

## Retrospective Study of Patients with Brain Metastases from Melanoma Receiving Concurrent Whole-brain Radiation and Temozolomide

NICHOLAS DEVITO<sup>1,2</sup>, MICHAEL YU<sup>2</sup>, REN CHEN<sup>1</sup> and EDWARD PAN<sup>2</sup>

<sup>1</sup>University of South Florida College of Medicine, Tampa, FL, U.S.A.;

<sup>2</sup>H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, U.S.A.

**Abstract.** *Background: Metastatic melanoma is the second most common cancer to metastasize to the brain. It is typically treated using stereotactic radiosurgery with or without whole-brain radiation (WBR) therapy. Recently, the alkylating agent temozolomide, which has demonstrated activity in patients with brain metastasis and primary tumors, was used alongside WBR to delay brain metastasis recurrence, increase survival, and improve quality-of-life in patients with brain metastases. Patients and Methods: In this retrospective study, we reviewed outcomes of 29 patients treated from 2005-2009 at the Moffitt Cancer Center with brain metastases of melanoma. Results were narrowed via retrospective chart analysis to a cohort with brain metastasis receiving concomitant temozolomide and WBR. Results: Median progression-free survival was 20.4 weeks and overall survival was 44.4 weeks compared to 16 week survival of patients treated with WBR alone. Conclusion: A prospective trial evaluating this combined regimen may be considered.*

Metastatic melanoma is the second most common cancer after lung cancer to metastasize to the brain. Treatment for brain metastases of melanoma has typically involved stereotactic radiosurgery with or without whole-brain radiation therapy (WBR) (1). Recently, the alkylating agent temozolomide has been suggested for use with concurrent WBR to delay metastasis recurrence, increase survival rate, and improve the quality of life of such patients (2). For patients with newly diagnosed glioblastoma, temozolomide administered concurrently with external beam radiation therapy is the standard of care (3). Temozolomide is an oral chemotherapeutic agent that is very well tolerated and has

excellent penetration into the blood brain barrier (4, 5). Temozolomide has demonstrated some activity in patients with brain metastases of melanoma (5, 6) and has been investigated for brain metastases in patients with other types of primary cancer (4, 7). At our institution, we utilize a modified Stupp regimen for brain metastases, in which WBR is given over 3 weeks with concurrent temozolomide at 75 mg/m<sup>2</sup> for 21 days, followed by monthly temozolomide at 200 mg/m<sup>2</sup> for 5 consecutive days every 28 days. Monthly temozolomide was administered until progression or excessive toxicities were observed. We completed this institutional retrospective study to evaluate the safety and outcomes of this combination therapy with concurrent WBR and temozolomide.

Melanoma typically arises from the skin but can be formed in any pigmented tissue. In 2009, 68,130 new cases of melanoma were diagnosed in the United States, with 8,700 deaths (8). Melanoma is a cancer of melanocytes, which are derived from neural crest cells. This could partially account for its high affinity for metastases, specifically to the brain. The prevalence of central nervous system (CNS) metastases in patients with a primary melanoma ranges from 10-40% in clinical series. Brain metastases are present in up to 75% of patients with disseminated malignant melanoma, and, 12-20% of the time, the brain is the initial site of metastasis. The diagnosis of metastatic melanoma to the brain is made by MRI with contrast. Clinically, patients suffer from seizures, loss of sensation, motor weakness, visual field deficits, memory loss, personality changes, or headache (1, 4, 9). The median survival in one retrospective study of over 700 patients was found to be 4.7 months (10). Another prospective trial using temozolomide in patients with brain metastases from breast, non-small cell lung cancer, and melanoma revealed a median overall survival (OS) of 100 days and a progression-free survival (PFS) of 56 days in patients with melanoma brain metastases (11). Brain metastases in melanoma involve numerous chromosomal deletions and translocations. A notable molecular aberration in CNS melanoma metastases is duplication of the long arm of chromosome 17 (12).

