Breast Cancer Research and Treatment (2019) 177:277–294
https://doi.org/10.1007/s10549-019-05317-6

REVIEW

Breast leptomeningeal disease: a review of current practices and updates on management

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Received: 30 May 2019 / Accepted: 7 June 2019 / Published online: 17 June 2019

Abstract

Purpose Leptomeningeal disease (LMD) is an advanced metastatic disease presentation portending a poor prognosis with minimal treatment options. The advent and widespread use of new systemic therapies for metastatic breast cancer has improved systemic disease control and extended survival; however, as patients live longer, the rates of breast cancer LMD are increasing.

Methods In this review, a group of medical oncologists, radiation oncologists, radiologists, breast surgeons, and neurosurgeons specializing in treatment of breast cancer reviewed the available published literature and compiled a comprehensive review on the current state of breast cancer LMD.

Results We discuss the pathogenesis, epidemiology, diagnosis, treatment options (including systemic, intrathecal, surgical, and radiotherapy treatment modalities), and treatment response evaluation specific to breast cancer patients. Furthermore, we discuss the controversies within this unique clinical setting and identify potential clinical opportunities to improve upon the diagnosis, treatment, and treatment response evaluation in the management of breast LMD.

Conclusions We recognize the shortcomings in our current understanding of the disease and explore the future role of genomic/molecular disease characterization, technological innovations, and ongoing clinical trials attempting to improve the prognosis for this advanced disease state.

Keywords Leptomeningeal disease · Neoplastic meningitis · Leptomeningeal carcinomatosis · Breast cancer · Intrathecal chemotherapy · Intrathecal trastuzumab

Introduction

Leptomeningeal disease (LMD), also known as neoplastic meningitis or leptomeningeal carcinomatosis, is broadly defined as infiltration of tumor cells into the meninges surrounding the brain and spinal cord. The three most common types of cancer associated with LMD are lung, melanoma and breast cancers [1]. In breast cancer, it is estimated that 5–16% of patients will develop central nervous system (CNS) metastases [2, 3], of which 10–25% will develop LMD [4–6]. The rarity of the disease along with the poor clinical performance of patients at time of LMD diagnosis makes it difficult to conduct large randomized trials. Therefore, prospective data for breast cancer LMD management is limited. In this review, we summarize the current evidence and management strategies to help guide treatment of breast LMD.

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Pathogenesis/epidemiology

The cerebrospinal fluid (CSF) is not a common site of metastases. The CSF's acellular, mitogen-poor microenvironment is hostile to tumor cells impairing disease migration, implantation, and proliferation. Attempts to understand the pathogenesis of LMD have focused on understanding the routes of metastatic spread and the biological risk factors within the disease itself predisposing particular cells to metastasize to the meninges.

The metastatic spread of breast cancer to the leptomeninges is believed to be due to dissemination via hematogenous and lymphatic channels as well as tumor cell shedding into the CSF from adjacent CNS disease [7, 8]. The development of LMD has been associated with concurrent presence of brain metastases in 30–50% of patients [9, 10]. Furthermore, surgical excision of intracranial lesions may increase the risk for leptomeningeal seeding, especially if the ventricles are violated [11]. This risk has been shown to be mitigated with radiotherapy following surgical excision [12]. For patients without concurrent brain metastases, the most common site for systemic metastases is within the vertebrae suggesting the potential for direct extension of the spinal tumor into the CSF or dissemination into the intervertebral/paravertebral venous plexus [8, 13].

The incidence of LMD in breast cancer varies between histologic and molecular subtypes [14] indicating the presence of tumor-specific biological risk factors. Triple-negative breast cancer has the highest propensity of all molecular subtypes for meningeal spread comprising approximately 30–40% of breast LMD [14]. In addition, triple-negative breast cancers often have the shortest interval to LMD development and commonly present as the first site of metastatic disease [15]. Median overall survival (OS) from diagnosis of LMD has been shown to be worse with triple-negative and invasive lobular breast cancers [6, 14, 16].

Lobular breast cancer accounts for about 35% of all cases of breast cancer LMD, but interestingly, only 7% of lobular breast cancers develop intracranial parenchymal disease suggesting a higher propensity for lobular breast cancer to spread to the leptomeninges [15]. This is supported by postmortem cadaver studies finding LMD in 12–16% of patients with lobular carcinoma compared to 0.5–5% for those with ductal carcinoma [17, 18]. It is believed the loss of E-cadherin, which is reported in over 90% of lobular breast cancers, is one of the main reasons for the high incidence of LMD in this histologic subtype [15]. The E-cadherin-catenin complex is necessary for normal cellular adhesion and structural cytoarchitecture [19]. As downregulation of E-cadherin has been associated with increased risk of distant metastases, the E-cadherin complex may represent a potential target for future therapies [20].

A recent paper by Boire et al. [21] has significantly advanced our understanding of the critical role of complement component C3 in the development of LMD. They found complement component C3 to be necessary for the proliferation of metastatic disease within the leptomeningeal space for a number of primary diseases. The researchers methodically described the mechanism of tumor-derived C3 activating C3a receptors within the choroid plexus epithelium, disrupting the blood–CSF barrier, and allowing mitogenic factors to enter the CSF. Increased complement C3 levels in the CSF were found to be predictive for LMD when compared to patients with intracranial parenchymal metastases without concurrent LMD and patients without CNS disease. Furthermore, there is emerging preclinical evidence that C3 inhibition may be able to decrease rates of LMD potentially offering a novel target in the treatment of LMD.

Diagnostic evaluation

There is currently no gold standard in the diagnosis of LMD. Diagnosis requires the combination of cytologic analysis, radiographic imaging, and thorough neurologic assessment. The lack of a standardized diagnostic tool with both a high sensitivity and specificity has led to differing LMD definitions between studies—further increasing the complexity when attempting to compare interventional trials in the treatment of LMD.

Historically, LMD presented with the onset of neurologic deficits followed by rapid clinical deterioration. Patients commonly present with headaches, nausea/vomiting, gait difficulties, cranial nerve deficits, seizures, motor/sensory dysfunction, and mental status changes depending on the disease burden and its anatomical distribution. Symptoms can be either secondary to increased intracranial pressure from obstructive hydrocephalus (and relieved with intervention) or due to disease infiltration of the neurologic tissue requiring urgent treatment. As more sensitive and frequent MRIs are being performed, the rates of asymptomatic LMD are increasing allowing clinicians the opportunity to initiate treatment prior to the onset of symptoms.

