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Precision Medical Approaches to the Diagnoses and Management of Brain Metastases

Ugonma N. Chukwueke, MD[1,2,*]
Priscilla K. Brastianos, MD[3,4]

Address
[*,1]Center for Neuro-Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA, 02215, USA
Email: Ugonma_Chukwueke@dfci.harvard.edu
[2]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 450 Brookline Avenue, Boston, MA, 02215, USA
[3]Department of Medical Oncology, Division of Neuro-Oncology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA, 02114, USA
[4]Department of Medicine, Harvard Medical School, 55 Fruit Street, Boston, MA, 02114, USA

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Opinion statement

Brain metastases represent a common and devastating complication of cancer with survival on the order of a few months in most patients. Melanoma, breast cancer, and lung cancer remain the primary disease histologies with the highest rates of metastatic spread to the brain. The incidence of brain metastases has continued to rise, likely explained by multiple factors. Improvement in progression-free survival in systemic cancer is likely attributable to advances in medical therapy, earlier supportive and symptomatic care, and improved precision around diagnosis and detection. In this context, longer survival and improved extracranial control disease has likely contributed to the increased development of metastatic spread intracranially. The foundation of management remains systemic therapy, as well as a combination of surgery and radiation therapy. In the era of targeted therapies, specific agents have demonstrated improved CNS penetration, however with varying degrees of durable responses. Most patients develop resistance to targeted agents, limiting their duration of use for patients. In this era of personalized medicine, the role of genomic characterization in cancer has been critical in the field of brain metastases, as alterations unique to both the brain metastases and its systemic predecessor have been identified, potentially offering new avenues for therapy.

Introduction

Despite advances in tolerance and durability of systemic therapies, prognosis associated with brain metastases has remained poor. To date, reporting measures have been unable to accurately capture the overall incidence of disease with rates up to 25% based on autopsy series [1]. Brain metastases represent the most commonly occurring neoplasm of the central nervous system (CNS) [2]. Recent work by Aizer et al. has sought to clarify these rates based on specific histology [3]. Among the primary cancer sites with the highest incidence proportion of brain metastases in this defined cohort were melanoma, adenocarcinoma of the lung, and small cell and non-small cell lung cancer [3]. Additionally, the brain has been a common site for deposition of metastatic disease in the CNS, with the spine, leptomeninges, and cerebrospinal fluid comprising smaller percentages of disease [4]. The past decade has seen improvement in progression-free survival from systemic cancers, likely attributable to improvement in systemic therapies, supportive management, and earlier detection of disease given advances in imaging and diagnostic tools [5]. Median overall survival from the time of recognition or diagnosis of brain metastases is based on multiple factors as summarized in the graded prognostic assessment (GPA) and, more recently, the diagnosis-specific graded prognostic assessment (dsGPA). Significant prognostic factors identified in the dsGPA include age, performance status, primary histology, and burden of both intra- and extracranial metastatic diseases [6].

The mainstay of management of brain metastases includes medical/systemic therapy, surgical resection, and radiation therapy such as stereotactic radiosurgery (SRS), fractionated radiation, and whole-brain radiotherapy (WBRT). Achieving intracranial response to CNS-directed medical therapies has proved to be challenging within this context, likely reflecting multiple complexities including circumventing the blood-brain barrier (BBB), systemic toxicity related to drug effects, and drug resistance mechanism such as efflux pumps [7]. Additionally, investigations of various therapies have been limited in brain metastasis patients as they were historically excluded from clinical protocols [8••].

Advances in genomics have heralded a new era in diagnosis and investigation in oncology, specifically in the study of brain metastases. Techniques including next-generation sequencing have allowed for the identification of disease-specific mutations and, as a result, new therapeutic targets. In this review, we will describe well-characterized as well as novel mutations in brain metastases and review the use of genomically guided agents, both in clinical use and in development.

