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Authors

Sperduto, Paul W
Jiang, Wen
Brown, Paul D
et al.

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The Prognostic Value of *BRAF, C-KIT,* and *NRAS* Mutations in Melanoma Patients With Brain Metastases

Paul W. Sperduto, MD, MPP, FASTRO[*], **Wen Jiang, MD**[†], **Paul D. Brown, MD**[†], **Steve Braunstein, MD**[‡], **Penny Sneed, MD**[‡], **Daniel A. Wattson, MD**[*,§], **Helen A. Shih, MD**[§], **Ananta Bangdiwala, MS**[‖], **Ryan Shanley, MS**[‖], **Natalie A. Lockney, MD**[¶], **Kathryn Beal, MD**[¶], **Emil Lou, MD, PhD**[#], **Thomas Amatruda, MD**[**], **William A. Sperduto, MS**[††], **John P. Kirkpatrick, MD, PhD**[††], **Norman Yeh, MD**[‡‡], **Laurie E. Gaspar, MD, MBA, FASTRO**[‡‡], **Jason K. Molitoris, MD**[§§], **Laura Masucci, MD**[‖‖], **David Roberge, MD**[‖‖], **James Yu, MD**[¶¶], **Veronica Chiang, MD**[¶¶], **Minesh Mehta, MD, FASTR0**[##]

[*]Minneapolis Radiation Oncology; Minneapolis, Minnesota [†]MD Anderson Cancer Center, Houston, Texas [‡]University of California San Francisco, San Francisco, California [§]Massachusetts General Hospital, Boston, Massachusetts [‖]Division of Biostatistics, University of Minnesota, Minneapolis, Minnesota [¶]Memorial Sloan Kettering Cancer Center, New York, New York [#]Department of Medical Oncology, University of Minnesota, Minneapolis, Minnesota [**]US Oncology, Minneapolis, Minnesota [††]Duke University, Durham, North Carolina [‡‡]University of Colorado Denver, Denver, Colorado [§§]University of Maryland, Baltimore, Maryland [‖‖]Centre Hospitalier de l'Universite de Montreal, Montreal, Quebec, Canada [¶¶]Yale University, New Haven, Connecticut [##] Miami Cancer Institute, Miami, Florida

Abstract

Purpose: Brain metastases are a common problem in patients with melanoma, but little is known about the effect of gene mutations on survival in these patients.

Methods and Materials: We created a retrospective multi-institutional database of 823 patients with melanoma and brain metastases diagnosed between 2006 and 2015. Clinical parameters, gene mutation status (*BRAF, C-KIT, NRAS*), and treatment were correlated with survival. Treatment patterns and outcomes were compared with a prior era (1985–2005).

Results: *BRAF* status was known in 584 of 823 patients (71%). *BRAF, NRAS,* and *C-KIT* mutations were present in 51%, 22%, and 11% of tested patients, respectively. The median time from primary diagnosis to brain metastasis was 32 months, and overall median survival (MS) from the time of initial treatment of brain metastases was 10 months. MS for *BRAF*-positive and *BRAF*-negative patients was 13 months and 9 months, respectively ($P = .02$). There was no significant difference in MS in patients with or without *NRAS* or *C-KIT* mutations. The time from primary diagnosis to brain metastasis did not vary by mutation and was not associated with

Reprint requests to: Paul W. Sperduto, MD, MPP, FASTRO, Minneapolis Radiation Oncology, 560 S Maple St, Ste 10, Waconia, MN 55387. Tel: (952) 442-6000; psperduto@mropa.com.

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survival after the diagnosis of brain metastases. MS for the 1985 to 2005 and 2006 to 2015 cohorts was 6.7 months and 10.0 months, respectively ($P<.01$). Reflecting treatment-trend changes, use of whole-brain radiation therapy decreased from 48% to 26% during this period. Among *BRAF*-positive patients, 71% received targeted *BRAF* and/or *MEK* inhibitors and 57% received some combination of targeted therapy, chemotherapy, and/ or immunotherapy.

Conclusions: For melanoma patients with brain metastases, *BRAF*-positive patients survive longer than *BRAF*-negative patients and overall survival has improved from 1985–2005 to 2006–2015.

Summary

This retrospective study of gene mutations in 823 melanoma patients with brain metastases shows that *BRAF*- positive patients survive longer than *BRAF*-negative patients after the diagnosis of brain metastases and that overall survival for these patients receiving diagnoses from 2006 to 2015 is improved compared with 1985 to 2005.