When there is clinical concern for LMD, it is necessary to perform a CSF evaluation. Cytologic analysis has a specificity > 95% with a positive test being diagnostic for LMD; however, the sensitivity is relatively poor with tumor cells being identified in only 45–75% of patients with known LMD [22–24]. The sensitivity of CSF analysis can be affected by limited sample size or delays in processing. Additional measures that can be taken to improve sensitivity include obtaining an adequate sample size (at least 5 ml), processing the CSF fluid within 30 min of collection, and avoiding hemorrhagic contamination [1]. Repeating CSF collection and cytology up to 3 times can raise the sensitivity

to 80–90% [1, 15]. In the setting of negative CSF studies, the presence of nonspecific abnormalities, such as increased opening intracranial pressure, leukocyte count, protein concentration and decreased glucose concentration may increase the clinical suspicion for meningeal disease involvement [1, 15, 25].

In addition to CSF examination, imaging is critical for adequate LMD evaluation. A T1-weighted MRI with gadolinium contrast [1, 15, 25] of the entire neuroaxis is necessary in order to evaluate both the brain and spine. There are no studies comparing the concordance rate of LMD diagnosis between MRI imaging and autopsy specimens, but estimates of MRI sensitivity range from 53 to 80% [1, 25–27]. Radiographic findings concerning for LMD include sulcal enhancement or obliteration, linear or nodular ependymal enhancement, and cranial or spinal nerve root enhancement (Fig. 1). Computed tomography (CT) imaging is significantly inferior in the evaluation of LMD and should only be utilized for those patients who cannot undergo MRI [28].

There have been efforts to identify useful diagnostic CSF biomarkers for LMD. Early attempts have evaluated several potential biomarkers including cancer antigen 15.3 (CA15.3) [29], β2-microglobulin [30], carcinoembryonic antigen [31], and vascular endothelial growth factor [32, 33]; but they have not yet been implemented into widespread clinical use due to either poor sensitivity/specificity or lack of clinical validation. There is promising research into the role of liquid biopsies using CSF circulating tumor cells (CTCs) and tumor DNA in the diagnosis and assessment of treatment response for LMD. Anti-epithelial cell adhesion molecules (EpCAM) antibodies detect CTCs within the CSF with a 76–100% sensitivity and 85–100% specificity [34–36]. Furthermore, EpCAM-based CTC assays are able to measure the number of tumor cells within a given CSF volume potentially allowing the ability to quantify LMD treatment response. Early research is also looking into the role of CSF ctDNA [37]. Cancer cells shed ctDNA into the serum and CSF as they undergo apoptosis and necrosis. Compared to plasma, the CSF has less circulating noncancerous genomic DNA increasing the signal-to-noise ratio for ctDNA within the CSF [38, 39]. With advancements in next-generation sequencing, early data suggests ctDNA may be a more sensitive method to detect LMD than CSF cytology [38]. Furthermore, CSF ctDNA analysis could potentially discern clonal, genetic differences between the primary breast tumor and metastatic LMD to identify potential therapeutic targets [40]. The Response Assessment in Neuro-Oncology (RANO) Leptomeningeal Metastasis and the RANO Brain Metastasis Working Group recently reviewed the current role of liquid biopsies in CNS metastases and proposed several clinical opportunities for future research, such as improving diagnosis rate, assessing for residual tumor following resection, measuring response to radiotherapy, and distinguishing pseudoprogression from radionecrosis [41].

Prognosis

LMD in solid tumors is notoriously associated with a poor prognosis. Median survival averages 6–8 weeks without malignancy-specific treatment; however, survival may be improved beyond a few months with personalized treatment plans. On average, the life expectancy for patients with LMD in breast cancer is 1.75–4.5 months [1, 6].

While various prognostic markers (i.e. age at diagnosis, histology, grade, and hormone receptor status) have been proposed, there is not a clear consensus on a uniform prognostication score [10, 42–44]. Thus far, the most important

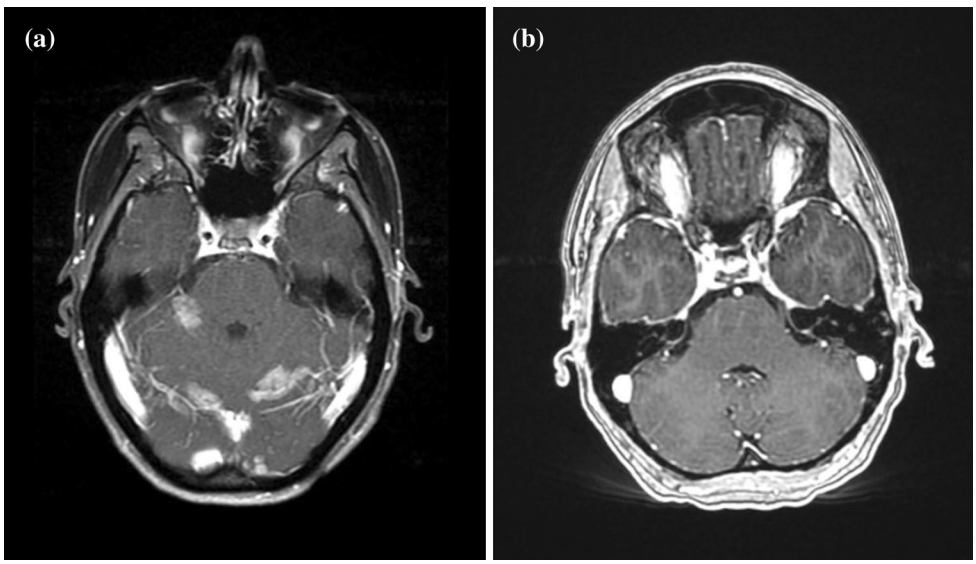

Fig. 1 Axial slice of T1-weighted MRI with contrast following **a** diagnosis of multifocal nodular areas of leptomeningeal tumor involving the left cerebellum, right cerebellum, and left occipital cortex and **b** complete response 4 months following treatment with intrathecal trastuzumab

prognostic factor for patient outcomes is performance status at the time of LMD diagnosis ([16] [45]. One retrospective study attempted to develop a prognostic score using hormone receptor status, performance status, number of prior chemotherapy lines, and cytokeratin-19 fragment (CYFRA 21-1) levels, but this has yet to be validated [43].

