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REVIEW ARTICLE

Leveraging Molecular and Immune-Based Therapies in Leptomeningeal Metastases

Jessica A. Wilcox[1] · Adrienne A. Boire[1,2]

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Abstract

Leptomeningeal metastases represent an aggressive stage of cancer with few durable treatment options. Improved understanding of cancer biology, neoplastic reliance on oncogenic driver mutations, and complex immune system interactions have resulted in an explosion in cancer-directed therapy in the last two decades to include small molecule inhibitors and immune checkpoint inhibitors. Most of these therapeutics are underexplored in patients with leptomeningeal metastases, limiting extrapolation of extracranial and even intracranial efficacy outcomes to the unique leptomeningeal space. Further confounding our interpretation of drug activity in the leptomeninges is an incomplete understanding of drug penetration through the blood–cerebrospinal fluid barrier of the choroid plexus. Nevertheless, a number of retrospective studies and promising prospective trials provide evidence of leptomeningeal activity of several small molecule and immune checkpoint inhibitors and underscore potential areas of further therapeutic development for patients harboring leptomeningeal disease.

Key Points

Several small molecule inhibitors, such as osimertinib and lorlatinib, demonstrate high penetrance into the cerebrospinal fluid, potent leptomeningeal activity, and superior survival outcomes relative to historical controls.

Immune checkpoint inhibitors can induce leptomeningeal responses in select patients with immunotherapy-responsive cancers, though the bioactivity of these agents may be hampered by a dysfunctional leptomeningeal immune microenvironment and relatively low cerebrospinal fluid drug penetrance with intravenous administration.

Clinical trials designed specifically for patients with leptomeningeal metastases, with inclusion of cerebrospinal fluid pharmacokinetic analyses, are needed to define the leptomeningeal bioactivity of novel agents in this patient population.

✉ Adrienne A. Boire
boirea@mskcc.org

[1] Department of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

[2] Human Oncology and Pathogenesis Program, Brain Tumor Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

1 Introduction

Leptomeningeal metastases (LM) represent an aggressive stage of advanced cancer, defined by the entry of metastatic cancer cells into the cerebrospinal fluid (CSF) [1, 2]. Upon influx into this unique nutrient-sparse microenvironment, LM disseminate along the entire neuraxis as free-floating cells in the CSF and adherent plaques to the brain and spinal cord [3–6]. The incidence of LM varies by cancer type, ranging from 5-20% based on population and autopsy studies, and is likely increasing as patients live longer with cancer [7–10]. Historical survival following the diagnosis of LM is 2–5 months [11, 12]. This grim prognosis is, to some extent, improving in the modern era of targeted small molecule inhibitors and immunotherapy. Prior to the advent of modern cancer therapeutics in the last two decades, the treatment of LM from solid tumor malignancies has traditionally involved intrathecal chemotherapy [13–18], palliative involved-field radiation therapy to bulky or symptomatic disease [19, 20], and CSF-penetrating systemic chemotherapies [21]. None of these approaches have demonstrated a survival benefit for patients with LM in prospective studies. Very recently, proton craniospinal irradiation has emerged as an efficacious and life-prolonging strategy compared with conventional involved-field radiation [22, 23].

Small molecule inhibitors and immune checkpoint inhibitors have revolutionized the treatment of both localized and advanced cancer, demonstrating a significant improvement

in cancer control and patient survival in large, controlled clinical trials. Patients with central nervous system (CNS) metastases, most particularly LM, have been excluded from the majority of these studies for several reasons. First, patients with CNS metastases possess a worse prognosis compared with those with extracranial-only disease, making them challenging to study in a larger patient population for efficacy endpoints. Second, assessing LM response to cancer therapeutics is inherently challenging given the dynamic disease state, and standardized grading systems for LM response have not been fully validated. Third, genomic divergence between the primary tumor and intracranial metastases underscores a potential opportunity for discordant intracranial and extracranial responses [24]. Last and very importantly, the existence of distinct blood–brain (BBB) and blood–CSF (BCSFB) barrier systems leads to uncertainty regarding drug access into the CNS, with inconsistent permeability potential between the brain parenchyma and intrathecal space [25]. For example, the well-established P-glycoprotein drug efflux transporter appears to have opposing functions at the BBB and BCSFB, transporting drugs out of the brain parenchyma but into the CSF [26, 27]. Comparative brain tissue and CSF pharmacokinetic sampling is essential to better understand differential drug transport into these two compartments of the CNS, and one should not assume that lack of BBB penetration has equivalent consequences at the BCSFB (or vice versa).