Introduction

The management of metastatic melanoma is rapidly evolving. Recent landmark trials have shown a survival benefit for immunotherapy (both CTLA-4 and PD-1 inhibition, independently and in combination) in selected patients (1–3), as well as for targeted therapies (both *BRAF* and *MEK* inhibitors, independently and in combination) (4–6). Despite these advances, brain metastases remain a common cause of morbidity and death in melanoma patients. In 2016, an estimated 76,380 patients were diagnosed with melanoma and approximately 10,000 will die from the disease (7). In nearly half of all melanoma patients, brain metastases will develop at some point in the course of their disease (8, 9), and brain metastases are the cause of death in 20% to 54% of patients with melanoma (10). Although melanoma represents only 4% of all cancers, it has garnered intense interest because of the progress achieved with targeted therapies and immunotherapies. Multiple preclinical studies (11–13) and case reports (14–16) have described radiation-induced immune enhancement (abscopal effect). Melanoma is also of interest because it has the highest propensity of all cancers to metastasize to the brain, and the underlying biological susceptibility for this is ill understood (17).

We previously demonstrated that the survival of patients with brain metastases varies widely by diagnosis and diagnosis-specific prognostic factors as defined by the Diagnosis-Specific Graded Prognostic Assessment (GPA) (18, 19). The melanoma cohort in our original study (1985–2005, n = 481) had a median survival of 6.7 months from the time of initial brain metastasis treatment. The only significant prognostic factors for survival in the study were Karnofsky Performance Status (KPS) and number of brain metastases. Our group recently reported prolonged survival in lung adenocarcinoma patients with *EGFR* and *ALK* alterations (20), and the 2010 lung GPA was updated accordingly (21). Little is known about the impact of gene mutations and the aforementioned systemic therapies on prognosis for melanoma patients with brain metastases. The purpose of this study was to determine the effect of gene mutations on survival and the time from primary diagnosis to brain metastasis (TPDBM).

Methods and Materials

We created a multi-institutional institutional review board—approved retrospective database of 823 patients with melanoma and brain metastases diagnosed between 2006 and 2015, nonoverlapping with our earlier cohort. Clinical parameters, gene mutation status (*BRAF, C-KIT, NRAS*), and treatment were recorded, and each was analyzed for association with survival (measured from time of initiation of treatment of brain metastases), TPDBM, and cause of death. The log-rank test and Wilcoxon rank sum test were used to compare median survival and TPDBM, respectively. Multivariate Cox regression was used to confirm that noted survival differences are independent of other prognostic factors in the GPA. Data regarding the source of the tissue (primary vs brain) used for mutation assessment were not collected. The mutation status was determined by a variety of different Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory methods used in the 10 participating academic institutions.

Results

Patient characteristics

Table 1 shows the patient characteristics. Salient observations include that two-thirds of patients were male patients, two-thirds of patients died of nonneurologic causes (as reported in the medical record or deduced on retrospective chart review), younger patients were more likely to be *BRAF* positive, and survival varied directly with KPS and indirectly with the number of brain metastases and the presence of extracranial metastases. Survival from the time of brain metastasis diagnosis did not correlate with the TPDBM. The 2010 melanoma GPA was again confirmed as an accurate tool to estimate survival.

Survival and TPDBM

Table 2 shows median survival and TPDBM by gene status. Among patients tested for gene status, *BRAF, NRAS,* and *C-KIT* mutations were present in 297 of 584 patients (51%), 63 of 285 patients (22%), and 32 of 293 patients (11%), respectively. Only 2% of patients showed positive results for multiple mutations. Unlike lung cancer, there was no strong interaction among these mutations with respect to overall survival, so each was analyzed separately. Median TPDBM was 32 months, and median overall survival was 10 months from the time of first treatment of brain metastasis. Patients with known *BRAF* status survived longer than those with unknown *BRAF* status (11 months [interquartile range (IQR), 5–30 months] vs 8 months [IQR, 4–17 months]; $P = .0007$). Notably, most of the patients with unknown *BRAF* status received diagnoses in 2006 to 2009 before *BRAF* testing became routine, and conversely, most of the patients with known *BRAF* status received diagnoses from 2010 to 2015. Vemurafenib, the first *BRAF*-targeted therapy, was approved by the Food and Drug Administration on August 17, 2011. The difference in the survival rate between known and unknown *BRAF* status correlates with the steady improvement in survival over time. Similarly, patients with known *NRAS* status survived longer than those with unknown *NRAS* status (12 months [IQR, 6–30 months] vs 9 months [IQR, 4–21 months]; $P = .002$). There was no significant survival difference between patients with known and unknown *C-KIT* status. *BRAF*-positive patients survived longer than *BRAF*-negative patients (13