Assessing response

As discussed earlier, there is no true gold standard in LMD diagnosis. Without a verified and reproducible sensitive test, it is difficult to confidently evaluate treatment response. Among the few randomized clinical trials completed in LMD, primary endpoints have ranged from overall survival, neurologic response rate, time to neurologic progression, and progression-free survival (PFS). Early studies looking at LMD in all malignancies defined complete response as negative CSF cytology and stability of neurologic symptoms/signs [46–48]. More recent trials have incorporated MRI imaging in the overall response criteria using a combination of clinical assessment, neuroimaging, and CSF cytology, but response criteria continues to vary among studies [45, 49, 50].

In response to the ambiguity and differences in evaluating response between studies, the RANO Leptomeningeal Metastases Working Group recently published a standardized consensus on treatment response for LMD [51] (Table 1). The group recommended the use of CSF cytology, contrast enhanced MRI imaging of the entire neuroaxis, and detailed neurologic assessment using a standardized evaluation form to be filled out at diagnosis and follow-up visits.

Clinical response

In the only randomized clinical trial for breast cancer LMD, response was based on clinical assessment only [49]. Response was defined as meaningful neurologic improvement of at least one symptom/sign without decline of another neurologic symptom/sign, while progression was defined as worsening of at least one symptom/sign or occurrence of new neurologic symptom/sign. These assessments are criticized as subjective and not reliable. This is especially difficult considering the disease, treatment, and concurrent brain metastases can cause changes in neurologic symptoms and signs. The RANO group recommends a standard evaluation form be filled out at diagnosis and follow-up visits. These criteria do not apply to patients with concomitant brain metastases, extracerebral disease progression, or treatment-related toxicity [1].

Neuroimaging response

Cerebrospinal MRI is the preferred imaging for baseline assessment and monitoring of LMD. There continues to be no role for MR spectroscopy, MR perfusion, or PET in the follow-up of LMD. Randomized clinical trials have not consistently reported MRI criteria for disease response [45, 48, 50]. Quantitative assessment on imaging is logistically difficult due to the small volume, structure complexity, and difficulty in reliable measurements of LMD lesions. Specifically, given the difficulty and subjective nature of radiographic response without discrete measurable lesions as seen with brain parenchymal disease, the group recommended to categorize response as progressive, stable, or improved. Thus, the RANO group proposed an MRI grid for the assessment of radiographic response [1]; however, recently the RANO leptomeningeal metastases group found neuroradiologists failed to arrive at consensus and concordant ratings. Therefore, the scorecard was determined to be inadequate for clinical trials and not feasible for widespread adoption. In response to their findings, the RANO group proposed a revised, simplified imaging response scorecard that requires future validation [51].

Table 1 Response determination in leptomeningeal metastases

Assessment	Treatment response	Progressive or refractory disease			Stable disease
		Neurological examination defined disease progression	CSF defined disease progression	Radiologic defined disease progression	
Neurologic exam	Improved	Worse	Stable	Stable	Stable disease
CSF flow cytometry	Negative	Negative	Positive	Negative	Negative or positive
CNS imaging	Definite improvement	Stable	Stable	Definite worsening	Stable or equivocally worsening or improved
Symptom assessment	Improved	Worse or stable	Worse or stable	Worse or stable	Stable

CSF cytology negative defined as either true negative or atypical. CSF cytology positive defined as true positive or suspicious. Stable defined as stable or indeterminate. Modified from Chamberlain et al. [118]

CSF cytology response

There is also no consensus for the classifications of disease response using CSF cytology with varying definitions of cytologic response between randomized clinical trials. Some believe that quantification of CSF cytology would be useful for assessing response (e.g. compare percentage of CSF malignant cell count), but this is not routinely available in clinical laboratories and lacks endorsement [45, 48, 50].

The RANO group recommends standard CSF cytology results be placed into two groups: negative/atypical versus positive/suspicious. This has been criticized as too complex for clinical use [1]. Therefore, the three categories widely accepted for use are positive, equivocal, and negative. Conversion of a previously positive to a negative CSF response must be maintained for at least 4 weeks to be considered a complete response [1, 45, 48, 50].

Evaluations of response (e.g. clinical, imaging, and CSF) should be performed at baseline, every 2 months for the first 6 months, and every 3 months thereafter in stable patients. If there is clinical suspicion of disease progression, imaging and CSF analysis should be repeated at that time.

Treatment

Currently, there is no accepted standard of care for breast cancer LMD. Due to the relative infrequency of LMD and patients' poor clinical status at time of diagnosis, substantial prospective clinical data is lacking. Furthermore, the few prospective studies performed oftentimes combine patients of various histologies, including both hematologic and solid tumor malignancies, to achieve the necessary study power for statistical analysis at the cost of introducing confounding variables. Given these limitations, the EANO–ESMO guidelines on LMD are explicit that their recommendations are based on expert clinical opinion rather than clinical trial evidence [1].

In comparison to parenchymal brain metastases which can be treated with local therapy (i.e. surgery and/or radiotherapy), the diffuse nature of LMD places the entire neuroaxis at increased risk for recurrence thereby minimizing the effectiveness of any local treatment. Therefore, each patient diagnosed with breast cancer LMD requires a thoughtful multidisciplinary and multimodality treatment approach with the combination of systemic therapy, radiotherapy, intrathecal therapy (IT), and/or supportive care individualized to a patient's particular disease, clinical status, and treatment goals.

Role of the blood–brain barrier

The combination of the blood–brain and the blood–CSF barrier restricts the delivery of anticancer medications from the blood into the CNS. While the blood–brain barrier (BBB) aligns the entire vasculature of the CNS, the blood–CSF barrier is specifically located at the choroid plexuses where blood is filtered to (1) form CSF (at a rate of 100–150 ml/day) and (2) maintain homeostasis between the CSF and plasma. Together, the two form a semi-permeable barrier that selectively allows for the passage of particular solutes into the CNS while simultaneously prohibiting others, such as neurotoxic agents—even if CNS penetration with intentional cytotoxins (i.e. chemotherapy) is desired. Drug-specific factors such as percent of protein binding, molecular weight/size, and lipid solubility all contribute to its ability to cross the BBB. Along with preventing the passage of cytotoxins into the CSF, the BBB has active-transport adenosine triphosphate pumps to efflux any solutes from the CSF that may have improperly crossed the BBB. Between these processes, the CNS is a chemotherapy-naïve sanctuary site within the body where metastatic disease can evade systemic agents and proliferate unabated. Interestingly, LMD itself has been shown to infiltrate and disrupt the normal cytoarchitecture and organization of the meninges increasing the permeability of the BBB for systemic agents; however, CSF concentrations of systemic agents oftentimes remain subtherapeutic despite the presence of LMD.