Genomic characterization

Over the past decade, our understanding of the genetic heterogeneity of cancers has evolved with the significant improvement in genomic technology. Within the realm of brain metastases, recent work has demonstrated the genetic divergence of these tumors from their systemic ancestors, likely exploiting new avenues for therapeutics. Notably, novel oncogenic drivers are found in the brain and not in the clinically sampled primary tumor [8••]. While further validation of these findings is underway, it is likely that the genetic heterogeneity between brain metastasis and its tumor of origin, may in part, underlie the differences in treatment responses. Unfortunately, given the inherent neurosurgical risk of repeat craniotomies for brain metastasis resection, obtaining tissue samples have been challenging, and thus, comprehensive genomic characterization has been limited. To this end, ongoing work around surrogate markers of

brain metastases is underway, specifically in improving the sensitivity of liquid biopsies in identifying tumor-associated DNA [9••].

Non-small cell lung cancer

Brain metastases are frequent in patients with non-small cell lung cancer (NSCLC) as up to 50% of patients are at risk for development of brain metastases in their disease course [10]. There is a 5-year cumulative incidence rate of 12.6% of developing brain metastases [11]. The backbone of treatment for brain metastases from NSCLC has included the combination of surgical management, radiation therapy, and systemic agents. While there are a number of cytotoxic agents in use for NSCLC with demonstrated CNS penetration, including various combinations of pemetrexed and platinum-based therapies, the benefit has been modest and without durability over time [12, 13]. Similar to other solid tumors, CSF dissemination of disease is uniformly associated with poorer disease prognosis and often prevents enrollment of patients to clinical protocols. A new era of genomic medicine has now challenged the historical perspectives on outcomes and therapeutic paradigms as the identification of driver mutations in NSCLC has opened up opportunities for front-line use of targeted agents [14•].

EGFR

Epidermal growth factor receptor (EGFR) is part of the erbB family, encoded by erbB-1 (HER1), erbB-2 (HER2), erbB-3 (HER3), and erbB-4 (HER4) and is frequently overexpressed in non-small cell lung cancer (NSCLC) [15–17]. Mutations in epidermal growth factor receptor (EGFR) are found in 15% of NSCLC patients and have been associated with specific features including adenocarcinoma histology, age < 35, women, light or never-smokers, and Asian descent [18]. Presence of the EGFR mutation is now known to confer sensitivity to EGFR tyrosine kinase inhibitors (TKI), thus providing a strong indication for mandatory testing for EGFR on tumors in patients meeting the criteria for possible presence of the mutation [19]. Use of EGFR tyrosine kinase inhibitors (TKI) now represent the standard of care for treatment of patients with metastatic NSCLC and activating mutations in EGFR [20]. In EGFR-mutated patients, initiation of EGFR TKIs in the newly diagnosed setting has led to prolonged progression-free (PFS) when compared to chemotherapy [18, 21–23]. The later generation EGFR TKIs have continued to demonstrate survival benefit in comparison to chemotherapy, both in local and metastatic NSCLC [21].

Erlotinib is a first-generation EGFR TKI which first demonstrated activity in brain metastases from NSCLC. In a retrospective review of 17 patients with EGFR-mutated NSCLC and brain metastases, the objective response rate was 82.4%. In this same cohort, median time to progression (TTP) in the brain in EGFR-mutated disease was 11.7 months as compared to 5.8 months in patients with EGFR-wildtype or unknown disease [24] and overall survival was 12.9 months vs. 3.1 months, respectively. A subsequent phase II trial studied second-line erlotinib in 48 patients with brain metastases, which showed longer median PFS, OS, and intracranial response rate in EGFR-mutant disease when compared to wild type [25].

Afatanib and osimertinib have emerged as later-generation EGFR TKIs demonstrating improved CNS penetration and responses. In the phase III trials, LUX-LUNG 3 and LUX-LUNG 6, afatinib was shown to have increased PFS and objective response rate, when compared to chemotherapy [22, 26, 27]. Differences in OS in both trials were not significantly increased in comparison to chemotherapy. However, in the subgroup of patients with exon 19 deletion, OS and PFS were increased, whereas only PFS was increased in patients with L858 substitution in the afatinib arm [26]. A challenge to the long-term use of EGFR TKIs is acquired resistance, which typically develops after 9–13 months [28]. Specific EGFR mutations most commonly found in resistant cases include exon19 deletions, L858R, and T790, present in 60% of EGFR-mutant cases [27].