months [IQR, 6–33 months] vs 9 months [IQR, 5–24 months]; $P = .02$) (Fig. 1). Furthermore, after we adjusted for the existing melanoma GPA, *BRAF*-positive patients had superior overall survival compared with *BRAF*-negative patients (hazard ratio, 0.74; 95% confidence interval, 0.61–0.90; $P<.01$). There was no significant survival difference between *NRAS*-positive and *NRAS*-negative patients (14 months [IQR, 5–36 months] vs 11 months [IQR, 6–32 months]; $P = .79$) or between *C-KIT*—positive and *C-KIT*—negative patients (9 months [IQR, 7–25 months] vs 11 months [IQR, 5–30 months]; $P = .95$). Regarding TPDBM, there was no significant difference between known and unknown or positive and negative gene status for *BRAF, NRAS,* or *C-KIT.*

Treatment

Table 3 shows an analysis of median survival and risk of death (hazard ratio) by treatment and by treatment era, adjusted by GPA. Salient observations include the following: (1) Use of whole-brain radiation therapy (WBRT) decreased from 48% to 26% between the 2 treatment periods (from 1985–2005 to 2006–2015); and (2) use of stereotactic radiosurgery (SRS) (76% and 78%) and surgery (18% and 17%) remained nearly the same. Chemotherapy data were not available for the earlier study period, and that period predated the use of targeted therapy and immunotherapy.

Chemotherapies, targeted therapies, and immunotherapies

Among *BRAF*-positive patients, 194 of 272 (71%) received *BRAF* and/or *MEK* targeted drugs and 156 of 272 (57%) received some combination of *BRAF* and/or *MEK* targeted drugs with either immunotherapy or chemotherapy. Immunotherapy use increased from 40% to 50% to over 70% between 2009 and 2011, whereas chemotherapy use declined from 70% in 2010 to 28% in 2014. From 2006 to 2015, almost half of all patients (405 of 823 [49%]) received chemotherapy (carboplatin [n = 228], paclitaxel [n = 99], temozolomide [n = 262], bevacizumab [n = 29], investigational agents [n = 18], other [n=105]). Regarding the timing of chemotherapy, nearly equal numbers of patients received chemotherapy before (228 of 405 [28%]) and after (239 of 405 [29%]) the diagnosis of brain metastases. More than half (224 of 405 [55%]) had complete data in terms of the start and stop dates of chemotherapy. The median duration of chemotherapy was 2 months. Table 4 shows the number of patients receiving immunotherapy, targeted therapy, and chemotherapy by year and *BRAF* status.

Cause of death

The cause of death was known in 485 of the 649 patients (75%) who died during the follow-up period, and the cause was nonneurologic in 304 of 485 (63%).

Comparison to historical cohort

In this series of 823 melanoma patients with brain metastases, not only did *BRAF-positive* patients survive longer than *BRAF*-negative patients from the time of initial treatment of the brain metastasis, but the overall survival of 10 months was significantly longer than in our prior report (1985–2005) (10 months vs 6.7 months, $P<.01$) (18). Furthermore, the data were analyzed before and after ipilimumab and vemurafenib were approved by the Food and Drug Administration (August 2011). There was no significant difference in median survival

between patients who received diagnoses of brain metastases from January 2006 to July 2011 and those who received diagnoses from August 2011 to December 2015 (Table 5).

Discussion

BRAF-positive melanoma patients with brain metastases survive longer than *BRAF*-negative patients. For individual patients and their physicians, such information about prognosis helps them make choices regarding whether treatment is appropriate and, if so, which treatment is appropriate.

In the larger context, there may be other implications. The management of patients with brain metastases is evolving away from the use of WBRT because of concern about neurocognitive toxicity (22–25). SRS alone is now a standard of care for patients with an increasing number of brain metastases. With the advent of targeted therapies and immunotherapies, an increasing percentage of patients in whom brain metastases develop will be treated with these agents before, after, or both before and after the diagnosis of brain metastases. There is conflicting literature showing both the risk (26, 27) and the reward (28–35) of combining targeted therapies and immunotherapies with SRS.