As a result of these limitations, the efficacy of targeted therapies and immune checkpoint blockade in the leptomeningeal space is largely unexplored, with potential therapeutic impact based on case-reported responses, retrospective institutional studies, post-hoc analyses, and small prospective studies designed specifically for patients with CNS metastases. A wide range of CSF drug penetrance has been established for numerous agents (Table 1), though variability in patient characteristics, pharmacokinetic assays, and reporting standards add complexity when making intraclass drug comparisons. Nevertheless, these encouraging studies provide proof-of-concept evidence of leptomeningeal activity and highlight several areas worthy of further investigation.

2 Small Molecule Inhibitors

The oncologic community has seen an enormous shift in cancer-directed therapy from cytotoxic chemotherapy to small molecule inhibitors [28]. Small molecule inhibitors in cancer therapy are defined as low molecular weight compounds ($\leq$ 1 kDa) capable of modulating extracellular and intracellular aberrant pathways involved in tumorigenesis. As a function of their small size, small molecule inhibitors are capable of translocating through the plasma membrane to access their molecular targets. Most small molecule inhibitors target critical pathways in cancer development, such as tyrosine and serine/threonine receptor kinases, signal transduction pathways, matrix metalloproteinases, heat shock proteins, and DNA repair enzymes. However, despite the relative specificity of small molecular inhibitors, many of these agents interact with multiple cellular proteins in both neoplastic and healthy tissues, increasing the risk for systemic toxicity. Additionally, pathway 'escape' mutations and other small molecule resistance mechanisms limit the long-term durability of these agents in some patients [29].

To date, approximately 80 small molecule inhibitors have been approved by the Food and Drug Administration (FDA) for hematologic and solid tumor malignancies [30–32]. A number of these agents, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors for non-small-cell lung cancer (NSCLC), human epidermal growth factor receptor (HER2)-targeting agents for breast cancer, and BRAF/MEK inhibitors for melanoma, have become the standard of care, reflecting their impact on disease control and patient survival [33–36]. However, despite the rising incidence of brain metastases across solid tumor malignancies, only a small portion of these small molecule inhibitors have been prospectively studied in patients with active, intracranial disease. The activity and durability of small molecule inhibitors on LM remains even more elusive.

2.1 EGFR Inhibitors

EGFR mutations are the most frequently encountered oncogenes in NSCLC. EGFR is a transmembrane glycoprotein receptor that is tightly regulated to cellular proliferation. This receptor tyrosine kinase (RTK) harbors an extracellular epidermal growth factor binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain which manipulates several downstream signaling pathways, including the Janus kinase (JAK)-signal transducer and activator of transcription(STAT), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK) pathways [37]. *EGFR* gene amplification and mutations resulting in receptor overactivation have been implicated in the pathogenesis of many human malignancies, namely NSCLC and glioblastoma [38, 39]. Activating mutations in the *EGFR* gene primarily occur in a portion of the tyrosine kinase domain encoded on exons 18–21. The most common mutations in NSCLC are exon 19 in-frame deletions and exon 21 L858R substitutions, accounting for over 80% of sensitizing mutations [40]. The exon 20 T790M mutation also holds significant relevance, often presenting as a second-site resistance mutation to early generation tyrosine kinase inhibitors (TKI), erlotinib and gefitinib. *EGFR*

Table 1 CSF Pharmacokinetics of Small Molecule Inhibitors and Immune Checkpoint Inhibitors