In initial and salvage therapy, osimertinib has also demonstrated improvement in central nervous system (CNS) penetration and durable response rates [29•, 30•]. Osimertinib has demonstrated efficacy in the treatment of CNS disease specifically in the context of acquired T790M resistance. A phase III trial of 419 patients with T790M-positive disease randomized to either osimertinib or platinum-based therapy in combination with pemetrexed included 144 patients with brain metastases. In the patients with brain metastases, median PFS was longer in those receiving osimertinib vs. cytotoxic therapy (8.5 months vs. 4.2 months) [30•]. Osimertinib was also found to be better tolerated based on patient reported symptoms [30•].

ALK

Reflecting pattern of disease also seen with EGFR-mutated NSCLC, patients who harbor the fusion of anaplastic lymphoma kinase (ALK) and echinoderm microtubule-like protein 4 (EML4) also tend to be younger, female, with little-to-no history of smoking, and with adenocarcinoma histology. This alteration is present in 3–7% of all NSCLC [31]. ALK tends to be exclusive with other driver mutations including EGFR, KRAS, and ERBB2 [32]. The presence of an ALK translocation predicts sensitivity to ALK inhibitors, thus necessitating mutational testing as part of the diagnostic process.

Crizotinib was the first ALK TKI to gain approval for use in metastatic ALK-mutated NSCLC as it demonstrated improvement in PFS and overall response rate (ORR) in comparison to standard chemotherapy [31]. While much of the current understanding of the role of crizotinib in brain metastases has been derived from retrospective analyses, PROFILE 1014 prospectively assessed first-line crizotinib vs. chemotherapy in patients with stable, previously treated brain metastases [33]. In the crizotinib-treated group, median PFS was 9.0 months as compared to 4.0 months in the chemotherapy group [33]. As with the EGFR TKIs, a challenge to prolonged treatment with crizotinib is acquired resistance. Notably, a subset of patients treated with crizotinib without prior evidence of intracranial involvement progress within the CNS [34].

The next-generation ALK TKIs, ceritinib and alectinib, both of which have shown improved CNS penetration, are now FDA-approved and available for clinical use. ASCEND-4 is a recently completed, phase III trial in which ceritinib was compared to chemotherapy for first-line treatment in patient with ALK-mutant NSCLC. In the 151 patients with baseline brain metastases, median PFS in the ceritinib group was 10.7 months vs. 6.7 months in the chemotherapy group [35]. Intracranial response rate was 72.7 vs. 27.3 in the ceritinib and the

chemotherapy groups, respectively [35]. In three phase III studies, ALEX, J-ALEX, and ALESIA, alectinib was compared to crizotinib in untreated, ALK-rearranged NSCLC. In all three trials, alectinib was associated with either prolonged PFS or reduction in the risk of disease progression or death [36–38]. Alectinib additionally has improved CNS penetration, achieving high brain-to-plasma ratios, intracranial response rates, and delayed risk of CNS progression in patients with baseline brain metastases [38].

Brigatinib is a next-generation ALK TKI with evidence of activity against ALK resistance mechanisms [34]. In a randomized phase II trial, brigatinib efficacy was examined in patients with crizotinib-refractory metastatic ALK-mutant disease at doses of 90 mg daily (arm A) and 180 mg daily (arm B) and 154 of 222 patients had baseline brain metastases. Patients in both arms had similar intracranial response rates with the median duration of intracranial response not yet reached. Median intracranial PFS is 15.6 months [34]. Additionally, brigatinib has also been shown to result in higher intracranial response rates in patients with baseline brain metastases, notably in patients who received prior treatment with crizotinib [39]. Pulmonary toxicity may ultimately limit the use of brigantinib in this patient population.

Breast cancer

Overall, breast cancer is the most common cancer affecting women in the US [40]. Following NSCLC, breast cancer is the second most common cancer leading to brain metastases as well as the second leading cause of cancer-related deaths in the USA [40, 41]. Reflecting broader trends in survival from cancer, in the context of improved and earlier disease detection, better therapies, and timely introduction of symptomatic management, the number of women at risk for development of brain metastases during the course of their disease is expected to increase [42]. The cornerstone of management of both initial and recurrent brain metastases from breast cancer includes surgical resection, radiation (SRS vs. WBRT), and introduction of systemic agents.