*Correspondence to:* Edward Pan, MD, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, U.S.A. Tel: +1 8137453871, Fax: +1 8137453068, e-mail: Edward.pan@moffitt.org

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Temozolomide (Temodar™) is an oral alkylating agent that has demonstrated efficacy in the treatment of a variety of solid tumors, including primary malignant brain tumors and metastatic melanoma. In one phase III study, temozolomide exhibited efficacy equivalent to that of dacarbazine for treating metastatic melanoma. Temozolomide has certain advantages over many existing alkylating agents because of its unique chemical structure and pharmacokinetic properties. Because of its small molecular weight, temozolomide efficiently crosses the blood brain barrier. In addition, temozolomide can be administered orally without dietary restrictions, and essentially 100% of the orally administered dose enters the bloodstream. Temozolomide is also associated with a lower incidence of severe adverse events, compared to other alkylating agents (6, 13). It has recently been discovered that the efficacy of temozolomide in melanoma treatment depends on the expression of NF- $\kappa$ B (due to the downstream anti-apoptotic effects) and the activity of MGMT (a mismatch repair protein). Both MGMT and NF- $\kappa$ B are affected by temozolomide (14, 15).

WBR is the treatment of choice for multiple brain metastases. About 80% of patients with metastatic melanoma to the brain have more than one lesion on contrast MRIs. For patients with only a single brain lesion, stereotactic radiosurgery is the standard of care (16). For these patients, acute side effects include alopecia, nausea, vomiting, lethargy, otitis media, and cerebral edema. Although some of these effects can be transient, dermatitis, alopecia, and otitis media can persist for months after irradiation. Chronic effects are even more serious, including atrophy, leukoencephalopathy, radiation necrosis, neurological deterioration, and dementia (17).

Exactly how temozolomide enhances WBR therapy has not been well described. Two prospective phase II trials using temozolomide with WBR (18) and with the addition of thalidomide (19) have been published that utilized 10-week temozolomide cycles plus WBR over two weeks. The first of these trials was established prior to the Stupp *et al.* study (3). In this retrospective study, we compared outcomes of patients with brain metastases of melanoma who were treated with the combined regimen *versus* patients who were treated with WBR alone.

## Patients and Methods

Patients with metastatic melanoma who were treated from 2005 to 2009 at the Moffitt Cancer Center were first identified through PowerChart (Cerner corporation, Kansas City, MO, USA) database queries. These results were then narrowed *via* retrospective chart analysis to a cohort of patients with brain metastasis receiving concomitant temozolomide and WBR. Internal Review Board approval was issued by the Moffitt Cancer Center for this study.

Data collected from PowerChart included the start and end dates of WBR and treatment with temozolomide, date and location of

initial site of melanoma, the date of diagnosis of metastatic melanoma progression-free survival (PFS), date of death (if applicable), date of last follow-up, side-effects and toxicity of the treatments, and an estimation of Karnofsky Performance Scale before and after treatment. Serial brain MRIs were reviewed to document progression and new metastatic lesions. Progression was defined as the appearance of new brain metastatic lesions or an increase in the size of the known metastatic lesion by greater than 25% in an area measured on MRI, according to radiographic McDonald criteria (20). Side-effects were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 guidelines using provider commentary within patient charts.

*Statistical analysis.* Progression was analyzed *via* Cox proportional regression models, and survival curves were estimated by the Kaplan-Meier method. PFS was measured from completion of concurrent WBR and temozolomide until the occurrence of progression. OS was measured from the date of diagnosis of melanoma brain metastases until date of death. Among the 29 total patients identified, 11 of them only had the year of diagnosis without month and day. To evaluate these data, the middle date of the year (6/15) was used as the diagnosis date of cutaneous malignant melanoma.

## Results

The 29 studied patients ranged from 30 to 83 years old (mean age of 58 years). Seventeen (59%) patients were male, and 12 (42%) were female. The majority of initial cutaneous melanoma sites were in the head/neck/face region (9/29); overall, most patients had initial sites in the upper body (21/29) (Table I). The majority of patients (16/29) had one CNS lesion at the time of diagnosis by MRI, while others (7/29) had three or more lesions (Table I). All but one patient had metastatic sites outside of the CNS at some point during the study, with seven having five or more metastatic sites other than CNS. The most common site by far was the lung, followed by subcutaneous and bone metastases (11 patients each) (Table I). Two patients had disease confined to the CNS at time of diagnosis and were therefore classified as recursive partitioning analysis (RPA) Class 1, one patient was RPA Class 3, and the other 26 patients were categorized as RPA Class 2 (Table I). Four or more temozolomide cycles after WBR were given to 10 patients, while 6 patients received only one cycle (Table I).