The risk of such treatment includes pseudoprogression, cerebral edema, and delayed vasculitic leukoencephalopathy with T-cell infiltration (pathologically confirmed in patients who required craniotomy after anti—PD-1 immunotherapy and SRS) (26). Another study showed an increased risk of symptomatic radiation necrosis with SRS and *BRAF* inhibitors (11% for SRS alone and 28% for SRS combined with *BRAF* inhibition) (27).

The underlying mechanism of improved survival in this and other retrospective studies remains unclear, but multiple studies have suggested that the combination of SRS with targeted therapies or with immunotherapy and/or targeted therapies not only is well tolerated (31–34) but may yield a survival benefit (28, 35). Retrospective analysis of data from 2 prospective anti—PD-1 (nivolumab) trials showed that the combination of nivolumab and SRS was well tolerated and that local control of brain metastases and overall survival appeared improved compared with historical controls (28).

What, if anything, is appropriate to conclude from conflicting literature? The most apparent difference in the management between the 2 treatment eras is the use of targeted therapies and immunotherapy. SRS alone or in combination with WBRT has improved 1-year local control rates of brain metastases to approximately 80% to 85% (22–25), but use of SRS was similar in both eras. There are limited data on immunotherapy alone for brain metastases. In a 2-arm prospective phase 2 trial of ipilimumab used as a single agent, the responses rates were 25% and 10% in melanoma patients with brain metastases who were asymptomatic not requiring steroids and symptomatic requiring steroids, respectively (36). A preliminary report of a phase 2 trial of pembrolizumab alone in patients with brain metastases showed a response was seen in 4 of 18 patients (22%) with melanoma (37, 38).

So, if immunotherapy alone offers limited response rates for melanoma patients with brain metastases and combined SRS and targeted therapies and/or immunotherapies offer greater response rates and improved survival in this and other retrospective series, it is reasonable to

argue that the combination is additive and synergistic and that the drugs act as radiosensitizers or, conversely, the radiation induces an enhanced immune response (abscopal effect). These data are consistent with the mounting literature (11–16, 29, 30) suggesting radiation may induce such an effect in this patient population, but these data cannot distinguish which, if any, of these possible mechanisms are responsible for the findings. Furthermore, there are other possible explanations for the apparent improvement in survival: lead-time bias from improved and/or more frequent imaging resulting in earlier disease detection and treatment, as well as selection bias inherent in any retrospective study.

Another concern that may result in missed therapeutic opportunity is the recent discovery of discordance in *BRAF* status between the primary tumor and brain metastases (39, 40). This finding suggests *BRAF* status should be assessed for both the primary and brain metastases whenever clinically feasible.

The observation that extracranial response to *BRAF* inhibitors exceeds intracranial response led to investigation of the relative concentration of vemurafenib in plasma and cerebrospinal fluid. The mean concentrations of vemurafenib in plasma and cerebrospinal fluid were 53.4 mg/L and 0.5 mg/L (approximately 1%), respectively (41). Reasonable explanations for the seemingly contradictory findings that *BRAF* inhibitors do not cross the blood-brain barrier and yet *BRAF*-positive patients with brain metastases survive longer than *BRAF*-negative patients with brain metastases include that: (1) *BRAF*-positive melanoma is an inherently less biologically aggressive disease, and survival after the diagnosis of brain metastases is unrelated to the use of targeted therapies; and/or (2) the *BRAF* inhibitors may enhance the radiosensitivity of *BRAF*-positive melanoma brain metastases, but *BRAF* inhibitors alone are inadequate treatment in these patients. This conclusion is consistent with a recent review and other literature that suggested an enhanced response in some series but no response in others and have yet to show that *BRAF* inhibitors extend survival of melanoma patients with brain métastasés (42, 43).

Many other questions remain, such as how the risk and reward of multimodality therapy varies by gene mutation; other prognostic factors; and/or radiation dose, volume, and fractionation. Prospective trials are needed to answer these questions and better define the effect of gene mutations, *BRAF* and/or *MEK* targeted drugs, and immunotherapy in melanoma patients with brain metastases. Until the results of these and other studies are known, retrospective data such as those presented in this article provide imperfect insights but nonetheless illuminate prognosis, as well as current practice patterns, and are hypothesis generating.

