Supplementary Materials: Efficacy, Safety, and Tolerability of Approved Combination BRAF and MEK Inhibitor Regimens for *BRAF*-Mutant Melanoma

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Table S1. Anticancer Treatment by Regimen Following Study Drug Discontinuation.

	Dabrafenib + Trametinib [1,2]		**Vemurafenib + Cobimetinib** [3]	**Encorafenib + Binimetinib** [4]
	COMBI-v † ***n* = 352**	**COMBI-d** ***n* = 209**	**coBRIM** ***n* = 183**	**COLUMBUS** ***n* = 192**
Any treatment	72 (20%)	101 (48%)	105 (57%)	80 (42%)
Immunotherapy	NR	117 (56%)	67 (37%)	NR
Any anti–PD-1/anti–PD-L1	NR	NR	28 (15%)	39 (20%)
Ipilimumab (anti-CTLA-4)	41 (12%)	86 (41%)	53 (29%)	33 (17%)
Nivolumab (anti-PD-1)	NR	15 (7%)	NR	NR
Pembrolizumab (anti–PD-L1)	4 (1%)	27 (13%)	NR	NR
anti-CTLA-4 + anti–PD-1/anti–PD-L1 ‡	NR	NR	4 (2%)	6 (3%)
Targeted therapies	NR	21 (10%) §	32 (18%)	NR
BRAFi + MEKi	NR	NR	15 (8%)	10 (5%) ¶
BRAFi	NR	NR	19 (10%)	11 (6%) #
MEKi	NR	NR	2 (1%)	NR
Chemotherapy	NR	37 (18%)	30 (16%)	14 (7%) **
Other	NR	NR	2 (1%) ††	5 (3%) ‡‡

NR = not reported. Data are *n* (%). PD-1 = programmed death cell receptor 1. PD-L1 = programmed death cell ligand 1. † Multiple uses of a type of therapy for an individual patient were only counted once in the frequency for that treatment category; patients mght have received multiple lines of treatment. Received by ≥2% of patients. ‡ Ipilimumab + nivolumab or ipilimumab + pembrolizumab. § Small-molecule targeted therapy. ¶ Dabrafenib + trametinib; dabrafenib + cobimetinib + trametinib; encorafenib + binimetinib; vemurafenib + cobimetinib; vemurafenib + protein kinase inhibitors. # Dabrafenib or vemurafenib. ** Abemaciclib; bleomycin; bleomycin + dacarbazine + lomustine + vincristine sulfate; carboplatin + dacarbazine + vinblastine sulfate; carboplatin + paclitaxel; carmustine + cisplatin + dacarbazine; carmustine + dacarbazine + hydroxycarbamide; cisplatin + dacarbazine; cisplatin + dacarbazine + vinblastine/vinblastine sulfate; cisplatin + temozolomide; cisplatin + vinblastine sulfate; dacarbazine; fotemustine; gemcitabine + treosulfan + trofosfamide; melphalan + norflox-tz; temozolomide; vinblastine sulfate. †† Other immunotherapy agents included granulocyte colony-stimulating factor and adoptive immunotherapy. ‡‡ Antineoplastic and immunomodulating agents; antineoplastic and immunomodulating agents + monoclonal antibodies; bevacizumab; bevacizumab + ipilimumab + nivolumab; binimetinib + buparlisib + encorafenib; binimetinib + capmatinib + encorafenib; binimetinib + encorafenib + ribociclib; dabrafenib + pembrolizumab; dabrafenib + pembrolizumab + trametinib; interferon; investigational drug; investigational drug + pembrolizumab; ipilimumab + vemurafenib; monoclonal antibodies; paclitaxel; radiotherapy; talimogene laherparepvec.

Table S2. Adverse Events in ≥20% of Patients in Any Combination Treatment Arm [5–7].

Adverse Event, *n*, (%) *	COMBI-v		coBRIM		COLUMBUS	
	D/T	V	V/C	V	E/B	V
	n = 350	*n* = 349	*n* = 247	*n* = 246	*n* = 192	*n* = 186
Diarrhea	112 (32)	131 (38)	148 (60)	76 (31)	70 (36)	63 (34)
Arthralgia	84 (24)	178 (51)	89 (36)	99 (40)	49 (26)	83 (45)
Nausea	121 (35)	125 (36)	102 (41)	62 (25)	79 (41)	63 (34)
Fatigue	101 (29)	115 (33)	85 (34)	80 (33)	55 (29)	57 (31)
Rash	76 (22)	149 (43)	98 (40)	94 (38)	27 (14)	54 (29)
Pyrexia	184 (53)	73 (21)	69 (28)	56 (23)	35 (18)	52 (28)
Vomiting	101 (29)	53 (15)	60 (24)	31 (13)	57 (30)	28 (15)
Headache	101 (29)	77 (22)	41 (17)	39 (16)	42 (22)	35 (19)
Photosensitivity reaction	13 (4)	78 (22)	82 (33)	45 (18)	8 (4)	45 (24)
Hypertension	92 (26)	84 (24)	37 (15)	19 (8)	21 (11)	21 (11)
Increased ALT	48 (14)	61 (17)	61 (25)	44 (18)	21 (11)	14 (8)
Constipation	48 (14)	61 (17)	24 (10)	26 (11)	42 (22)	12 (6)
Increased AST	40 (11)	45 (13)	58 (23)	31 (13)	16 (8)	4 (2)
Cough	69 (20)	34 (10)	19 (8)	30 (12)	16 (8)	13 (7)
Increased blood CK	7 (2)	1 (<1)	80 (32)	7 (3)	44 (23)	4 (2)
Chills	110 (31)	27 (8)	NR	NR	9 (5)	10 (5)

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CK = creatinine phosphokinase; D/T = dabrafenib plus trametinib; E/B = encorafenib plus binimetinib; NR = not reported; V = vemurafenib, V/C = vemurafenib plus cobimetinib. * Events are presented in descending order of overall incidence in the combination arms.