*Other therapies.* The number of patients who received other chemotherapies was as follows: interferon alpha=7, interleukin-2=2, vinblastine=5, cisplatin=5, carboplatin=11, taxotere/paclitaxel/taxol=11, dacarbazine and sunitib/dasatinib=3, fludarabine=2, and lumustine=1. For patients who received interferon-alpha or interleukin-2, these agents were given before temozolomide, over one year before the first dose. For all other therapies, agents were given after temozolomide, with the exception of two patients who received overlapping cycles of vinblastine, cisplatin, and temozolomide due to disease progression during temozolomide therapy.

Table I. *Patient characteristics.*

Characteristic	Number of patients (%)
Gender	
Men	17 (59%)
Women	12 (42%)
Age, years (median)	30-83 (58)
Initial melanoma site	
Head/face*/neck	9
Arm/shoulder	6
Unknown	5
Back	4
Chest	2
Foot	2
CNS	1
Number of metastatic lesions	
1	16
2	2
3	5
>3	7
Number of sites outside CNS	
0	1
1	5
2	5
3	7
4	4
Recursive partitioning analysis results	
1	2
2	26
3	1
Temozolomide cycles after whole brain radiation treatment	
1 cycle	6
2 cycles	7
3 cycles	6
4 or more cycles	10

\*Head and facial locations included lip (1 patient), nose (1 patient), eyelid (1 patient), and scalp (1 patient). Most common sites of non-central nervous system metastasis were as follows: 23 lung, 11 subcutaneous, 11 bone, 9 abdominal (mesenteric), and 8 liver.

In addition, 10 patients underwent craniotomy and 26 patients had stereotactic radiosurgery at some point in their disease course. Three of these patients received stereotactic radiosurgery after WBR, whereas the other 23 patients received stereotactic radiosurgery prior to WBR. Radiosurgery was performed for one lesion in 5 patients, two lesions in 1 patient, three lesions in 3 patients, four lesions in 4 patients, and five or more lesions in 13 patients.

*Side effects.* Seven patients experienced thrombocytopenia; three of these were grade 3 and one was grade 4 CTCAE. Two study patients discontinued temozolomide due to significant side effects, one due to fatigue greater than grade 3 and the other from persistent thrombocytopenia (count <20 k/ $\mu$ L). Notably, all patients with thrombocytopenia had also

Table II. *Side-effects (grade 3 or above) by CTCAE guidelines.*

Toxicity	Number of patients	
	Grade 3	Grade 4
Thrombocytopenia	3	1
Fatigue	1	0
Neutropenia	1	0
Lymphedema	1	0

CTCAE, Common terminology criteria for adverse events.

been treated with interferon, a treatment known to cause thrombocytopenia (9). Other side-effects reported, that were at least grade 3, included leukopenia/neutropenia and lymphedema (Table II). Other reported side-effects that were less than grade 3 included nausea, vomiting, diarrhea, alopecia, fatigue, and numbness. Only the two patients who discontinued temozolomide due to thrombocytopenia and fatigue experienced relief from side-effects. For the majority of patients with more severe side-effects, namely, those who experienced lymphedema and neutropenia, side-effects persisted after discontinuation of temozolomide. It should be noted that side-effects could not be obtained from all patients retrospectively.

*Outcomes.* The estimated median survival time from date of initial melanoma diagnosis was 221.9 weeks (95% Confidence Interval=160.0-459.6 weeks) (Figure 1). The median time between the date of melanoma diagnosis and that of CNS involvement was 43 months; no significant association was found between the survival time and the time between these dates ( $p=0.20$ , by Cox proportional model). The estimated median survival time from the date of diagnosis of CNS melanoma was 44.4 weeks (95% CI=30.6-74.7 weeks) (Figure 2). The PFS was 20.4 weeks (95% CI=16.6-30.9 weeks) (Figure 3). The PFS in patients who underwent craniotomy was 31.2 weeks and 17.1 weeks for those who did not (Figure 4). The estimated median survival from date of CNS melanoma diagnosis in patients who underwent craniotomy was 44.1 weeks and 36.6 weeks for those who did not (Figure 5). No significant survival difference between these two groups was found based on log-rank tests.

