Supplementary Appendix:

Supplement to : Sosman JA, Kim KB, Schuchter L, et al. Long-term survival in vemurafenib treated $BRAF^{V600}$- mutated advanced melanoma

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1. SUPPLEMENTARY METHODS

TUMOR ASSESSMENTS BY THE IRC

BRAF^{V600} mutation analysis

STATISTICAL ANALYSIS (continued)

TUMOR ASSESSMENTS BY THE IRC

Blinded IRC assessments for response were conducted either at the time of disease progression or at scheduled time points (e.g., clinical data-cuts). Tumor assessments by the IRC were judged according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).

All IRC tumor evaluations were performed by two individual radiologists unaware of the others tumor assessments. If the results of their tumor measurements were not consistent, then a third reviewer would adjudicate the difference and determine the final measurement. In this manner all scans were reviewed by a minimum of two independent radiologists and some scans by three radiologists in addition to the investigator assessments.

BRAF^{V600} mutation analysis

BRAF^{V600}mutation analysis was determined by a real-time polymerase chain reaction assay — the cobas® 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Pleasanton, CA, USA), an FDA-approved companion diagnostic for vemurafenib. This test, which was designed to detect the predominant V600E (1799T→A) mutation in DNA isolated from formalin-fixed, paraffin-embedded tumor tissue, has cross-reactivity with some variant non-V600E mutations such as V600K. DNA was isolated using the cobas® DNA Sample Preparation Kit (Roche Molecular Systems, Inc., Pleasanton, CA, USA). Mutation testing was performed at two central laboratories.

STATISTICAL ANALYSIS (continued)

Duration of response was defined only for the patients whose best overall response was CR or PR, as the time interval between the date of the earliest qualifying response and the date of progressive disease (PD) or death from any cause, whichever occurred first. Progression-free survival (PFS; defined as the interval between the date of first treatment and the date of progression or death from any cause) and OS (defined as the interval between the date of first treatment and the date of death from any cause) were estimated by the Kaplan-Meier method. For patients who were alive without progression following the qualifying response, duration of response was censored on the date of last evaluable tumor assessment before the data cutoff date. Data for patients who were lost to follow-up prior to documented progression were censored at the last tumor assessment date during which the patient was known to be progression-free prior to the data cutoff date. Median values with corresponding two-sided 95% CIs were calculated

using the Brookmeyer-Crowley method.[21] Survival rates were assessed using the Kaplan-Meier method, and Greenwood's formula was used to calculate the standard error and 95% CIs. Descriptive statistics were used for adverse events (AEs).

2. SUPPLEMENTARY TABLE

Supplementary Table A. **Evaluation of target lesions by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).[19]** Tumor assessments by both the Independent Review Committee and investigators were judged according to these criteria during the study; modified from reference 19.

Supplementary Table A.

Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive disease (PD)	At least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study

3. SUPPLEMENTARY FIGURES

Supplementary figure legends

Supplementary Figure A. **cobas® BRAF^{V600} mutation screening for BRIM-2.** Flow and results of mutation screening and enrollment of screened population. CNS denotes central nervous system.

Supplementary Figure B. **Sanger sequencing/pyrosequencing of samples from patients enrolled in BRIM-2.** Flow and results of Sanger (blue boxes) and 454 pyrosequencing (brown boxes). WT denotes wild type.

Supplementary Figure C. **Response rate to vemurafenib (with 95% confidence intervals), as assessed by independent review committee*.** Previously treated patients with BRAF^{V600} mutant metastatic melanoma received vemurafenib 960 mg orally twice daily.

* Six patients (5%) had missing/unavailable data. CR denotes complete response, PD, progressive disease, PR, partial response, and SD, stable disease.

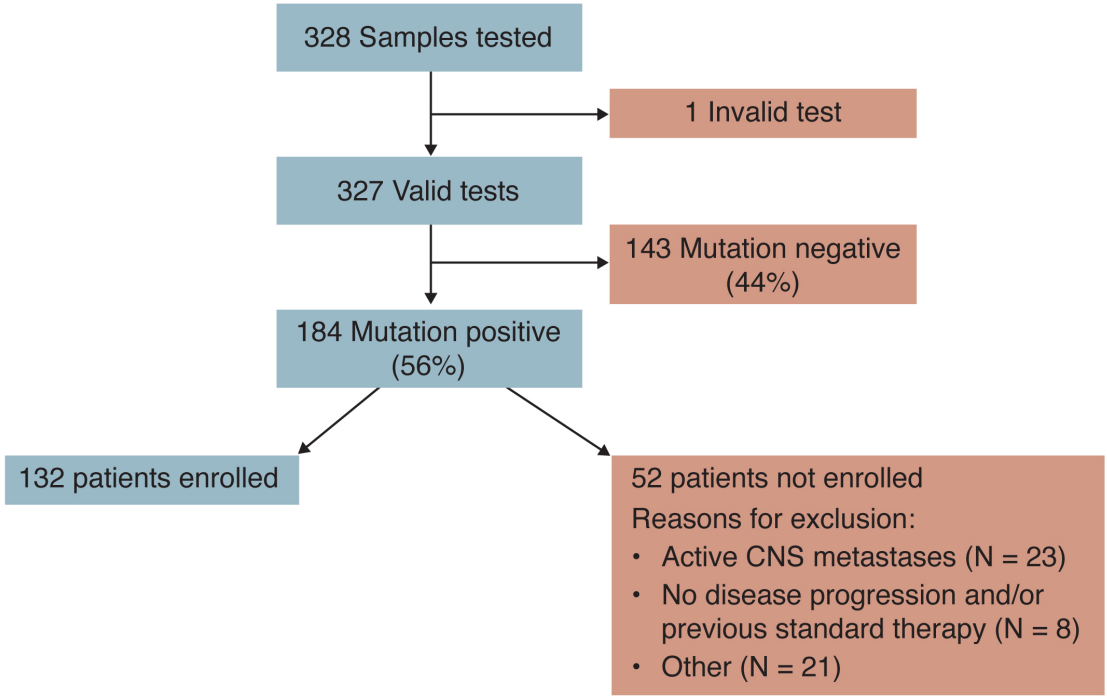
Supplementary Figure D. **Overall response rates by predefined subgroups***. Overall response rates and 95% confidence intervals in patient subgroups defined by baseline demographic or disease characteristics.

