

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Online Supplement

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Supplementary Table A. **Adverse Events of Any Grade Reported in At Least 5% of Patients in Either Treatment Arm.***

Event, number of patients (percent)	Vemurafenib (N=336[†])	Dacarbazine (N=282)
Arthralgia	165 (49)	9 (3)
Rash	121 (36)	3 (1)
Alopecia	117 (35)	6 (2)
Fatigue	112 (33)	87 (31)
Nausea	101 (30)	115 (41)
Photosensitivity reaction	101 (30)	10 (4)
Diarrhea	84 (25)	34 (12)
Pruritis	74 (22)	4 (1)
Headache	72 (21)	26 (9)
Hyperkeratosis	67 (20)	0
Skin papilloma	62 (18)	0
Pyrexia	59 (18)	25 (9)
Dry skin	54 (16)	3 (1)
Decreased appetite	53 (16)	20 (7)
Vomiting	50 (15)	67 (24)

Edema peripheral	50 (15)	13 (5)
Pain in extremity	45 (13)	17 (6)
Dysgeusia	44 (13)	9 (3)
Squamous cell carcinoma of the skin	40 (12)	1 (<1)
Myalgia	39 (12)	4 (1)
Erythema	38 (11)	4 (1)
Constipation	32 (10)	65 (23)
Sunburn	31 (9)	0
Rash maculo-papular	29 (9)	1 (<1)
Asthenia	28 (8)	22 (8)
Keratoacanthoma	27 (8)	0
Blood alkaline phosphatase increased	25 (7)	0
Seborrhoeic keratosis	24 (7)	3 (1)
Cough	23 (7)	16 (6)
Abdominal pain upper	23 (7)	5 (2)
Pain	22 (7)	14 (5)
Palmar-plantar erythrodysesthesia syndrome	22 (7)	1 (<1)
Actinic keratosis	21 (6)	9 (3)
Musculoskeletal pain	21 (6)	9 (3)
Skin lesion	21 (6)	1 (<1)

Back pain	20 (6)	13 (5)
Dizziness	20 (6)	10 (4)
Weight decreased	20 (6)	6 (2)
Dyspnea	19 (6)	20 (7)
Insomnia	19 (6)	12 (4)
Abdominal pain	19 (6)	12 (4)
Neutropenia	2 (<1)	32 (11)

*Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0.

¶One patient randomized to dacarbazine was treated in error with vemurafenib and is included in the vemurafenib cohort for the purposes of toxicity assessment.

Supplementary Figure. Disposition of patients accrued to BRIM3.

Disposition of 2107 patients screened on BRIM3. * Among the 1432 screen failures, data are available on 519 patients as to the reason for screen failure. These were: BRAF^{V600E} mutation not detected (413), brain metastases discovered (50), other inclusion/exclusion criteria not met (36), no tumor tissue available for BRAF testing (7), patient withdrew consent (7), deteriorating performance status or death (6). Because of resource allocation issues, data collection procedures were changed to minimize the amount of data collected on screen failure patients. Therefore, for 913 screen failure patients, the reason for screen failure was coded by the investigator as “not specified”.

‡Pulmonary embolism (1 patient), not eligible (1 patient), clinical deterioration (1 patient), brain metastasis (2 patients), not known (2 patients).

N = 2107 Patients screened

N = 675
Patients randomized

N = 1432*
Screening failures

N = 337
vemurafenib

N = 338
dacarbazine

N = 335
treated

N = 2
not treated

N = 289
treated

N = 49
not treated

- Patient did not start treatment because of low hemoglobin at baseline (N = 1)
- Patient with no BRAF mutation was randomized in error (N = 1)

- Withdrawal of consent (N = 20)
- Refused Treatment (N = 17)
- Other † (N = 7)
- Progression (N = 3)
- No measurable tumor (N = 1)
- Received vemurafenib instead of dacarbazine (N = 1)