## Discussion

There are limited treatment options and a lack of proven effective therapies for patients with brain metastases of melanoma. Once diagnosed, a dismal prognosis exists for the vast majority of patients. Survival depends on several factors, including disease progression, the extent to which it can be controlled, and the patient's overall health. While surgical

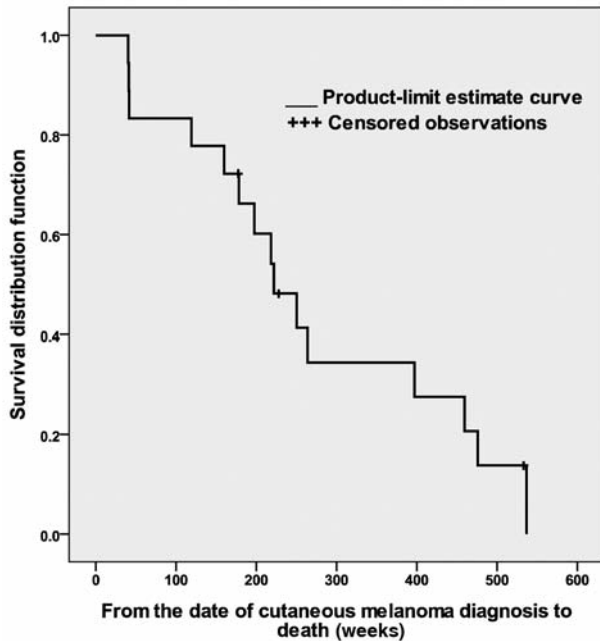


Figure 1. Estimated median survival time from the date of cutaneous melanoma diagnosis. Of the total twenty-nine patients, eighteen patients were included, as nine patients only had the year of diagnosis and two had unknown diagnosis dates. The estimated median survival time from the date of initial melanoma diagnosis was shown to be 221.9 weeks (95% CI=160.0-459.6 weeks).

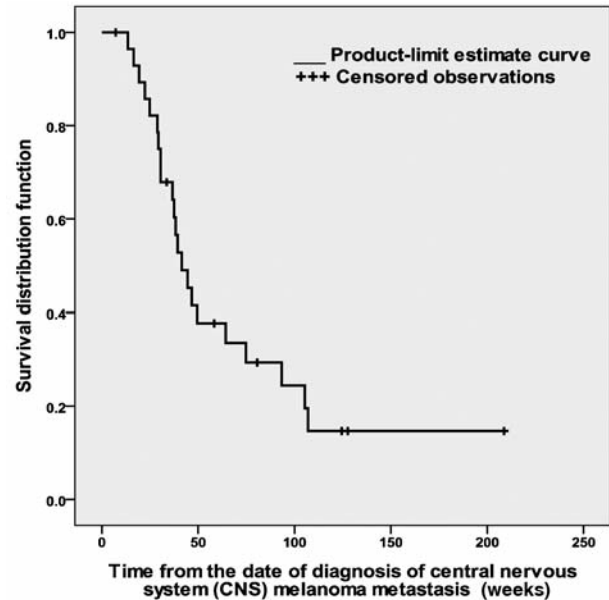


Figure 2. Statistical analysis for survival from the date of diagnosis of central nervous system (CNS) melanoma metastasis. Survival analysis was based on (i) event (death), (ii) time of origin (CNS melanoma diagnosis date), and (iii) last follow-up date (for those who were alive when the study ended). The time between diagnosis date of melanoma and CNS involvement date was about 56 months (mean) (43 months median). No significant association was found between the survival time and the time between the diagnosis and CNS involvement ( $p=0.20$ , by Cox proportional model). The estimated median survival time from the date of diagnosis of CNS melanoma was 44.4 weeks (95% CI=30.6-74.7 weeks).

intervention may be the best option for some patients with fewer metastases, WBR has become the standard of care for patients with multiple lesions. Chemotherapy is often utilized after surgical and radiation treatments have been exhausted. After the standard of care regimen was established for newly diagnosed glioblastoma patients, patients with melanoma brain metastases at the Moffitt Cancer Center are treated with a modified Stupp regimen (3). The two prospective trials for concurrent WBTR with temozolomide used a daily dosing temozolomide regimen that was created prior to the Stupp trial. Although the results of those trials suggested that there was no additional benefit with concurrent temozolomide, we completed our study in order to evaluate the potential benefit to outcome based on a temozolomide regimen that reflects our current practice.