Several limitations must be noted: (1) The database used is retrospective with inherent selection bias; (2) the myriad types, combinations, sequences, and timing of the targeted therapies and immunotherapies, as well as the type and dose of radiation therapy, preclude any conclusion from these data regarding which treatment is most effective in this patient population; and (3) limited data were available regarding the toxicity of combined-modality therapy. Last, transition to a diagnosis-specific GPA that incorporates molecular variables (molecular melanoma GPA), such as gene status, is needed to more accurately estimate survival for these patients in the modem era of targeted therapies and immunotherapy, guide

clinical decision making, and stratify future clinical trials to ensure comparison of similar patient groups.

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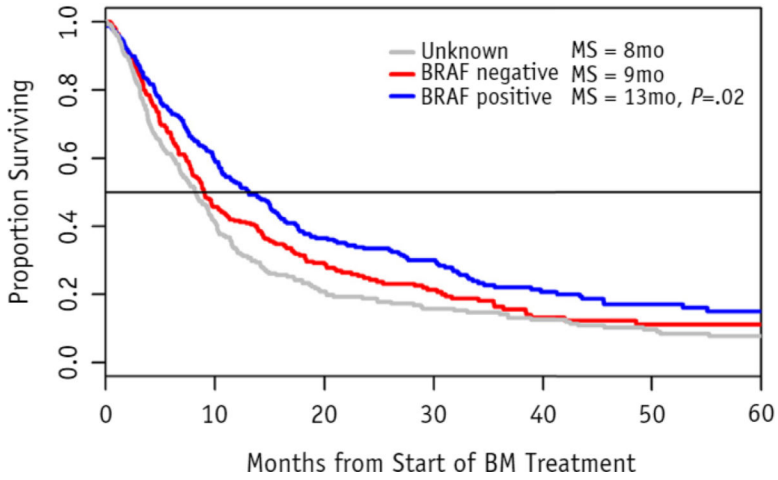

Fig. 1.

Kaplan-Meier curve of survival by *BRAF* mutation status. *Abbreviations:* BM = brain metastasis; MS = median survival.

Table 1

Patient characteristics by mutation status

				BRAF						*NRAS*						*C-KIT*					
		Overall		Positive		Negative		Unknown		Positive		Negative		Unknown		Positive		Negative		Unknown	
Variable	**Category**	**n**	**MS, mo**	**n (%)**	**MS, mo**	**n (%)**	**MS, mo**	**n (%)**	**MS, mo**	**n(%)**	**MS, mo**	**n (%)**	**MS, mo**	**n (%)**	**MS, mo**	**n(%)**	**MS, mo**	**n(%)**	**MS, mo**	**n (%)**	**MS, mo**
Overall		823	10	297 (36)	13	287 (35)	9	239 (29)	8	63 (8)	14	222 (27)	11	538 (65)	9	32(4)	9	261 (32)	11	530 (64)	10
Melanoma GPA	0–1	159	6	66 (42)	8	53 (33)	4	40 (25)	5	8(5)	3	39 (25)	7	112 (70)	6	7(4)	8	48 (30)	6	104 (65)	6
	2	220	9	83 (38)	11	76 (35)	9	61 (28)	6	12(5)	6	65 (30)	12	143 (65)	7	7(3)	8	76 (35)	9	137 (62)	8
	3	239	10	78 (33)	15	82 (34)	9	79 (33)	8	17 (7)	32	67 (28)	12	155 (65)	9	11 (5)	10	71 (30)	13	157 (66)	10
	4	205	17	70 (34)	22	76 (37)	18	59 (29)	12	26 (13)	22	51 (25)	18	128 (62)	15	7(3)	10	66 (32)	19	132 (64)	15
Cause of death	Neurologic	181	8	67 (37)	10	66 (36)	7	48 (27)	8	16(9)	8	31 (17)	10	134 (74)	7	6(3)	14	41 (23)	10	134 (74)	7
	Nonneurologic/ cancer	296	7	100 (34)	10	116 (39)	7	80 (27)	6	24(8)	9	114 (39)	8	158 (53)	7	14(5)	7	119 (40)	7	163 (55)	7
	Nonneurologic/ noncancer	8	8	2(25)	10	2(25)	10	4(50)	6	24(8)	9	2(25)	9	6(75)	8	14(5)	7	2(25)	9	6(75)	8
	Unknown	164	8	49 (30)	9	40 (24)	5	75 (46)	8	7(4)	7	16 (10)	9	141 (86)	8	5(3)	7	34 (21)	9	125 (76)	8
Time from PD to BM	0–12 mo	188	9	70 (37)	12	68 (36)	9	50 (27)	5	14(7)	13	49 (26)	10	125 (66)	8	7(4)	9	66 (35)	12	115 (61)	8
	12–30 mo	199	8	62 (31)	10	75 (38)	8	62 (31)	8	14(7)	18	51 (26)	8	134 (67)	8	11 (6)	7	59 (30)	10	129 (65)	8
	30–60 mo	216	10	84 (39)	14	80 (37)	9	52 (24)	10	19(9)	7	66 (31)	14	131 (61)	10	7(3)	14	68 (31)	12	141 (65)	10
	>60 mo	220	11	81 (37)	16	64 (29)	11	75 (34)	8	16(7)	17	56 (25)	11	148 (67)	10	7(3)	28	68 (31)	11	145 (66)	11
Age at BM diagnosis	<50 y	192	15	98 (51)	15	39 (20)	11	55 (29)	14	11 (6)	34	55 (29)	14	126 (66)	14	10(5)	-	56 (29)	15	126 (66)	14
	50–59 y	221	9	76 (34)	11	71 (32)	12	74 (33)	8	17 (8)	17	53 (24)	12	151 (68)	8	8(4)	8	63 (29)	13	150 (68)	9

