Supplementary Table 1. Individualized data for the cohort of patients with germline *CDKN2A* pathogenic variants and *BRAF* V600 mutated metastatic melanoma treated with BRAF and MEK inhibitors included in our study.

ID	Region	Sex	Germline *CDKN2A* variant	Age at Tx start	AJCC 8th ed.	Baseline LDH	Treatment	Response	PFS *	OS*	Censor Date	Alive at censor Date	G3-4 AEs
ST2	Sweden	F	p.Pro81Ser	62	M1c	Normal	Dabra+Tram	PR	23	27+	Feb 2018	YES	NO
GO2	Sweden	M	p.Arg112dup	34	M1c	NA	Encor+Bini	PR	9	10	Mar 2016	NO	NO
BCN1	Barcelona	M	p.Gly101Trp	67	M1d	NA	Dabrafenib	PR	30	30	29/10/2013	NO	NO
BCN2	Barcelona	F	c.106delG	68	M1c	NA	Dabra+Tram	PR	11+	11+	06/01/2018	YES	NO
BCN3	Barcelona	F	c.-34G>T (homozygous)	43	M1d	NA	Dabra+Tram	PR	3	5	04/01/2018	NO	NO
BCN4	Barcelona	F	p.Arg124Cys	64	M1c	NA	Dabra+Tram+PDR001 (double blind clinical assay: CPDR001F2301)	PR	4	4+	15/01/2018	YES	NO
LE1	Leiden	M	19bp del	46	M1a	NA	Dabra+Tram	PR	3	4+	Jul 2017	YES	NO
LE2	Leiden	M	19bp del	62	M1c	NA	Vemurafenib	PR	3	4	Apr 2012	NO	NO
LE3	Leiden	M	19bp del	29	M1d	NA	Dabrafenib	PR	2	25+	Jul 2017	YES	YES
GE2	Genoa	F	G101W	57	M1c	Elevated	Dabra+Tram	PR	12	16	Oct 2016	NO	NO
GE3	Genoa	M	S56I	54	M1c	Elevated	Vemurafenib	PD	2	5	Sep 2015	NO	NO
GE6	Genoa	M	M1R	49	M1a	Normal	Dabra+Tram	PR	30+	30+	Aug 2019	YES	NO
GE8	Genoa	F	G101W	54	M1c	Elevated	Vemurafenib	PD	2	17	Apr 2016	NO	NO

GE9	Genoa	F	G101W	69	M1c	NA	Vemurafenib	SD	6	13	Jun 2015	NO	NO
GE10	Genoa	F	A68L	59	M1c	Elevated	Encor+Bini	PR	10	16	Mar 2017	NO	NO
GE11	Genoa	M	F90S	49	M1b	NA	Vemurafenib	PR	5	19	Mar 2015	NO	NO
GE12	Genoa	M	F90S	52	M1c	Elevated	Dabra+Tram	PR	5	9	Mar 2019	NO	NO
GE13	Genoa	M	E27X	69	M1d	Normal	Dabra+Tram	PR	9	19	May 2019	NO	NO
GE14	Genoa	F	G101W	60	M1d	Elevated	Dabra+Tram	PR	12+	12+	Sep 2019	YES	NO

Abbreviations: Bini= binimetinib; Dabra= dabrafenib; Encor= encorafenib; NA= not available; Tram= trametinib. *Survival rates with + prefix indicates that patient still has an ongoing PFS or OS

Supplementary Table 2. Summary of data from phase 3 clinical trials on patients with metastatic melanoma treated with BRAF and MEK inhibitors.