Our study patients had a median PFS of 4.7 months and a median OS of 10.3 months. This is comparable to historical outcomes for such patients who received WBR alone, where the median survival was approximately 4 months (9, 21). A few other studies that compared the efficacy of temozolomide with WBR to controls showed mixed results. One cohort study of 60 patients showed a difference of 4.3 months for temozolomide with WBR and 3.8 months for WBR alone, which was not statistically

significant (22). Another retrospective trial showed a 6-month survival with adjuvant temozolomide after WBR and a 3-month survival without, which was statistically significant (2). A prospective trial evaluating the efficacy of temozolomide in the treatment of brain metastases of melanoma showed a median PFS of 1.2 months and a median survival of 3.5 months in patients who had not received prior chemotherapy (23).

One prospective phase II trial from the Cytokine Working Group used temozolomide in combination with WBR followed by daily temozolomide dosing in 10-week cycles. This trial enrolled 31 patients and showed a median PFS of 2 months and a median OS of 6 months (18). This study was completed prior to the Stupp study (3). Although the patient characteristics (e.g., RPA classification) were similar between our study and the study by the Cytokine Working Group, there was a suggested benefit of concurrent temozolomide with WBR in our study that was not demonstrated in the Cytokine Working Group study. Although multiple potential factors could account for this difference, one important factor may be the difference in the dosing regimens between the two studies.



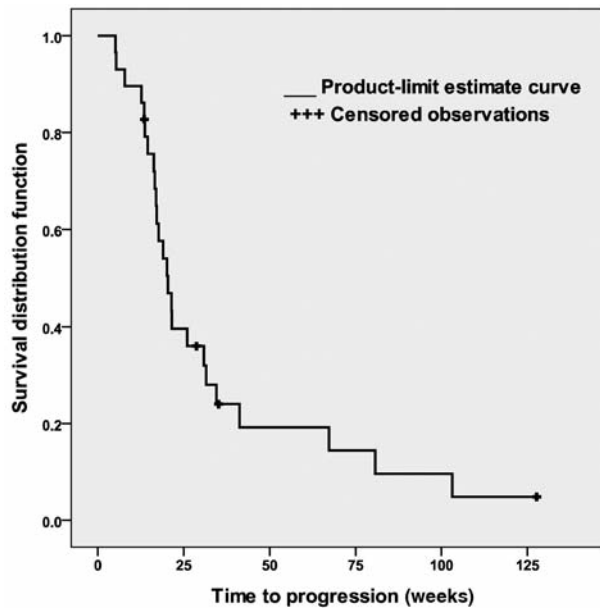


Figure 3. Statistical analysis for progression of CNS disease from initial CNS diagnosis (time to progression). Survival analysis was based on (i) event (CNS progression), and (ii) time of origin (CNS melanoma diagnosis date). The median time to progression of CNS disease was 20.4 weeks (95% CI=16.6-30.9 weeks).

In another prospective phase II trial by the Cytokine Working Group, the same treatment regimen as their prior trial was evaluated but the addition of with thalidomide. This trial enrolled 39 patients and reported a median OS of 17.3 weeks and PFS of 7.4 weeks (19). In addition to the difference in dosing regimens with temozolomide, our retrospective trial did not include patients on thalidomide. These distinctions could partly explain the disparity in side-effect profile and toxicities between our study and theirs. Both Cytokine Working Group trials established a favorable side-effect profile for temozolomide; however, the usage of thalidomide clearly led to additional side effects (18, 19). Moreover, the most prominent side-effects (headache, nausea, vomiting, fatigue, and thrombocytopenia) shown in patients included in our analysis, were comparable to those shown in prior studies involving only temozolomide (9, 11, 18, 23).

