-function mutations in Janus kinase 1 and 2), as well as antigen presentation [68]. Emerging data also suggest that immune evasion may play a role in acquired resistance to BRAF/MEK inhibitors, given observations of CD8+ T-cell depletion and exhaustion that may suggest cross-resistance to subsequent anti-PD-1/PD-L1 therapy [69].

As follow-up continues in most of the studies discussed, new investigations are underway to determine the potential of several combinations for treating metastatic melanoma. These include combinations in which pembrolizumab is combined with T-VEC (NCT02965716) and PD-1 or PD-L1 inhibitors are combined or sequenced with BRAF-MEK inhibitors (NCT02967692, NCT02902029). At the same time, the benefits of BRAF-MEK and immune checkpoint inhibitors are being translated into earlier use in the adjuvant setting [71, 72], where they are improving recurrence-free survival. Finally, biomarkers for treatment selection and monitoring are rapidly progressing, which may help guide treatment selection in each patient. The totality of this research suggests that just beyond the near-term horizon, a much more nuanced and individual patient-level treatment decision-making process will be necessary to choose between the therapies already available and those yet to come.

Conclusion

Major advances in metastatic melanoma have been accomplished via dual BRAF and MEK inhibition as well as immune checkpoint blockade targeting programmed death receptor 1 alone and in combination cytotoxic T-lymphocyte–associated antigen 4. The optimal therapy for an individual patient remains unclear, however, as the therapies have not been

compared head to head. Here, a comprehensive clinical trial data summation is presented for the therapeutic utility for each approach and context is provided for the general practitioner to consider when choosing therapy for previously untreated metastatic melanoma.

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