Various attempts have been made to improve the CNS penetration of anti-neoplastic agents for the management of LMD. Two approaches have been to (1) directly administer the agent within the CSF to bypass the BBB or (2) radiate the brain to increase the permeability of the BBB. Along with treating the disease, whole-brain radiation therapy (WBRT) has been shown to disrupt the organization of the BBB and increase the CSF concentration of systemic agents [52].

Principles of intrathecal treatments

IT offers the opportunity to achieve therapeutic dose-levels throughout the CSF potentially treating the entire surface area of the neuroaxis. IT is dependent on nonobstructed CSF circulation to ensure diffuse distribution of the drug. There is emerging evidence that LMD is a heterogeneous entity with improved survival outcomes for patients with a nodular disease compared to those with the classical, 'sugar-coated' radiographic appearance [53]. Intrathecal monotherapy theoretically may not be ideal in treating nodular LMD as intrathecal agents are only able to diffuse 1–5 mm into the subependymal tissue [54, 55].

Intrathecal therapies may be administered via either repeated lumbar punctures or through an implanted intraventricular catheter system with a subgaleal reservoir, called an Ommaya reservoir. As intrathecal therapies require repeat access to the CSF, the EANO/ESMO guidelines recommend practitioners use the intraventricular approach due to the ease of use and improved patient tolerance. Repetitive lumbar punctures increase the risk for post-procedural complications, such as bleeding, infections, and post lumbar puncture headaches along with requiring the patient to remain in the supine position for 1 h following each procedure [55].

IT is not recommended for patients with obstructive hydrocephalus. CSF flow studies using radionucleotide-tagged ventriculograms may help identify sites of LMD causing abnormal CSF circulation in nearly 70% of patients without MRI-evidence of obstruction or elevated intracranial pressure [56, 57]. Radiotherapy should be considered to treat the obstructive site and potentially restore CSF circulation prior to initiating IT.

Intrathecal therapy delivery

IT is a theoretically attractive treatment option for breast cancer LMD, but prospective clinical data is scarce with most data guiding current treatment decisions derived from observational retrospective studies. Therefore, the optimal intrathecal treatment paradigm in the management of breast cancer LMD is currently unknown. One of the first studies evaluating the feasibility and potential efficacy of intrathecal treatments was performed by Wasserstrom et al. in [24]. Retrospectively reviewing a total of 90 patients, of which 46 had breast cancer, nearly half experienced an improvement in their neurologic symptoms following initiation of intrathecal chemotherapy. In a disease with historical overall survival of 16 weeks, the authors reported a median survival of 5.8 months with a handful of patients demonstrating survival > 12 months. It was one of the first studies to demonstrate intrathecal agents can improve a patient's neurologic clinical status, and in a subset of patients, potentially improve overall survival.

Currently, the commonly used agents for intrathecal chemotherapy are methotrexate, thiotepa, and cytarabine [58, 59]. The optimal dosing, frequency, and duration for each agent has yet to be determined. Intrathecal methotrexate and thiotepa are commonly prescribed to 10–12 mg twice a week for 4 weeks, weekly for 4 weeks, then every two weeks or monthly thereafter dependent on CSF response to treatment. Liposomal cytarabine (i.e. depocyt) is preferred to free cytarabine due to its increased efficacy, ease of use, and an extended half-life of 140 h within the CSF, only requiring administration every 2 weeks. Prior to each intrathecal drug administration, a volume of CSF (equal to the volume of drug solution to be administered) should be removed and sent for cytologic analysis to continue to monitor treatment response.

Prospective intrathecal trials

There are only four randomized prospective trials evaluating the role of intrathecal chemotherapy in solid tumors, all of which were multi-institutional open label trials (Table 2). Only one included strictly breast cancer LMD. Statistical analysis by histology was not performed for the remaining three randomized trials, confounding the ability to make conclusive recommendations for those patients with breast cancer LMD.

One of the initial prospective randomized trials was performed by Grossman et al. The study randomized 59 patients (25 with breast cancer) to receive either intrathecal methotrexate (10 mg) or intrathecal thiotepa (10 mg) twice weekly. The efficacy of both treatments were poor with a median survival of 15.9 and 14.1 weeks, respectively. Of note, treatment arms were well balanced, except that more patients randomized to methotrexate had breast cancer (61% vs. 33%) [45].

Glantz et al. analyzed 61 patients (22 with breast cancer) with LMD who were randomized to receive six doses of intrathecal depocyt (50 mg) or sixteen doses of intrathecal methotrexate (10 mg) over 3 months. There was no significant difference in response rates (26% vs. 20%, $p = 0.76$) or median overall survival (105 vs. 78 days, $p = 0.15$). However, there was evidence of improved median time to neurological progression (58 vs. 30 days, $p = 0.007$) and potentially improved median neoplastic meningitis-specific survival (343 vs. 98 days, $p = 0.074$) with intrathecal depocyt [47].

Another approach aimed to improve the efficacy of IT was to combine intrathecal agents. Hitchin et al. [48] performed a prospective trial with 44 patients (11 with breast cancer) with LMD treated with intrathecal methotrexate (15 mg) ± cytosine arabinside (50 mg). There was no improvement in response with the use of this combined intrathecal chemotherapy (61% vs. 45%, $p > 0.10$).

The only randomized prospective trial for breast cancer LMD was performed by Boogerd et al. [49] published in 2004. Their group compared the outcomes for patients treated with systemic therapy and involved-field radiation therapy and randomized patients to receive or not receive intrathecal methotrexate. The protocol intrathecal regimen was 10 mg intrathecal methotrexate weekly until clearance of CSF cytology, followed by 10 mg every 4 weeks for 3 months, and 10 mg every 4 months thereafter. Despite a goal of 50 patients, the study accrued 35 patients, of which 17 received intrathecal methotrexate. They were unable to demonstrate an improvement in response rate (59% vs. 67%)

Table 2 Prospective, randomized trials evaluating intrathecal therapy for leptomeningeal disease