In parallel with the tumor/node/metastasis (TNM) classification and histology, breast cancer is additionally characterized by its receptor subtype, which is largely used for predicting treatment response and prognosis. Along with tumor subtype, other factors contributing to prognosis include age < 40, African-American background, presence of lung metastases, and KPS [6, 43, 44]. There are four major tumor subtypes: basal (triple-negative), luminal A (estrogen receptor or ER-positive, progesterone receptor or PR-positive, human epidermal growth factor receptor 2, or Her2-negative), luminal B (triple-positive), and Her2 (ER-negative/PR-negative/Her2-positive). Prior work by Sperduto et al. demonstrated that women with basal subtype disease are most at risk for both CNS relapse and are observed to have a shorter time period from diagnosis of primary disease to development of brain metastases [6]. Median overall survival in this population is less than 6 months [6, 45].

Given the dismal prognosis for brain metastases from breast cancer, there is growing need for identification of clinically actionable targets and therapies for these patients. Recent work has provided growing evidence around the genetic alterations exclusive to the brain metastasis when compared to the clinically sampled primary tumor. Additionally, intriguing results demonstrate that

multiple brain metastases sampled from different regions harbor alterations which are similar to one another and divergent from the primary breast tumor, again reflecting the need for sampling of CNS tissue or urgency for validated assays for which surrogate biomarkers may be identified.

Her2

Human epidermal growth factor receptor 2 or Her2 is overexpressed in approximately 20–30% of breast cancers [46]. Prior work has reported brain metastases in > 50% of women with Her2-positive breast cancer and decrease in overall survival [45, 47]. Overexpression of Her2 has been predictive of response to Her2-directed drugs including trastuzumab, pertuzumab, ado-trastuzumab emantasine, and lapatinib, with demonstration of improved outcomes in woman with metastatic breast cancer and CNS disease (both parenchymal and leptomeningeal involvement) [48]. RegistHER was an observational study examining the incidence as well the factors determining outcomes in women with Her2-positive breast cancer and brain metastases. In the analyzed cohort of 1,012 patients, about 1/3 of women had CNS metastases. The factors identified suggesting risk of development of brain metastases included younger age, higher disease burden, and negative ER/PR status [49]. In women who received trastuzumab, median survival following diagnosis of CNS metastases was 11.6 months vs. 6.1 months in comparison to women who did not receive trastuzumab, also reflecting previously reported statistics [49]. Potential extension of the role of trastuzumab to intrathecal administration is now under investigation for management of leptomeningeal disease [4].

Small molecule inhibitors including lapatinib and neratinib have been investigated for their roles in halting cancer cell survival and proliferation [50]. Lapatinib, specifically, has been studied in combination with temozolomide as part of a phase I trial of 16 women with Her2-positive disease and progressive brain metastases. Stable disease was achieved in 10 patients [51]. In the LANDSCAPE trial, 45 women with Her2-positive disease and untreated brain metastases were treated with both lapatinib and capecitabine. Partial responses were observed in 29 of 44 patients with median time to progression of 5.5 months and overall survival at 6 months of 91% [52]. Neratinib is a dual-kinase inhibitor approved for adjuvant treatment following trastuzumab for early HER2-positive breast cancer [53]. It has not yet shown improvement in PFS or intracranial response rates in the setting of brain metastases [53].

Other mutations (CDK pathway)

Whole-exome sequencing of 21 women with various hormone receptor and Her2 status revealed frequent alterations of the CDK and PI3K pathways [8••]. The PI3K pathway is frequently altered in brain metastases from breast cancer with changes often unique to the brain metastasis [8••]. These findings suggest the potential for use of CDK and PI3K inhibitors as a therapeutic avenue for treatment of brain metastases with these genetic alterations.

Abemaciclib is an oral CDK inhibitor FDA-approved for initial treatment of postmenopausal women with HR-positive, HER2-negative breast cancer, as shown in the phase III study MONARCH 3 [54]. It has also

now been used in the management of HR-positive, HER2-negative breast cancer brain metastases [54].