				BRAF						*NRAS*						*C-KIT*					
		Overall		**Positive**		**Negative**		**Unknown**		**Positive**		**Negative**		**Unknown**		**Positive**		**Negative**		**Unknown**	
Variable	**Category**	**n**	**MS, mo**	**n (%)**	**MS, mo**	**n (%)**	**MS, mo**	**n (%)**	**MS, mo**	**n(%)**	**MS, mo**	**n (%)**	**MS, mo**	**n (%)**	**MS, mo**	**n(%)**	**MS, mo**	**n(%)**	**MS, mo**	**n (%)**	**MS, mo**
	60–69 y	238	10	76 (32)	12	105 (44)	9	57 (24)	9	23 (10)	13	59 (25)	13	156 (66)	9	8(3)	9	82 (34)	11	148 (62)	9
	70–97 y	172	7	47 (27)	13	72 (42)	7	53 (31)	5	12(7)	4	55 (32)	10	105 (61)	7	6(3)	9	60 (35)	8	106 (62)	7
Sex	Male	541	9	183 (34)	11	207 (38)	9	151 (28)	8	43 (8)	17	166 (31)	10	332 (61)	8	25 (5)	8	185 (34)	10	331 (61)	9
	Female	281	11	114 (41)	15	79 (28)	10	88 (31)	9	20 (7)	13	56 (20)	14	205 (73)	11	7(2)	11	76 (27)	13	198 (70)	11
KPS	<70	76	7	29 (38)	8	26 (34)	5	21 (28)	4	1 (1)	2	14 (18)	10	61 (80)	5	3(4)	8	20 (26)	10	53 (70)	5
	70	102	6	34 (33)	7	39 (38)	7	29 (28)	4	4(4)	7	19 (19)	5	79 (77)	6	2(2)	7	26 (25)	7	74 (73)	6
	80	192	8	72 (38)	12	58 (30)	6	62 (32)	8	13(7)	6	46 (24)	11	133 (69)	8	5(3)	9	55 (29)	8	132 (69)	8
	90	343	12	124 (36)	15	118 (34)	14	101 (29)	9	34 (10)	20	111 (32)	13	198 (58)	11	13(4)	8	122 (36)	13	208 (61)	12
	100	110	17	38 (35)	22	46 (42)	17	26 (24)	10	11 (10)	49	32 (29)	15	67 (61)	16	9(8)	28	38 (35)	17	63 (57)	15
No. of brain metastases	1	328	12	112 (34)	15	111 (34)	14	105 (32)	10	30 (9)	20	72 (22)	19	226 (69)	11	10(3)	9	88 (27)	20	230 (70)	10
	2	151	10	52 (34)	16	54 (36)	10	45 (30)	8	11 (7)	20	48 (32)	13	92 (61)	9	7(5)	25	56 (37)	10	88 (58)	11
	3–5	190	8	56 (29)	14	75 (39)	7	59 (31)	8	11 (6)	29	44 (23)	9	135 (71)	7	8(4)	11	60 (32)	7	122 (64)	9
	>5	154	7	77 (50)	9	47 (31)	5	30 (19)	5	11 (7)	3	58 (38)	8	85 (55)	7	7(5)	7	57 (37)	8	90 (58)	7
Extracranial metastases	No	136	20	47 (35)	35	41 (30)	24	48 (35)	10	15(11)	27	34 (25)	46	87 (64)	12	5(4)	8	50 (37)	34	81 (60)	16
	Yes	687	9	250 (36)	11	246 (36)	8	191 (28)	8	48 (7)	12	188 (27)	10	451 (66)	8	27(4)	10	211 (31)	10	449 (65)	9