Table S3. Grade 3/4 Adverse Events Reported in ≥5% of Patients in Any Combination Treatment Arm [5–7].

Adverse event, % *	COMBI-v		coBRIM ǂ		COLUMBUS	
	D/T	V	V/C	V	E/B	V
	n = 350	*n* = 349	*n* = 247	*n* = 246	*n* = 192	*n* = 186
Increased GGT	4	5	13	10	9	3
Hypertension	14	9	5	2	6	3
Increased ALT	3	4	11	6	5	2
Rash	1	9	5	6	1	3
Rash maculopapular	<1	4	7	5	0	4
Increased blood CK	1	<1	11	0	7	0
Increased AST	1	3	9	2	2	2
Diarrhea	1	<1	7	<1	3	2
Neutropenia	5	1	–	–	1	1
Nausea	<1	<1	–	–	2	2
Vomiting	1	<1	–	–	2	1

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CK = creatinine phosphokinase; D/T = dabrafenib plus trametinib; E/B = encorafenib plus binimetinib; GGT = gamma-glutamyl transferase; V = vemurafenib; V/C = vemurafenib plus cobimetinib.* Events are presented in descending order of overall incidence in the combination arms.ǂ Data for neutropenia, nausea, vomiting were not available.

Table S4. Scientific Literature Search Criteria.

- Literature Databases
  - National Library of Medicine
  - EMBase
  - OVID
  - BIOSIS
- Search Terms
  - Clinical Trial
    - Clinical Trial; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study; Controlled Clinical Trial; Multicenter Study; Observational Study; Randomized Controlled Trial
- MeSH Headings
  - Melanomas
  - Malignant Melanoma
  - Malignant Melanomas
  - Melanoma, Malignant
  - Melanomas, Malignant
- Boolean Terms
  - BRAF-mutant Malignant Melanoma
  - BRAF-mutant
  - Combination Treatment
  - BRAF Inhibitor
  - MEK Inhibitor
  - BRAF / MEK Inhibitor
  - BRAF and MEK Inhibitor
- Search Type
  - Boolean-based AND / OR analysis
- Study Population(s)
  - All
- Age
  - All
- Study Ethnicity
  - All
- Species
  - Human
- Language(s)
  - English
- Publication Types
  - All
- Journal Categories
  - All
- Timeframe
  - January 1, 2000 to December 1, 2018
- Exclusions
  - Clinical Trial
    - Clinical Trial, Phase I; Pre-clinical
  - Publication Types
    - Literature Review; Case Studies; Secondary Analysis;
  - Search terms
    - None
  - Population
    - None

Table S5. Data Sources and Cutoff Dates for COMBI-v, coBRIM and COLUMBUS Trials.

	COMBI-v		coBRIM		COLUMBUS	
	Source	**Data Cutoff**	**Source**	**Data Cutoff**	**Source**	**Data Cutoff**
Baseline characteristics	Robert et al. primary publication [2]	17 Apr 2014	Larkin et al. primary publication [8]	9 May 2014	Dummer et al. primary publication [5]	19 May 2016
PFS, OS, ORR, DOR,	Efficacy U.S. dabrafenib label (6/2017) [9] Robert et al. primary publication [2]	17 Apr 2014	Efficacy U.S. cobimetinib label (5/2016) [10] EPAR [7]	16 Jan 2015 [7]	Dummer et al. primary publication [5]	19 May 2016
	Robert et al. 2015 [11] EPAR [6]	13 Mar 2015	Ascierto et al. 2016 [3]	28 Aug 2015	Dummer OS [4]	07 Nov 2017
Safety summary, most common AEs, Grade 3/4 AEs Most common AEs, Grade 3/4 AEs	Safety Robert et al. primary publication [2]	17 Apr 2014	Safety Larkin et al. primary publication [8]	19 Sept 2014 (update)	Safety Dummer et al. primary publication [5]	19 May 2016
	dabrafenib/trametinib		vemurafenib/cobimetinib		encorafenib/binimetinib	
ADRs *	U.S. trametinib label (6/2017) [12]	12 Jan 2015	U.S. cobimetinib label (5/2016) [10]	19 Sep 2014 (update)	U.S. encorafenib label (6/2018) [13,14]	19 May 2016

ADR = adverse drug reaction; AE = adverse events; DOR = duration of response; EPAR = European public assessment report; NA = not applicable; ORR = objective response rate; OS = overall survival; LDH = lactate dehydrogenase; PFS = progression-free survival. * Main sources of data; other sources noted in Table 8.

Reference

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14. Array BioPharma Inc. *Mektovi [package insert]*; Array BioPharma Inc.: Boulder, CO, USA, 2018.

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