Study trial	Pt population	Total number of pts (number of BC LMD)	Treatment arms (total number of pts, # of BC LMD pts)	BC LMD RR % (all pts RR %)	BC LMD OS (all pts OS)	Median OS for all BC LMD pts
Boogerd [49]	BC LMD	35 (35)	Systemic therapy + IFRT with IT MTX ($n=17$, 17)	59 (59)	18.3 wks (18.3 wks)	NR
			Systemic therapy + IFRT without IT MTX ($n=18$, 18)	67 (67)	30.3 wks (30.3 wks)	
Glantz [47]	Any solid tumor LMD	61 (22)	IT MTX ($n=30$, 11)	18 (20)	NR (78 days)	NR
			IT Depocyte ($n=31$, 11)	0 (26)	NR (105 days)	
Grossman [45]	Any solid tumor LMD	52 (25)	IT MTX ($n=28$, 17)	NA (0)	NR (15.9 wks)	15.1 wks
			IT Thiotepa ($n=24$, 8)	NA (0)	NR (14.1 wks)	
Hitchins [48]	Any solid tumor LMD	44 (11)	IT MTX ($n=22$, 3)	67 (61)	NR (12 wks)	9 wks
			IT MTX + Ara-C ($n=20$, 8)	25 (45)	NR(7 wks)	

BC breast cancer, *LMD* leptomeningeal disease, *RR* response rate, *OS* overall survival, *IFRT* involved-field radiotherapy, *IT* intrathecal, *MTX* methotrexate, *wks* weeks, *Ara-C* cytarabine, *NR* not reported, *pts* patients

or median survival (18.3 weeks vs. 30.3 weeks, $p=0.32$) with the addition of intrathecal methotrexate. There were statistically significant increased rates of toxicities with the addition of intrathecal methotrexate. Given no evidence of improved clinical outcomes and increased rates of toxicity, the authors concluded that intrathecal chemotherapy could be withheld for patients with breast LMD without inferior clinical outcomes.

Intrathecal chemotherapy toxicities

Intrathecal chemotherapy is not a benign treatment and is associated with several potential toxicities [60]. The most common toxicity with intrathecal chemotherapy is ventriculitis/arachnoditis, commonly presenting as a headache, nausea, vomiting, nuchal rigidity and/or fever. Ventriculitis may be either infectious or chemically induced. The risk of infectious ventriculitis can be minimized with the use of proper aseptic technique at the time of Ommaya placement and at each subsequent Ommaya access. Bacterial ventriculitis requires prompt CSF cultures prior to initiation of empiric, broad-spectrum antibiotics and removal of any indwelling intrathecal catheters. Chemically induced ventriculitis occurs in 10–23% of patients, most commonly for those receiving intrathecal depocyt [48, 61]. Corticosteroids are oftentimes administered concurrently with intrathecal chemotherapy to minimize meningeal inflammation and irritation.

Intrathecal therapies can also cause systemic toxicities. Methotrexate is not metabolized within the CSF, but rather excreted into the serum where it may cause myelosuppression [62]. Routinely, intrathecal methotrexate requires concurrent oral folinic acid, or leucovorin, to be administered within 24 h following IT administration to prevent pancytopenias. Leucovorin is unable to cross the BBB and affect methotrexate's efficacy within the CSF. Intrathecal thiothepa has also been reported to cause myelosuppression and is not recommended to be used in patients with bone marrow disorders [63].

One of the most devastating complications associated with intrathecal methotrexate is the potential for neurotoxicity. One proposed mechanism is through methothrexate's effect on adenosine. Methotrexate competitively inhibits dihydrofolate reductase increasing adenosine concentrations. Adenosine causes drastic cerebral vasodilation leading to cellular injury [64, 65]. Intrathecal methotrexate-induced neurotoxicity can present as subacute to acute encephalopathy [66] and/or transverse myelopathy [67]. Up to 59% of long-term cancer patients treated with intrathecal methotrexte can develop late leukoencephalopathy impairing patients' quality of life [68, 69]. The risk of leukoencephalopathy increases with cumulative methotrexate exposure [70] and combination with radiotherapy [71, 72]. Clinical sequalae may range from asymptomatic radiographic

changes (i.e. white matter hyperintensities on T2 imaging or cortical atrophy), to gradual cognitive impairments, to potentially severe functional disabilities, such as dementia, motor dysfunction, and aphasia. Furthermore, case reports have described the progression of fatal intrathecal methotrexate-associated disseminated necrotizing leukoencephalopathy [73, 74]. There is currently no treatment for intrathecal methotrexate-induced encephalopathy and the development of any neurologic changes necessitates the discontinuation of intrathecal methotrexate and transition to another intrathecal agent.

No intrathecal chemotherapy agent has consistently demonstrated superior clinical outcomes with median overall survivals ranging from 14 to 16 weeks [45, 47] with no additional benefits with combining intrathecal agents [48]. While the role of intrathecal cytotoxic chemotherapy for breast cancer LMD remains controversial, there is growing interest in the use of intrathecal-targeted agents. As breast cancer's biological mechanisms become increasingly understood, various molecular-targeted agents may offer novel approaches to treat breast LMD.

Intrathecal trastuzumab

The advent of anti-HER2+ monoclonal antibodies, such as trastuzumab and pertuzumab, have improved systemic disease control and extended patient survival. However, due to trastuzumab's inability to penetrate the BBB, the neuroaxis continues to be subject to an increased risk of intracranial metastases and development of LMD.

HER2+ breast cancer patients account for 10–15% of breast LMD cases [10, 14, 75]. Early pharmacologic studies have demonstrated trastuzumab concentrations 420 times less within the CSF compared to the serum following intravenous administration [76]. Radiotherapy can increase trastuzumab concentration to nearly 76:1 by disrupting an intact BBB, which is further improved to nearly 49:1 for those patients with LMD [52]; however, these concentrations remain subtherapeutic.

Rather than administering intrathecal chemotherapy, studies have evaluated the feasibility of intrathecal trastuzumab for HER2+ breast cancer LMD. This approach has been described in several case reports [77–80] with a proportion of patients demonstrating a durable CNS response. A systematic review and pooled analysis of 13 articles evaluating 17 patients treated with intrathecal trastuzumab demonstrated clinical, cytologic, and radiographic responses in 69%, 67%, and 56% of cases, respectively [81]. Furthermore, a recent retrospective single institutional series reported significantly improved craniospinal progression free survival with intrathecal trastuzumab compared to intrathecal chemotherapy or whole-brain radiotherapy alone [82]. Patients receiving intrathecal trastuzumab had a median CNS progression free survival and overall survival of 5.4 months and 13.2 months, respectively, superior to historical controls. Furthermore, a considerable portion of patients who experienced CNS progression while on trastuzumab were able to undergo salvage treatment, with either whole-brain radiation or the addition of another IT agent, while continuing intrathecal trastuzumab. MRI images from a patient treated from this series revealing a response to IT trastuzumab are detailed in Fig. 1.