Abbreviations: BM = brain metastasis; GPA = Graded Prognostic Assessment; KPS = Karnofsky Performance Status; MS = median survival (Kaplan-Meier estimate); PD = primary diagnosis.

Percentages are based on the overall number in each row.

Table 2

MS and TPDBM by gene status

			Survival			TPDBM		
Gene	**Status**	**n(%)**	**Median, mo**	**IQR, mo**	***P* value**	**Median, mo**	**IQR, mo**	***P* value**
Overall		823	10	4–26		32	14–63	
BRAF	Unknown	239 (29)	8	4–17		33	15–72	
	Known	584 (71)	11	5–30	.0007 *†	32	14–59	.34 †‡
	Negative	287 (35)	9	5–24		30	13–54	
	Positive	297 (36)	13	6–33	.02 *§	35	14–65	.11 ‡§
NRAS	Unknown	538 (65)	9	4–21		32	13–65	
	Known	285 (35)	12	6–30	.002 *†	34	14–60	.92 †‡
	Negative	222 (27)	11	6–32		34	15–62	
	Positive	63 (8)	14	5–36	79 *§	35	14–60	.82 ‡§
C-KIT	Unknown	530 (64)	10	4–25		33	15–64	
	Known	293 (36)	10	5–28	.09 *†	31	12–62	.15 †‡
	Negative	261 (32)	11	5–30		32	12–62	
	Positive	32(4)	9	7–25	.95 *§	29	14–43	.58 ‡§

Abbreviations: IQR = interquartile range (25th percentile-75th percentile); TPDBM = time from primary diagnosis to brain metastasis. Percentages are based on the total number of patients (N = 823). All tests were performed within each gene.

* *P* values are from log-rank tests comparing survival distributions between groups.

† *P* values are from comparison of the group with known gene alteration status and the group with unknown status.

‡ *P* values are from Wilcoxon rank sum tests comparing TPDBM between groups.

§ *P* values are from comparison of the group with positive gene alteration and the group with negative gene alteration.

Table 3

Median survival and risk of death by treatment and by treatment era

	Overall	WBRT	SRS	WBRT + SRS	S + SRS	S + WBRT	S + WBRT + SRS	S
Historical cohort								
n	481	86 (18%)	221 (46%)	89 (18%)	30 (6%)	29 (6%)	26 (5%)	
Median survival, mo	7	3	7	7	13	11	13	
Mean GPA	2.5	1.9	2.7	2.4	2.9	3.1	2.7	
Risk of death (HR)		1.00	0.74	0.83	0.76	0.60	0.49	
95% Cl			0.51–1.07	0.57–1.21	0.45–1.29	0.38–0.99	0.28–0.86	
P value			.11	.33	.30	.04	.01	
Current study								
n	823	91 (11%)	464 (56%)	73 (9%)	95 (12%)	34 (4%)	12 (1%)	43 (5%)
Median survival, mo	10	6	10	9	13	11	11	22
Mean GPA	2.6	1.7	2.8	2.1	2.6	1.5	2.4	2.8
Risk of death (HR)		1.00	0.69	0.62	0.50	0.54	0.70	0.42
95% Cl			0.54–0.89	0.45–0.86	0.36–0.69	0.35–0.84	0.36–1.36	0.27–0.63
P value			<.01	<.01	<.01	<.01	.29	<.01

Abbreviations: Cl = confidence interval; GPA = Graded Prognostic Assessment; HR = hazard ratio; S = surgery; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

HR, 95% Cl, and *P* values (each treatment vs WBRT alone within each cohort) are adjusted for GPA. Median survival is unadjusted. Eleven patients in this study had no treatment.