In addition to chemotherapy and radiation, surgical resection is often used as a treatment for single metastases to the brain. Studies by Patchell *et al*. noted that there was a modest decrease in mortality when surgery was combined with WBR (24). However, a more recent meta-analysis by the Cochrane Collaboration did not demonstrate a significant improvement in OS in patients with brain metastases who underwent surgical resection with WBR compared to patients who underwent WBR alone. This meta-analysis consisted of three randomized controlled trials, including the 1990

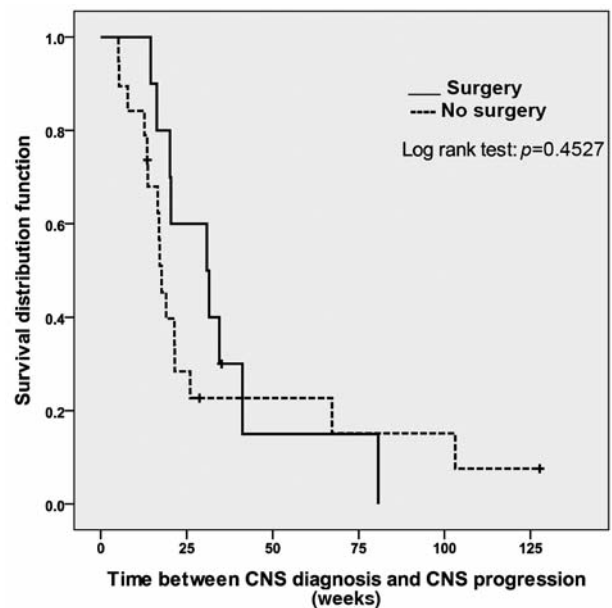


Figure 4. Progression-free survival of patients who underwent craniotomy (n=10, median PFS of 31.2 weeks) and those without resection (n=19, median PFS of 17.1 weeks).

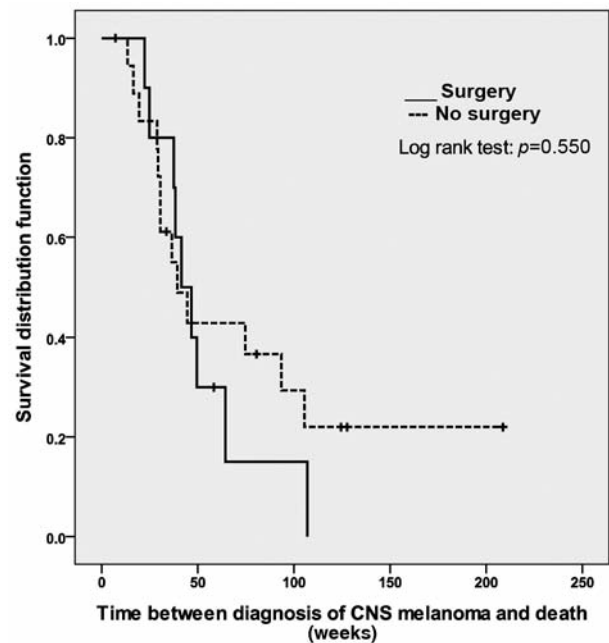


Figure 5. Overall survival of patients who underwent craniotomy (median OS of 44.1 weeks) and those without resection (median OS of 36.6 weeks).

Patchell trial (25). The difference in OS between those who received craniotomy and those who did not in our study was not significant. Thus, surgical resection did not notably impact survival outcomes, although the numbers in our study are too low for definitive conclusions to be drawn.

Our data showed that both OS and PFS of our study patients treated with this combination regimen were increased compared to prior retrospective studies of this patient population (22, 23). However, given the retrospective nature of this study, direct comparisons with prior prospective studies cannot be made. This study is also limited by a small sample size, which did not allow for detailed statistical analyses of factors such as performance status, side-effect duration, treatment, and steroid use.

Our retrospective study was conducted to investigate the important question of whether adding concurrent temozolomide to WBR using a modified Stupp regimen confers improved outcomes with acceptable toxicity. Since the toxicities were not notably increased for patients receiving combination therapy and the outcomes for these patients were comparable to those described in prior studies, it is reasonable to consider a prospective trial with this treatment regimen. In previous studies that examined the combination of WBR and temozolomide, many of the prior trials were retrospective (22, 23), and the two prospective trials for this patient population utilized a treatment regimen that was established prior to the Stupp trial (18, 19). Knowledge of the molecular biology and genetics of metastatic melanoma is constantly expanding, and further exploration with prospective clinical trials that employ molecular markers may lead to improved survival and quality of life for patients suffering from this devastating disease.

## Disclosure Statement

The Authors have no conflicts of interest to disclose.

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