Several ongoing prospective studies are evaluating the role of IT trastuzumab in the setting of HER2+ breast cancer LMD. A prospective multi-institutional phase I/II dose escalation trial was recently published in abstract form evaluating the efficacy and safety (phase I) and the response rate (phase 2) of intrathecal trastuzumab in 34 patients. Intrathecal trastuzumab was well tolerated at the maximum dose level of 80 mg with no reported dose-limiting toxicities at the following dose schedule: 2x/week for 4 weeks, weekly for 4 weeks, and every 2 weeks thereafter. At a median follow-up of 9.1 months, the primary endpoint of a 25% response rate was not met, but 69% of patients showed a clinical benefit (stable disease or better) with a median OS of 12.1 months exceeding historical controls [83]. Another prospective phase I trial dose escalation trial by Bonneau et al. [84] achieved their pre-specified target residual concentration for therapeutic trastuzumab within the CSF at the maximum dose level of 150 mg and reported no associated dose-limiting toxicities. The subsequent phase II trial is currently ongoing utilizing 150 mg of IT trastuzumab weekly.

Intrathecal trastuzumab appears to have a more tolerable toxicity profile compared to intrathecal chemotherapy. In the largest single institutional experience comparing intrathecal therapies, there were no documented episodes of toxicities with the use of intrathecal trastuzumab. In comparison, there were three episodes of ventriculitis in patients who received intrathecal methotrexate—two of which were infectious and the other chemically induced [82]. These findings were supported in the systemic review and pooled analysis which found no serious adverse events in 88% of patients who received intrathecal trastuzumab with one patient developing grade 3 anemia/neutropenia and another developing an asymptomatic, radiographically diagnosed ischemic lesion in the left frontal lobe [81].

Radiotherapy

Radiotherapy can be utilized in the management of LMD as a single modality or in combination with intrathecal or systemic agents. RT is effective in improving the neurologic function in patients with symptomatic LMD, but does not improve overall survival [14]. As discussed earlier, RT is a

local treatment, but in the setting of LMD, the entire neuroaxis is at risk for recurrence. Complete craniospinal (CSI) radiation for neuroaxis disease control has been proposed, but given the associated toxicities, CSI for breast cancer LMD is not performed.

EANO/ESMO recommends the use of WBRT for extensive nodular or symptomatic classical, 'sugar-coated' LMD. WBRT should be performed using either 30 Gy in 10 fractions or 20 Gy in 5 fractions [1, 85], covering the meningeal space, brain parenchyma and spinal cord to the level of the second vertebral body [85, 86]. National Comprehensive Cancer Network (NCCN) guidelines recommend IT should only be considered in combination with RT in patients deemed to have a good prognosis defined by an adequate performance status, no fixed neurologic deficits, minimal systemic disease, and reasonable options for systemic treatments [87]. However, caution must be employed with the use of concomitant radiation and intrathecal chemotherapy, most notably methotrexate, due to the increased risk for treatment-related toxicities [88].

Up to 46% of patients with LMD have abnormal or impaired CSF flow [89]. Radiotherapy can relieve and restore CSF circulation in 30% of spinal and 50% of intracranial blocks [90]. The use of focal or WBRT may be considered in this clinical setting to improve intrathecal drug diffusion and CNS penetration [91].

Stereotactic RT has historically not been utilized in the treatment of LMD; however, in particular clinical scenarios, stereotactic radiation may be considered to delay WBRT. Wolf et al. reported on 14 patients with follow-up imaging who received stereotactic RT for LMD. Eight patients had responsive LMD and five were stable following treatment. Seven patients developed distant LMD at a median of 7 months after stereotactic RT, of which nearly all were able to undergo salvage WBRT [92].

Systemic agents

Most systemic therapy is not considered ideal treatment for LMD given its restricted ability to cross the BBB. However, a handful of cytotoxic agents are able to diffuse freely within the CNS; most notably, high-dose methotrexate and capecitabine. In comparison to intrathecal therapies, the role of systemic agents is limited due to potential systemic adverse toxicities and incompatibility when combined with the ongoing chemotherapy for systemic disease.

One prospective study evaluating the role of high-dose methotrexate in the treatment of LMD from any primary solid tumor found a cytologic and clinical response rate of 81% with a median OS survival of 13.8 months [93]. Furthermore, systemic high-dose methotrexate had longer therapeutic concentrations of methotrexate within the CSF, faster clearance of malignant cells on CSF analysis, and improved overall survival compared to those treated with intrathecal methotrexate (14 vs. 2.3 months, $p = 0.003$) [93]. However, this study did not specifically discuss the subset of breast cancer patients. Given these results, there is a currently accruing prospective phase II trial evaluating the role of high-dose methotrexate for breast cancer LMD (NCT02422641).

Capecitabine has also been used in the management of breast LMD. It is an oral third-generation fluoropyrimidine prodrug which is converted into active 5-fluorouracil. Early case reports have demonstrated an effect of capecitabine on breast LMD [94, 95]. Compared to the previously discussed concerns of neurotoxicity with combined radiotherapy and methotrexate, there does not appear to be increased neurotoxicity with concurrent radiotherapy and capecitabine [96].

Lapatinib is an oral, nonspecific, tyrosine kinase inhibitor (TKI) interrupting the HER1, HER2, and EGFR pathways. While one case report demonstrated LMD response [97], it has shown limited efficacy when used alone in the treatment of breast cancer brain metastases [98, 99]. Lapatinib has demonstrated some CNS response in combination with either trastuzumab [100] or capecitabine. A systematic review and pooled analysis by Petrelli et al. looked at 799 patients in 12 studies treated with combination lapatinib and capecitabine for HER2+ breast cancer brain metastases [101]. The authors found an overall response rate of 29.2% with the combination of lapatinib and capecitabine compared to 21.4% with lapatinib alone with a pooled median progression free survival and overall survival of 4.1 months and 11.2 months, respectively. The authors concluded the combination of lapatinib and capecitabine combination may be considered for HER2+ breast cancer with intracranial disease when local therapy has failed and reirradiation is not possible.