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Table 4

Number of patients receiving immunotherapy, targeted therapy, or chemotherapy by year and *BRAF* status

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Immunotherapy/all patients (%)	16/39 (41)	17/38 (45)	42/75 (56)	29/66 (44)	53/86 (62)	88/121 (73)	114/155 (74)	94/130 (72)	71/96 (74)	11/17 (65)
Immunotherapy/BRAF positive (%)	2/2 (100)	1/1 (100)	5/8 (63)	12/22 (55)	16/30 (53)	29/49 (59)	47/71 (66)	47/70 (67)	23/36 (64)	5/8 (63)
Immunotherapy/BRAF negative (%)	0/1 (0)	1/2 (50)	6/8 (75)	5/13 (38)	18/30 (60)	48/55 (87)	62/72 (86)	43/53 (81)	41/46 (89)	4/7 (57)
Immunotherapy/BRAF untested (%)	14/36 (39)	15/35 (43)	31/59 (53)	12/31 (39)	19/26 (73)	11/17 (65)	5/12 (42)	4/7 (57)	7/14 (50)	2/2 (100)
Targeted therapy/all patients (%)	6/39 (15)	6/38 (16)	11/75 (15)	13/66 (20)	26/86 (30)	47/121 (39)	65/155 (42)	58/130 (45)	39/96 (41)	6/17 (35)
Targeted therapy/BRAF positive (%)	2/2 (100)	1/1 (100)	5/8 (63)	9/22 (41)	16/30 (53)	39/49 (80)	57/71 (80)	52/70 (74)	29/36 (81)	5/8 (63)
Targeted therapy/BRAF negative (%)	0/1 (0)	0/2 (0)	2/8 (25)	3/13 (23)	5/30 (17)	7/55 (13)	5/72 (7)	3/53 (6)	8/46 (17)	0/7 (0)
Targeted therapy/BRAF untested (%)	4/36 (11)	5/35 (14)	4/59 (7)	1/31 (3)	5/26 (19)	1/17 (6)	3/12 (25)	3/7 (43)	2/14 (14)	1/2 (50)
Chemotherapy/all patients (%)	26/39 (67)	27/38 (71)	52/75 (69)	45/66 (68)	60/86 (70)	54/121 (45)	60/155 (39)	51/130 (39)	27/96 (28)	3/17 (18)
Chemotherapy/BRAF positive (%)	2/2 (100)	1/1 (100)	6/8 (75)	17/22 (77)	19/30 (63)	18/49 (37)	24/71 (34)	23/70 (33)	7/36 (19)	1/8 (13)
Chemotherapy/BRAF negative (%)	0/1 (0)	1/2 (50)	8/8 (100)	9/13 (69)	27/30 (90)	30/55 (55)	32/72 (44)	26/53 (49)	16/46 (35)	2/7 (29)
Chemotherapy/BRAF untested (%)	24/36 (67)	25/35 (71)	38/59 (64)	19/31 (61)	14/26 (54)	6/17 (35)	4/12 (33)	2/7 (29)	4/14 (29)	0/2 (0)

Of all patients, 535 (65%) received immunotherapy either before or after brain metastasis, which included interferon (n= 154), granulocyte- macrophage colony-stimulating factor (n=16), interleukin 2 (n=126), ipilimumab (n = 446), PD-1 inhibitors (n=100), or other (n=18); 277 (34%) received targeted therapy, including dabrafenib (n = 94), vemurafenib (n= 137), other *BRAF* inhibitors (n = 8), trametinib (n = 74), other *MEK* inhibitors (n = 18), imatinib (n = 3), other *C-KIT* inhibitors (n = 9), or investigational (n = 25); and 405 (49%) received chemotherapy, including carboplatin (n = 228), paclitaxel (n = 99), temozolomide (n = 262), bevacizumab (n = 29), investigational (n=18), or other (n=105).

Table 5

Survival in current and historical cohorts

Era	Survival from primary diagnosis			Survival from start of BM treatment		
	MS (IQR), mo	n	*P* value	MS (IQR), mo	n	*P* value
1985–2005	44.0 (20–88)	428	<.01	6.7 (3–14)	481	<.01
January 2006-July 2011	54.7 (29–102)	363	Ref	10.2 (4–28)	363	Ref
August 2011-Dcccmber 2015	55.0 (28–106)	460	.23	9.6 (4–25)	460	.48

Abbreviations: BM = brain metastasis; IQR = interquartile range; MS = median survival (Kaplan-Meier estimate); Ref = reference category.

P values compare overall survival of each era versus January 2006 to July 2011.

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