Reference	Study type	Drug	Study population	*N*	Time of collection	CSF concentration[a]	Plasma concentration[a]	CSF penetration rate[b,c]	Clinical outcome
EGFR inhibitors									
Togashi et al., 2012 [44]	Prospective	Erlotinib 150 mg daily	EGFR-mutant NSCLC ± LM	8	N/A	66.9 ± 39.0 nM	N/A	2.77 ± 0.45%	PR in 4/7, SD in 1/7, PD in 2/7
		Gefitinib 250 mg daily	EGFR-mutant NSCLC ± LM	7	N/A	8.2 ± 4.3 nM	N/A	1.13 ± 0.36%	PR in 1/3, SD in 2/3
Jackman et al., 2006 [47]	Single patient dose escalation	Gefitinib 500 mg daily	EGFR-mutant NSCLC LM	1	N/A	6.2–18 nM	N/A	N/A	Clinical, cytologic, and radiographic improvement in LM at dose of 1000 mg daily. Prolonged high-dose exposure limited by transaminitis and somnolence
		Gefitinib 750 mg daily			N/A	32 nM	N/A	N/A	
		Gefitinib 1000 mg daily			N/A	42 nM	N/A	N/A	
		Gefitinib 1250 mg daily			N/A	39 nM	3730 nM	1.06%[c]	
Jackman et al., 2015 [48]	Phase I	Gefitinib alternating 750 mg daily with 500 mg daily q2wk	EGFR-mutant NSCLC LM	3	Steady state	14.7–54.0 nM	1345.8–4993.0 nM	1.09%[c]	Median neurologic PFS = 2.3 mo (range 1.6–4.0). Median OS = 3.5 mo (range 1.6–5.1)
		Gefitinib alternating 1000 mg daily with 500 mg daily q2wk	EGFR-mutant NSCLC LM	4	Steady state	17.3–143.1 nM	1552.3–5094.4 nM	1.11–2.81%[c]	
Tamiya et al., 2017 [49]	Prospective	Afatinib 40 mg daily	EGFR-mutant NSCLC LM	11	8 d	3.16 ± 1.95 nM	233.26 ± 195.40 nM	2.45 ± 2.91%	ORR 27.3%. Median PFS = 2.0 mo (95% CI: 0.6–5.8). Median OS = 3.8 mo (95% CI: 1.1–13.1)
Nanjo et al., 2018 [57]	Prospective	Osimertinib 80 mg daily	EGFR T790M-mutant NSCLC LM	13	N/A	14.4 ± 2.8 nM	555.3 ± 51.5 nM	2.5 ± 0.3%	Median PFS = 7.2 mo (95% CI: 4.0–UD). PFS longer in CSF-T790M+ (7.8–9.6+ mo) vs CSF-T790M- (1.0–4.7+ mo). Median OS = NR

Table 1 (continued)

Reference	Study type	Drug	Study population	*N*	Time of collection	CSF concentration[a]	Plasma concentration[a]	CSF penetration rate[b,c]	Clinical outcome
Xing et al., 2020 [61]	Prospective	Osimertinib 80 mg daily	EGFR-T790M–mutant NSCLC BM + LM	12	6 wk	10.8 nM (5.2–30.4 nM)	47.2 nM (11.9–69.5 nM)[d]	31.7% (19.8–57.8%)[d]	CR 1/3 and PR 1/3 in LM cohort. Intracranial ORR = 68.8% (95% CI: 50.0–83.9) and DCR = 96.9% (95% CI: 83.8–99.9) in total cohort (*N* = 32)
Yang et al., 2020 [59]	Phase I	Osimertinib 160 mg daily	EGFR-mutant NSCLC LM	35	22 d	5.6 nM (2.2–17.2 nM)	N/A	16%[d]	LM ORR = 62% (95% CI: 45–78). LM DoR = 15.2 mo (95% CI: 7.5–17.5). Median OS = 11.0 mo (95% CI: 8.0–18.0) in total cohort (*N* = 41)
MET inhibitors									
Ninomaru et al., 2021 [70]	Case report	Tepotinib 500 mg daily	MET exon 14-mutant NSCLC LM	1	2–8 wk	49.7–59.3 nM	2869–4945 nM	1.19–1.73%	LM disease control for 5+ mo, with clinical and radiographic improvement
Tanaka et al., 2021 [71]	Case report	Tepotinib 500 mg daily	MET exon 14-mutant NSCLC LM	1	20 d	62 nM (30.6 ng/mL)	1648 ng/mL	1.83%	LM disease control for 5 mo, with clinical and radiographic improvement
ALK inhibitors									
Okimoto et al., 2019 [77]	Case report	Crizotinib 250 mg BID	ALK-rearranged NSCLC BM + LM	1	15 d	4.32 ng/mL	158 ng/mL	2.60%	Clinical, radiographic, and cytologic response lasting 2 mo. Drug withdrawn due to transaminitis
Gadgeel et al., 2014 [81]	Phase I/II	Alectinib 600–900 mg BID	ALK-rearranged NSCLC BM + LM	5	Steady state	2.69 nM[e]	3.12 nM[d,e]	86.2%[c,d]	PR in 1 patient with LM. CNS ORR 52% in total cohort (*N* = 21)