HER2+ breast cancer patients with disease progression despite treatment with trastuzumab, pertuzumab, or trastuzumab-emanstine have minimal treatment options. While lapatinib has been utilized in refractory HER2+ disease, it is not specific and its anti-EGFR activity causes off-target toxicities, such as rash and diarrhea [102]. A new generation of anti-HER2 small molecule inhibitors, such as tucatinib, are potent TKIs with increased HER2+ specificity. Tucatinib has been shown to elicit treatment response in patients refractory to previous anti-HER2 therapies [103, 104]. Furthermore, the addition of tucatinib to capecitabine and trastuzumab has shown to have adequate toxicity profiles along with antitumor efficacy for both systemic and parenchymal brain metastases in metastatic HER2+ patients [105]. Of note, these studies evaluating anti-HER2 agents for CNS metastases did not treat patients with LMD and therefore data should not be extrapolated for widespread clinical adoption. The use of

Table 3 Current ongoing trials treating leptomeningeal disease

Clinical trial ID	Study title	Study type	Status	Start date	Estimated study completion date	Patient population	Estimated enrollment	Intervention
Breast cancer LMD patients with intrathecal therapy								
NCT01645839	Role of Intrathecal Chemotherapy With Liposomal Cytarabine (DepoCyte®) in Patients With Leptomeningeal Metastasis of Breast Cancer	Phase III	Active, not recruiting	August 2011	January 2019	BC LMD	74	Standard systemic treatment ± IT Depocyte (50 mg) every 2 weeks for 5 cycles, then every 4 weeks until progression
NCT01325207	Phase I/II Dose Escalation Trial to Assess Safety of Intrathecal Trastuzumab for the Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer	Phase I/II	Active, not recruiting	April 2011	March 2020	HER2+ BC LMD	34	IT trastuzumab twice weekly × 4 weeks, weekly × 4 weeks, then every 2 weeks (escalating doses 10–40 mg)
NCT01373710	Phase 1–2 Study of Safety and Efficacy of Intrathecal Trastuzumab Administration in Metastatic HER2 Positive Breast Cancer Patients Developing Carcinomatous Meningitis	Phase I/II	Active, not recruiting	May 2011	May 2019	HER2+ BC LMD	34	IT trastuzumab weekly × 8 weeks (escalating doses 30–150 mg)
NCT03661424	A Phase I Study of Anti-CD3 x Anti-Her2/Neu (Her2Bi) Armed Activated T Cells (ATC) in Patients With Breast Cancer Leptomeningeal Metastases	Phase I	Recruiting	February 2019	August 2023	BC LMD	16	IT HER2 bispecific antibody armed T cells (5 or 10 million cells per infusion) weekly × 8 weeks
NCT03696030	A Phase 1 Cellular Immunotherapy Study of Intraventricularly Administered Autologous HER2-Targeted Chimeric Antigen Receptor (HER2-CAR) T Cells in Patients With Brain and/or Leptomeningeal Metastases From HER2 Positive Cancers	Phase I	Recruiting	November 2018	November 2021	HER2+ BC LMD	30	IT HER2 CAR T cells weekly × 3 weeks
Breast cancer LMD patients with systemic therapy								

Table 3 (continued)

Clinical trial ID	Study title	Study type	Status	Start date	Estimated study completion date	Patient population	Estimated enrollment	Intervention
NCT02422641	Prospective Evaluation Of High-Dose Systemic Methotrexate In Patients With Breast Cancer And Leptomeningeal Metastasis	Phase II	Recruiting	April 2015	July 2019	BC LMD	16	HD-MTX (8 g/m^2) every 2 weeks
NCT03613181	A Randomized Open-Label, Multi-Center Pivotal Study of ANG1005 Compared With Physician's Best Choice in HER2-Negative Breast Cancer Patients With Newly Diagnosed Leptomeningeal Carcinomatosis and Previously Treated Brain Metastases (ANGLeD)	Phase III	Not yet recruiting	September 2019	December 2021	Her2− BC LMD	150	ANG1005 (paclitaxel trevatide) vs. physician's best choice
NCT03501979	A Phase II Non-randomized Study to Assess the Safety and Efficacy of the Combination of Tucatinib and Trastuzumab and Capecitabine for Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer	Phase II	Recruiting	March 2019	September 2023	HER2+ BC LMD	30	Tucatinib po 300 mg bid, capecitabine po 1000 mg/m2 bid on days 1–14 of 3 week cycle. IV trastuzumab every 3 weeks, 8 mg/kg loading dose and 6 mg/kg for all subsequent cycles.
NCT02308020	A Phase 2 Study of Abemaciclib in Patients With Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-small Cell Lung Cancer, or Melanoma	Phase II	Active, not recruiting	April 2015	November 2019	Arm F: HR + BC LMD	247	Abemaciclib po 200 mg bid
Any primary solid tumor LMD (including breast cancer)								
NCT03719768	Phase IB Study of Avelumab With Radiotherapy in Patients With Leptomeningeal Disease	Phase IB	Recruiting	January 2019	March 2022	BC, NSCLC, or Melanoma LMD	23	Avelumab IV 800 mg every 2 weeks and 30 Gy WBRT

Table 3 (continued)

Clinical trial ID	Study title	Study type	Status	Start date	Estimated study completion date	Patient population	Estimated enrollment	Intervention
NCT03507244	Intrathecal-pemetrexed Combined With Concurrent Involved-field Radiotherapy for Leptomeningeal Metastasis From Solid Tumor	Phase I/II	Active, not recruiting	April 2018	June 2019	Solid tumor LMD	30	IT pemetrexed 10 mg + dexamethasone 5 mg weekly ×5–8 weeks and RT (WBRT 40 Gy in 20 fx or spine 40–50 Gy in 20–25 fx)
NCT03082144	Involved-field Radiotherapy Combined With Concurrent Intrathecal-MTX Versus Intrathecal-Ara-C for Leptomeningeal Metastases From Solid Tumor	Phase II	Completed	February 2017	December 2018	Solid tumor LMD	53	RT (WBRT 40 Gy in 20 fx or spine 40–50 Gy in 20–25 fx) and IT MTX 15 mg weekly×4 weeks vs. IT cytarabine 50 mg weekly×4 weeks
NCT02886585	Phase II Trial of Pembrolizumab in Central Nervous System Metastases From Multiple Histologies	Phase II	Recruiting	October 2016	January 2024	Cohort C: Solid tumor LMD	102	Pembrolizumab IV every 3 weeks
NCT03091478	Pembrolizumab in Patients With Leptomeningeal Disease	Phase II	Recruiting	April 2017	May 2022	Solid tumor LMD	18	Pembrolizumab IV 200 mg every 3 weeks
NCT02939300	Phase II Trial of Ipilimumab and Nivolumab in Leptomeningeal Metastases	Phase II	Recruiting	January 2017	January 2024	Solid tumor LMD	18	Combination Of nivolumab with ipilimumab followed by maintainence nivolumab monotherapy
NCT03520504	A Phase Ib Study With Dose Expansion Cohort of Proton Craniospinal Irradiation for Leptomeningeal Metastases From Solid Tumors	Phase IB	Recruiting	April 2018	April 2020	Solid tumor LMD	26	Proton craniospinal irradiation (CSI) receiving 30 Gy or 25 Gy RBE in 10 fx