Vertical dashed line represents the 30% response rate (protocol target response rate).

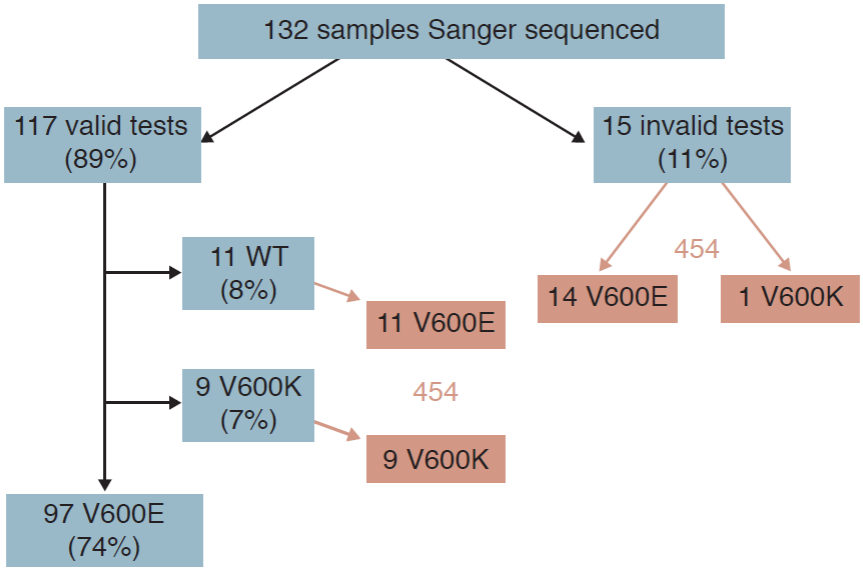
O represents the response rate for each subset; horizontal line represents the 95% confidence interval for each subset. ECOG denotes Eastern Cooperative Oncology Group, IL-2, interleukin-2, LDH, lactate dehydrogenase, ULN, upper limit of normal.

Supplementary Figure E. **Time to incidence of first cutaneous squamous cell carcinoma/keratoacanthoma (cuSCC/KA) lesion.** Each dot represents weeks to development of the first cuSCC/KA lesion. Median time to development of initial cuSCC/KA was 8 weeks at ↓.