Table 1 (continued)

Reference	Study type	Drug	Study population	*N*	Time of collection	CSF concentration[a]	Plasma concentration[a]	CSF penetration rate[b,c]	Clinical outcome
Bauer et al., 2018 [92]	Phase I/II[f]	Lorlatinib 100 mg daily	ALK-rearranged NSCLC BM + LM	5	N/A	N/A	N/A	73 ± 14%	LM response data not provided
Sun et al., 2022 [93]	Phase I/II	Lorlatinib 100–150 mg daily	ALK or ROS1+ NSCLC LM	5	N/A	2.64–125 ng/mL	12.7–457[4] ng/mL	77% (61–96%)[4]	CR in 3/5, SD in 1/5, NE in 1/5 in patients with suspected or confirmed LM
KRAS inhibitors									
Sabari et al., 2022 [108]	Phase I	Adagrasib 600 mg BID	KRAS-G12C-mutant NSCLC BM	2	Steady state	24.2–34.6 nM	N/A	N/A	PR in 1/2 and SD in 1/2 patients with BM
HER2 inhibitors									
Freedman et al., 2019 [117]	Phase II	Neratinib 240 mg daily	HER2+ breast BM + LM	3	7–21 d pre-operatively	<1.50 ng/mL	34.3–53.8 ng/mL	0–3.41%[c]	LM response data not available due to drug discontinuation following toxicity in 1 patient with LM
Gori et al., 2014 [120]	Case series	Lapatinib 1250 mg daily	HER2+ breast BM	2	5 h	1.3–4.5 ng/mL	1515–3472 ng/mL	0.9–1.3%	Stable CNS disease for 14 and 19 mo in 2 patients with BM
Stringer-Reasor et al., 2021 [130]	Phase II[f]	Tucatinib 300 mg BID	HER2+ breast LM	15	Cycle 1–2	0.57–25 ng/mL	N/A	83 (19.0–210.0%)[d]	LM response data not available
CDK 4/6 inhibitors									
Tolaney et al., 2020 [166]	Phase II	Abemaciclib 150–200 mg BID	HR+ breast BM + LM	14	Cycle 3, or 4–15 d pre-operatively	[Abemaciclib, CSF] exceeded the CDK4 and CDK6 IC50[g]	N/A	[Abemaciclib, CSF] and [abemaciclib, plasma] were equivalent[g]	SD in 2/7 (HER2−) and 1/3 (HER2+) patients with LM. 1 patient with HER2− LM achieved SD ≥6 mo
Tien et al., 2019 [170]	Phase 0	Ribociclib 900 mg daily	Glioblastoma	12	5 d	0.267 μmol/L (0.043–0.838 μmol/L)	0.184 μmol/L (0.030–0.720 μmol/L)[d]	180% (60–440%)[d]	LM response data not available
BRAF/MEK inhibitors									
Sakji-Dupré et al., 2015 [190]	Case series	Vemurafenib 960 mg BID	BRAF-mutant melanoma BM + LM	6	N/A	0.47 ± 0.37 mg/L	53.4 ± 26.2 mg/L	0.98 ± 0.84%	LM response data not available

Table 1 (continued)