NCT National Cancer Trial IBC, breast cancer, *LMD* leptomeningeal disease, *IT* intrathecal, *CAR* chimeric antigen receptor, *HD-MTX* high dose methotrexate; po, per os (orally), bid, twice daily, *IV* intravenous, *NSCLC* non-small cell lung cancer, *WBRT* whole-brain radiotherapy, *fx* fractions, *Ara-C* cytarabine

anti-HER2 small molecule inhibitors for breast LMD remain experimental and future studies are necessary.

The role of hormonal agents in CNS disease has not been studied extensively. Tamoxifen is a highly lipophilic compound able to cross the BBB with therapeutic concentrations being observed within the CNS following oral administration [106]. Boogerd et al. [107] published a case series of two patients with a prolonged neurologic response to hormonal therapy with survivals of 14 and 19 months. Criticisms of the paper acknowledge these findings have not been supported in other studies and may not be widely applicable in clinical practice as oftentimes patients have been heavily pretreated with hormonal therapy and are already resistant to hormonal therapy at time of LMD diagnosis [108].

The use of cyclin-dependent kinase (CDK) 4/6 inhibitors combined with endocrine therapy has been increasing for advanced hormone receptor-positive breast cancer. The role of CDK4/6 inhibitors in the management of brain metastases is currently unclear. Early data demonstrates the ability of abemaciclib to cross the BBB leading to therapeutic concentrations within the CSF and brain parenchymal tissue [109]. Furthermore, interim results of prospective phase II trials have demonstrated treatment responses to abemaciclib in patients with hormone receptor HR+/HER2− breast cancer brain metastases [110] and breast cancer LMD [111]. Prospective studies are ongoing to assess the efficacy of abemaciclib (NCT02308020) [111] and palbociclib (NCT02774681) in the treatment of brain metastases.

Immune checkpoint inhibitors (ICIs) have demonstrated clinical potential with substantial systemic, and more importantly durable, responses in a range of primary cancers. However, the role of ICIs for breast cancer LMD is currently unknown. ICIs augment the antitumor activity of T cells by blocking CTLA-4, PD-1 or PDL-1 receptors. Activated T cells are able to cross both the BBB and the blood–CSF barrier and have demonstrated efficacy for both brain metastases [112, 113] and LMD [114, 115] in melanoma patients. There is currently no data on the role of checkpoint inhibitors in the setting of breast cancer brain metastases nor LMD, but clinical trials are currently ongoing (NCT02886585, NCT03091478, NCT03719768).

Supportive care

Supportive care is oftentimes the only reasonable treatment option depending on a patient's performance status or individualized goals of care. Symptom management is vital in the management of LMD and palliative care and maintenance of quality of life should be integrated for patients who are no longer candidates for further therapy.

Symptoms such as headaches, nausea, and seizures should be treated with appropriate medications. The role of steroids has not been adequately evaluated in the setting of breast LMD. However, extrapolating from the brain metastases literature, steroids can help alleviate meningeal inflammation. The ESMO/EANO guidelines recommend using the lowest dose achieving a clinical benefit. A ventriculoperitoneal shunt should be considered if a patient demonstrates clinical signs of increased intracranial pressure [89]. Prophylactic antiepileptics are not recommended [116], but if necessary, should be managed with careful attention for potential interactions with other systemic agents.

Future trials

Given the lack of robust prospective data, the optimal treatment for breast cancer LMD is unknown—a problem further exacerbated by no definitive definition for either diagnosis or treatment response of LMD. A recent meta-analysis aimed to answer this question. After reviewing 178 studies (including four prospective, randomized controlled trials, 19 non-randomzied interventional studies, and 149 retrospective studies), the authors were unable to perform any cross-trial comparisons given the heterogeneity in the clinical parameters and study methodologies [117].

Significant advances have been made in the use of targeted therapies in the role of systemic breast metastases and ongoing studies are attempting to incorporate these therapies in the management of LMD (Table 3). Current trials are evaluating a variety of treatment approaches, such as systemic and/or intrathecal immune checkpoint inhibitors, intrathecal bispecific antibody armed T cells (NCT03661424), intrathecal HER2-directed chimeric antigen receptor (CAR) T cells (NCT03696030), and multiple permutations of combining systemic agents with radiotherapy. Given the difficulty in conducting prospective trials for these patients, institutional collaboration with improved intertrial methodologic consistency will be needed to introduce novel therapies and help guide future treatment recommendations.

Conclusions

LMD remains a significant challenge for practitioners. As breast cancer patients live longer with improved systemic management options, the incidence of LMD continues to rise with poor survival outcomes. Each patient diagnosed with LMD requires thoughtful multidisciplinary care with consideration of radiotherapy, intrathecal and systemic treatments, and/or supportive measures. Continued clinical and research efforts are needed to improve LMD detection, monitor treatment response, and introduce novel therapies for the future management of breast cancer LMD.

Compliance with ethical standards

Conflict of interest Nicholas B. Figura, Victoria T. Rizk, Avan J. Armaghani, John A. Arrington, Arnold B. Etame, and Brian J. Czerniecki declares that they have no conflict of interest. Hyo S. Han declares that she has received a speaker's honorarium from Lilly Pharmaceuticals, research funding to the institution from Abbvie, Tesaro, TapImmune, Novartis, Bristol-Myers Squibb, Pfizer, SeattleGenetics, Prescient, Horizon, and Karyopharm. Peter A. Forsyth has received research funding from Pfizer and Celgene and is on the advisory boards of Novocure, BTG, Inovio, AbbVie, Ziopharm, Tocagen, and Pfizer; Kamran A. Ahmed has received research funding from Bristol-Myers Squibb and Genentech.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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