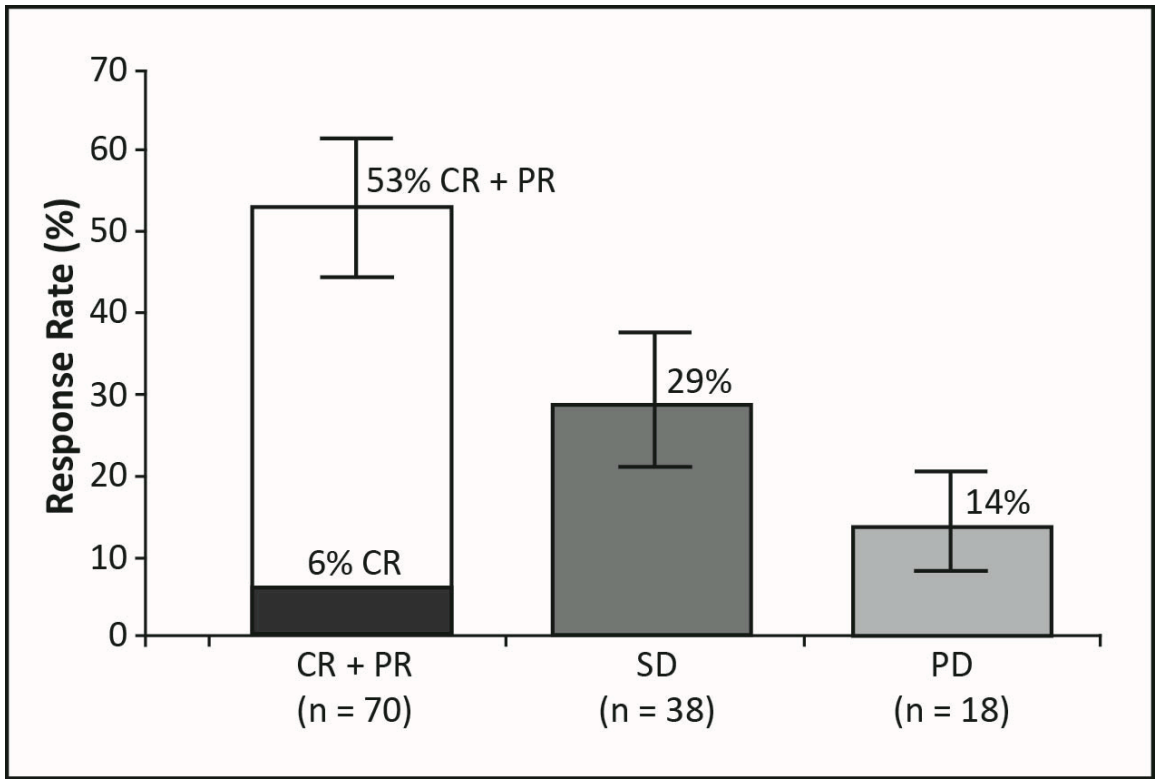
Supplementary Figure A.



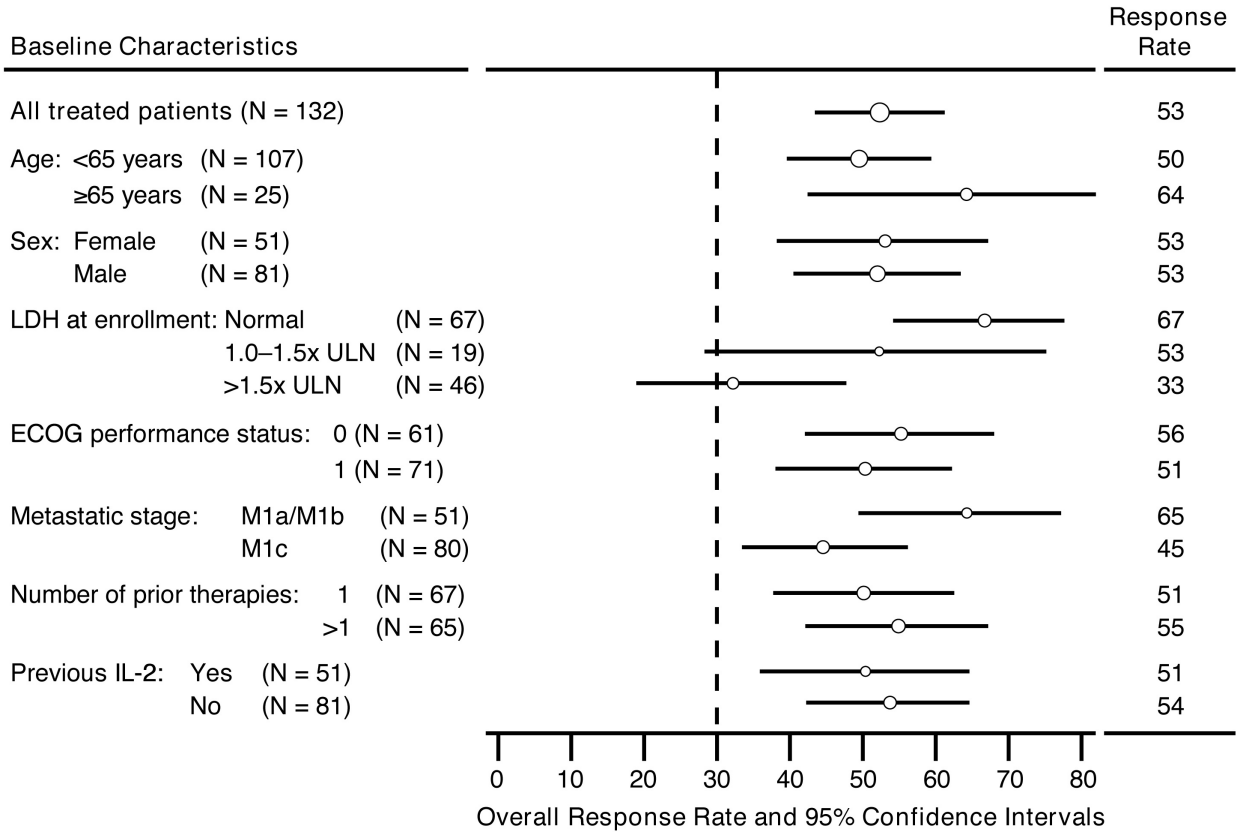
Supplementary Figure B.



Supplementary Figure C.



Supplementary Figure D.



Supplementary Figure E.