Reference	Study type	Drug	Study population	*N*	Time of collection	CSF concentration[a]	Plasma concentration[a]	CSF penetration rate[b,c]	Clinical outcome
NTRK inhibitors									
Mayr et al., 2020 [214]	Case study	Entrectinib 600 mg daily	EML4-NTRK3 fusion gliosarcoma + LM	1	40 d	~14–25 nM[g]	N/A	N/A	Clinical improvement and radiographic regression of focally irradiated and non-irradiated LM deposits lasting 5 mo
Immune checkpoint inhibitors									
Portnow et al., 2020 [235]	Case series	Pembrolizumab 200 mg q3wk	Glioblastoma	10	24 h	215 ng/mL (104–436 ng/mL)	37905 ng/mL (26462–54297 ng/mL)	0.9% (0.4–1.4%)	LM response data not available
Pluim et al., 2019 [236]	Case series	Nivolumab 1–3 mg/kg q2–3wk	Solid tumor BM + LM	5	Steady state	14.5–304 ng/mL	1831–33454 ng/mL	0.33–1.91%[c]	LM response data not available

ALK anaplastic lymphoma kinase, *bid* twice daily, *BM* brain metastases, *CDK* cyclin dependent kinase, *CR* complete response, *CSF* cerebrospinal fluid, *DCR* disease control rate, *DoR* duration of response, *EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *LM* leptomeningeal metastases, *MET* c-met, *N* number, *N/A* not applicable, *NE* not evaluable, *NR* not reported, *NSCLC* non-small cell lung cancer, *NTRK* neurotrophic tropomyosin receptor kinase, *ORR* objective response rate, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *q2–3wk* every 2–3 weeks, *ROS1* ROS proto-oncogene 1, *SD* stable disease

[a]Mean, median, range selection, and units of measurement as per authors' definitions

[b]Author-defined CSF-to-plasma ratio or CSF penetrate rate used interchangeably and converted to percentage, when applicable

[c]If not defined by authors, CSF penetration rate estimated by formula [CSF,average]/[Plasma,average] × 100%

[d]Measurement specifies unbound plasma drug level

[e]Specifically the extrapolated CSF trough of alectinib 600 mg BID

[f]Published results from a study abstract. Final data not currently published

[g]Exact CSF and plasma values were not provided

mutation incidence varies by geographic region, present in 30–50% of cases of East Asian descent and 10–13% of cases of North American and European descent [41]. Patients harboring *EGFR* mutations have a higher incidence of CNS metastases, with an LM rate of 9.4% compared with 3.4% among their *EGFR*-wildtype counterparts [42, 43].

EGFR-TKIs are among the earliest examples of small molecule inhibitors in solid tumor malignancies, and therefore also among the most studied in patients with LM. The first- and second-generation EGFR-TKIs (erlotinib, gefitinib, afatinib) have demonstrated measurable drug levels within the CSF and have been investigated in patients with LM in a few small prospective and retrospective studies. At standard dosing, erlotinib has been observed to have superior CSF drug levels to gefitinib, with a CSF concentration of 66.9 ± 39.0 nM versus 8.2 ± 4.3 nM, respectively [44]. Consequently, retrospective analysis supports that erlotinib may outperform gefitinib in the treatment of NSCLC LM [45, 46]. The relatively low CSF concentrations of gefitinib, however, increase with gefitinib dose escalation (CSF level up to 42 nM at gefitinib 1000 mg/day), and in a single patient, corresponded to CSF cancer cell clearance at peak drug levels [47]. This finding prompted a phase I study of gefitinib alternating high dose (750–1000 mg/day) and maintenance dose (500 mg/day) every 2 weeks in patients with NSCLC LM, with a reported median neurological progression-free survival (PFS) of 2.3 months and a median overall survival (OS) of 3.5 months [48]. Despite the observation of CSF cancer cell clearance with higher CSF gefitinib concentrations in the case report, this correlation was not observed in the controlled prospective study. Afatinib also has observed CSF penetration in 11 patients treated with afatinib 40 mg/day, with a CSF level of 3.16 ± 1.95 nM corresponding to a CSF penetration rate of 2.45 ± 2.91% [49]. Survival in this small prospective LM cohort was 3.8 months, analogous to that shown with other early-generation EGFR-TKIs.

Osimertinib, a third-generation EGFR-TKI, was developed to overcome the acquired resistance to early-generation EGFR-TKIs by selectively and irreversibly inhibiting a broad range of *EGFR* mutations, including T790M [50, 51]. Osimertinib has also demonstrated superior BBB penetration in preclinical pharmacokinetic studies [52, 53], radiolabeled ^{11}C-osimertinib CNS uptake by PET brain in healthy controls [54], and unprecedented CNS control rates in prospective clinical trials [55, 56].