Melanoma

Melanoma is the third most frequent of the solid tumors to lead to brain metastases, following lung and breast, accounting for 10% of all patients with brain metastases [55]. Estimates predict that up to 75% of patients with metastatic melanoma will have evidence of CNS involvement determined at the time of autopsy [56]. Neurologic morbidity associated with melanoma is significant, namely due to the propensity of melanoma-related brain metastasis to bleed, leading to permanent deficit including neurocognitive decline and poor quality of life [57]. Longer duration of disease is associated with development of brain metastases in advanced melanoma. Median overall survival from the time of diagnosis of melanoma brain metastasis is 4 months [56]. Factors associated with shorter survival include active extracranial disease, greater than three brain metastases, poor performance status, and CSF dissemination [58]. v-Raf murine sarcoma viral homology or *BRAF* has been found as a contributing factor to earlier disease onset and more aggressive phenotype [59].

BRAF and *MEK*

The traditional treatment paradigm in management of melanoma brain metastases included surgery (for solitary or symptomatic brain metastases), radiation (SRS vs. WBRT), and chemotherapy. Over the past decade, advances within genomics has led to the identification of disease-specific alterations. v-Raf murine sarcoma viral homology or *BRAF* is a driver mutation found in up to 50% of advanced melanoma patients, occurring more frequently in younger patients [60]. The majority of *BRAF* mutations are the result of a single substitution of valine to glutamate at codon 600 (V600E), comprising 80%; valine for lysine at codon 600 occurs at a frequency of 14% [61]. Thus far, the presence of *BRAF* mutations is not predictive of or associated with increased risk of development of brain metastases [62].

Vemurafenib and dabrafenib are currently two FDA-approved BRAF-inhibitors for treatment of melanoma brain metastases. Vemurafenib demonstrated a survival benefit when compared to dacarbazine. Additionally, in patients with intracranial disease, use of vemurafenib resulted in an intracranial response rate of 71% in comparison to historical controls [63]. BREAK-MB was a phase II trial investigating the response to dabrafenib in patients with *BRAF*-mutated advanced melanoma in untreated or previously treated disease. Both groups were found to have increased intracranial response rate of 30% as well as improvement in both PFS and OS [62].

MEK or mitogen-activated protein kinase is a downstream of *BRAF* in the MAP kinase pathway. MEK inhibitors are now routinely used in combination with BRAF inhibitors in patients with *BRAF V600E*–mutated metastatic melanoma. In addition to the combination regimens discussed here, investigation of newer BFAF/MEK agents encorafenib and binimetinib in brain metastases are ongoing [64••].

Immunotherapy

Interleukin-2 (IL-2) had early success in the management of metastatic melanoma, however with associated severe toxicity [65••]. Checkpoint inhibitor therapy including nivolumab and pembrolizumab (PD-1 inhibitors) and ipilimumab (CTLA-4 inhibitor) have demonstrated more durable responses, resulting in prolonged overall survival. Ipilimumab has shown activity in patients with brain metastases. In 51 patients with asymptomatic brain metastases not on corticosteroids, 12 patients had either stable disease or partial response [66]. In the cohort of 24 patients with symptomatic intracranial disease, one patient was found to have a complete response and another was shown to have stable disease [66]. Preliminary work had demonstrated more profound responses with use of anti-PD1 agents, specifically nivolumab either as monotherapy or in combination with ipilimumab [67••]. A recently completed, randomized phase II study comparing nivolumab monotherapy with nivolumab followed by combination of ipilimumab and nivolumab in patients with metastatic melanoma showed higher rates of intracranial response with a trend towards longer intracranial progression-free survival [68]. In another phase II study of nivolumab and ipilimumab in 94 patients with metastatic melanoma and untreated brain metastases, intracranial response was noted in more than half of patients who were treated [69].

Small cell lung cancer

Brain metastases occur frequently in small cell lung cancer (SCLC) patients, with a 5-year cumulative incidence (CI) of 29.7% [11]. In patients with limited-stage SCLC (disease limited to ipsilateral hemithorax) with complete response to upfront chemotherapy, prophylactic cranial irradiation (PCI) is indicated given its efficacy in improving overall survival and decreasing incidence of brain metastases [70]. In the context of extensive-stage SCLC, the efficacy of PCI on overall survival is less certain; however, it is established in decreasing incidence of symptomatic brain metastases [71]. Despite aggressive therapies, SCLC is likely to recur in most patients [72].