Study	**BRIM-3**[1, 2] **N= 337**	**BREAK-3**[3] **N=187**	**COBRIM**[4] **N=247**	**COMBI-d/COMBI-v**[5] **N= 563**	**COLUMBUS**[6] **N=192**
Treatment	Vemurafenib	Dabrafenib	Vemurafenib+cobimetinib	Dabrafenib+trametinib	Encorafenib+binimetinib
Previous treatments	Untreated	Untreated	Untreated	Untreated	Untreated and previously treated
Age, years					
Median (range) [IQR]	56[47–65]	53 (22–93)	56 (23–88)	55 (22–89)/ 55 (18–91)	57 [20–89]
AJCC 7th edition stage, N (%)					
M0	20 (6%)	6 (3%)	21 (9%)	19 (3%)	9 (5%)
M1a	34 (10%)	23 (12%)	40 (16%)	75 (13%)	26 (14%)
M1b	62 (18%)	34 (18%)	40 (16%)	105 (19%)	34 (18%)
M1c	221 (66%)	124 (66%)	146 (59%)	363 (64%)	123 (64%)
Baseline LDH, N (%)					
Normal	142 (42%)	119 (64%)	Not reported	365 (65%)	137 (71%)
Elevated	195 (58%)	67 (36%)	112 (46%)	194 (34%)	55 (29%)
Unknown	0 (0%)	1 (<1%)	Not reported	4 (1%)	0 (0%)
Overall Response, N (%)					
CR	19 (6%)	6 (3%)	39 (16%)	109 (19%)	37 (19%)
PR	173 (51%)	87 (47%)	133 (54%)	274 (49%)	108 (56%)
SD	Not reported	78 (42%)	44 (18%)	130 (23%)	33 (17%)
PD	Not reported	10 (5%)	19 (8%)	31 (6%)	14 (7%)

Not evaluable	Not reported	6 (3%)	12 (5%)	17 (3%)	0 (0%)
Median progression-free survival	6.9 months	5.1 months	12.3 months	11.1 months	14.9 months

Abbreviations: IQR= interquartile range

Supplementary Table 3. Summary of data from "real world" studies of patients with metastatic melanoma treated with BRAF and MEK inhibitors.

Study	**Vemurafenib safety study**[7, 8]	**Vemurafenib safety study (subanalysis of Italian population)**[9]	**Describe I**[10]	**Compassionate use of dabrafenib (retrospective analysis of Spanish population)**[11]	**Describe II**[12]	**Compassionate use of dabrafenib+trametinib (retrospective analysis of Spanish population)**[11]
Number of patients	3219	385	331	49	162*	87
Treatment	Vemurafenib	Vemurafenib	Dabrafenib	Dabrafenib	Dabrafenib+trametinib	Dabrafenib+trametinib
Previous treatments	Untreated and previously treated	Untreated and previously treated	Untreated and previously treated	Untreated and previously treated	Untreated	Untreated and previously treated
Age, years						
Median (range) [IQR]	55 (13-95)	NA	58 (18–86)	56.8 [26.2–84.3]	55.5 (22–87)	53.2 (24.8–81.3)
AJCC 7th edition stage						
M0	49 (2%)	4 (1%)	14 (4%)	6 (12%)	14 (9%)	0 (0%)
M1a	270 (8%)	48 (12%)	Not reported	7 (14%)	Not reported	12 (14%)
M1b	336 (10%)	53 (14%)	Not reported	8 (16%)	Not reported	19 (22%)
M1c	2562 (80%)	280 (73%)	Not reported	28 (57%)	Not reported	56 (64%)
Brain metastases, n (%)	753 (23%)	83 (22%)	132 (40%)	Not reported	62 (38%)	Not reported
Baseline LDH, n (%)		Not reported	Not reported	Not reported	Not reported	Not reported

Normal	1508 (47%)					
Elevated	1625 (50%)					
Unknown	86 (3%)					
Overall Response, n (%)						
CR	125 (5%)	14 (4%)	23 (7%)	7 (15%)	21 (13%)	18 (21%)
PR	865 (32%)	87 (26%)	129 (39%)	21 (45%)	88 (54%)	43 (51%)
SD	1399 (51%)	181 (54%)	67 (20%)	14 (29%)	20 (12%)	14 (17%)
PD	339 (12%)	43 (13%)	98 (30%)	5 (11%)	27 (17%)	9 (11%)
Not evaluable	9 (<1%)	7 (2%)	14 (4%)	Not reported	6 (4%)	Not reported
Median progression-free survival	5.6 months	5.9 months	5.2 months	8.1 months	7.5 months	10.2 months

*BRAF-inhibitor naive population only

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