Similarly, patients with EGFR-mutant NSCLC LM treated with osimertinib at doses ranging 80–160 mg/day achieve higher CSF drug concentrations and improved LM control when compared with studies of early generation TKIs [57–61]. A small prospective study of osimertinib 80 mg in 13 patients with possible or confirmed LM harboring T790M resistance mutations demonstrated a PFS of 7.2 months (95% CI 4.0–NR). In this study, survival was not reached, with higher CSF clearance rates in those with a detectable T790M mutation in the CSF [57]. The AURA program (AURA extension, AURA2, AURA17, and AURA3) evaluated osimertinib 80 mg daily in patients with T790M resistance mutations and disease progression on prior TKIs. These studies included patients with stable or asymptomatic LM. Twenty-two patients with LM in this dataset were retrospectively evaluated by neuroradiologic assessment, achieving an LM objective response rate (ORR) of 55% (95% CI 32–76) [58]. Median LM-PFS was 11.1 months (95% CI 4.6–NC) and OS was 18.8 months (95% CI 6.3–NC). While encouraging in the duration of LM disease control, interpretation of this study is limited due to the retrospective design, post-hoc analysis, and lack of correlative CSF cytologic data.

In an effort to achieve greater leptomeningeal durability and driven by encouraging dose-escalation preclinical models, the phase I BLOOM study enrolled 41 patients with EGFR-mutant NSCLC LM to a double dose of osimertinib 160 mg daily after prior treatment with TKIs [59]. A slightly higher LM-ORR of 62% (95% CI 45–78) was achieved compared with the retrospective AURA LM analysis, with approximately half of responders achieving a complete response and with a duration of LM control of 15.2 months (95% CI 7.5–17.5) on blinded independant central review. The entire cohort demonstrated a median OS of 11.0 months (95% CI 8.0–18.0). Osimertinib and its metabolites were detectable in the CSF at steady-state drug levels, with an osimertinib CSF-to-free plasma ratio of 16%. A similar, phase II study evaluated osimertinib 160 mg daily in 40 patients with T790M-positive LM [60]. An intracranial disease control rate (DCR) of 92.5% was reported with 5 complete responders, and a median PFS and median OS of 8.0 months (95% CI 7.2–NR) and 13.3 months (95% CI 9.1–NR), respectively. Importantly, the use of double-dose osimertinib 'rescued' intracranial disease control in 6 of 8 patients who had leptomeningeal progression on osimertinib 80 mg daily, though the duration of LM response in this small subgroup analysis was not reported. Whether osimertinib 80 mg versus 160 mg is superior in treatment-naïve EGFR-mutant NSCLC LM is yet to be determined, and of particular importance given greater systemic toxicity at higher doses [50]. CSF penetration rate has been reported as between 2.5 and 31.7% with osimertinib 80 mg [57, 61], and 16% with osimertinib 160 mg [59]. Given the overlapping CSF drug levels and differences between pharmacokinetic assessments, accurate conclusions cannot be drawn regarding the impact of CSF concentration and LM control. A comparative double-arm prospective study with CSF and plasma pharmacokinetic sampling would be informative.

Combinations of osimertinib with other agents in LM, such as pemetrexed and platinum-based therapy (FLAURA2, NCT04035486) and the vascular endothelial growth factor

(VEGF) inhibitor bevacizumab (NCT04425681), are currently under investigation. Additional third-generation EGFR-TKIs, such as lazertinib and almonertinib, are also in development and require further testing to understand potential activity within the leptomeninges [62]. Lazertinib is currently under investigation in combination with amivantamab, an EGFR-MET bispecific antibody with immune cell-directing activity [63], in patients with brain and leptomeningeal metastases in a two-arm phase II study (NCT04965090).

2.2 MET Inhibitors

Acquired resistance to EGFR inhibitors in NSCLC is common after 6–12 months of treatment by two non-mutually exclusive mechanisms: secondary resistance mutations (such as exon 20 T790M in 50–60% of patients) and 'oncogene kinase switch' pathways (including *MET* gene amplification in 5–22% of patients) [64].