Unlike in NSCLC, frequent driver mutations targetable by molecular agents have yet to be identified in SCLC. Efforts in comprehensive genomic characterization are underway. In primary SCLC, the *NOTCH* family of genes have been found to be critical regulators of neuroendocrine differentiation [72]. Alterations which have been established in other cancers were found, however only infrequently, such as *BRAF* and *KIT* [72]. Ongoing work-around investigating unique alterations in brain metastases from SCLC is in nascent stages. Prior characterization of brain metastases from SCLC taken from 15 patients showed upregulation of *PDGFRB* and *ANGPTL4* with downregulation of *TGFB1* [73]. Validation and discovery of other candidate mutations is necessary to advance this work.

Colorectal cancer

As with other gastrointestinal cancers, colorectal cancer (CRC) infrequently metastasizes to the CNS, with a reported incidence rate of 1–2% in primary

disease and 3–5% in metastatic CRC [74–77]. Given improvement in outcomes relative to survival from systemic disease, it is likely that the incidence of brain metastases may rise [72]. Although the incidence of disease is low, there have been ongoing investigations around potential factors which may predict development or recurrence of CRC within the brain. Factors identified include presence of lung metastases, long survival, rectal involvement, and metachronous metastatic disease [75]. In this same cohort of 531 patients, sequencing of the primary tumor and the brain metastases was performed on 407 patients, with results suggesting a trend towards mutations involving *PIK3CA* and *BRAF* being potential risk factors for brain metastases, however without achieving statistical significance [75]. Other work has demonstrated the role of *RAS* oncogene mutations in aggressive tumor biology and development of brain metastases [76–78]. Co-occurrence of *RAS* and *PIK3CA* mutations have been associated also with a more aggressive disease phenotype [79].

Gynecologic cancer

Gynecologic malignancies including cancers of endometrial, ovarian, and cervical origin are among the rarest of tumors to metastasize to the CNS. As seen with other primary tumors, with improved outcomes around progression-free survival from systemic disease, the incidence and detection of brain metastases are expected to rise. The prognosis following diagnosis of brain metastases is poor with median overall survival of 0.5–2 months in the absence of treatment [80–82, 83]. Overall survival has been found to be higher in patients with solitary brain lesions without evidence of other disease, following maximum therapy of surgery and WBRT [82]. To date, few clinical actionable mutations in brain metastases have been found.

Renal cell carcinoma

Brain metastases occur in ~ 10% of patients with renal cell carcinoma (RCC) [11, 84]. Consistent with patterns observed in the field of oncology, earlier and more precise diagnostic tools have correlated with increased incidence of disease and likely improved overall survival outcomes from the standpoint of systemic disease [85]. Unfortunately, median OS following diagnosis of BMs in RCC continues to remain poor. Historically, this has been attributed to limited CNS penetration of systemic agents and the radioresistance of BM from RCC [86]. Additionally, factors associated with poor outcomes include Karnofsky Performance Scale (KPS) < 60, short diagnosis to treatment time, and > 3 sites of brain metastases [87].

Evolution of the collective understanding of the underlying molecular biology of RCC has paved the way for identification of agents which target angiogenesis, including vascular endothelial growth factor (VEGF) and their corresponding receptors. While these agents have been approved for use in advanced RCC, patients with BMs have been excluded from most clinical trials. In a retrospective review, 338 patients treated with tyrosine kinase inhibitor (TKI), those treated prior to development of BMs, were found to have a reduced incidence of BMs as well as improved OS [88]. This investigation was limited

by multiple factors including patient heterogeneity, lack of randomization, and selection bias [88].

The PI3K/AKT/mTOR has also been established as a critical signaling pathway in tumorigenesis. Recent work has identified alterations exclusive to the BM not found in the primary RCC tumor, including mutations in *PTEN* and *PIK3CA* [8••].

Conclusion

As collective understanding of the molecular and genomic underpinnings of brain metastases continue to grow, management of this unfortunate and devastating complication of systemic cancer will hopefully improve. While the mainstay of therapy has historically been local surgery and radiation therapy, the identification of critical alterations is informing additional options for treatment, with the goal of reducing morbidity and improving survival.

Compliance with Ethical Standards

Conflict of Interest

Ugonma N. Chukwueke declares that she has no conflict of interest. Priscilla K. Brastianos has received research funding from Merck, Pfizer, and Bristol-Myers Squibb and has received compensation from Genentech-Roche, Merck, Lilly, TESARO, and AngioChem for service as a consultant.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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