MET (or c-MET) gene amplification results in upregulation of the MET RTK on the cellular membrane, resulting in signal transduction through the PI3K/Akt and MAPK pathways. Numerous genetic alterations (including point mutations, deletions, insertions, and indels) have also been shown to induce *MET* exon 14 skipping, which results in impairment in CBL-mediated receptor degradation, subsequent MET receptor accumulation, and aberrant *MET* oncogene signaling [65]. MET exon 14 mutations occur in approximately 3–4% of patients with NSCLC, seen more commonly in older patients, those with a smoking history, and pleomorphic carcinoma or adenosquamous cell carcinoma subtypes [66].

Two highly selective and brain-penetrant MET inhibitors, capmatinib and tepotinib, are FDA-approved for the treatment of advanced MET exon 14-skipping mutant NSCLC [67, 68]. There are no prospective studies investigating the activity of either MET inhibitor in patients with LM. However, a case report of capmatinib in a patient with MET exon 14 mutant NSCLC demonstrated symptom resolution and LM radiographic improvement after 2 months of treatment [69]. Duration of disease control was not reported. Two case reports also demonstrate leptomeningeal response to tepotinib lasting for at least 5 months [70, 71]. A CSF penetration rate between the two patients was calculated to be 1.2–1.8%, which is greater than the known half-maximal inhibitory concentration (IC50) of tepotinib and therefore suggestive of pharmacokinetic potential in the leptomeninges.

2.3 ALK Inhibitors

Genetic rearrangements affecting the *ALK* gene resulting in RTK overexpression are also often implicated in tumor biology, present in approximately 5% of patients with NSCLC [72]. ALK-fusion proteins retain a C-terminus tyrosine kinase, joined to a unique protein at the N-terminus, resulting in kinase overactivation and signal transduction of cell survival and proliferation pathways. In the case of NSCLC, the most common ALK rearrangement is the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion protein, which is enriched in the young, non-smoker population [73, 74]. Patients with EML4-ALK rearrangements have a higher rate of CNS metastases at both initial presentation and relapse, and approximately 5% of patients will develop LM at an advanced stage of disease [75].

Crizotinib, a first generation ALK and c-ros oncogene 1 (ROS1) inhibitor, was associated with reasonable extracranial disease control but displayed a less robust intracranial response, with the CNS as a new site of disease in 20% of patients at the time of progression [76]. Case reports of leptomeningeal response to crizotinib tend to be disappointing, likely owing to the low CSF-to-plasma drug ratios (range 0.0006–0.026) [77, 78]. Second-generation (ceritinib [79], alectinib [80–83], brigatinib [84–86]) and third-generation (lorlatinib [34, 87–90]) ALK inhibitors have since emerged with improved brain and leptomeningeal response rates and CSF penetration. For example, a linear relationship was observed between CSF and free plasma alectinib levels, with a CSF trough of 2.69 nM notably greater than the compound's in vitro IC50 [81]. Case reports and small retrospective studies have reported LM response to alectinib for a median of 13 months, with both clinical and radiographic improvement [82, 83].

Lorlatinib, a dual ALK/ROS1 inhibitor and third-generation ALK-TKI, was designed to have superior CNS penetration and demonstrated potent preclinical brain uptake as visualized with PET scans using radiolabeled ^{11}C-lorlatinib [91]. Not surprisingly, the phase III CROWN study confirmed a robust intracranial ORR of 82% (95% CI 57–96) among lorlatinib-treated TKI-naïve patients with measurable brain metastases [34], prompting FDA approval of lorlatinib as first-line treatment of ALK-rearranged NSCLC. CSF sampling of 10 total patients treated with lorlatinib 100 mg daily in phase I/II studies revealed a CSF-to-plasma ratio of 0.73 [92] and 0.77 [93], far higher than what had been previously demonstrated for crizotinib. Prospective studies of lorlatinib in patients with LM are lacking, however a phase II subgroup analysis and several case reports in patients with ALK+ LM have highlighted rapid symptom improvement and long-lasting intracranial responses, ranging 8–22 months [88, 94–96]. The largest cohort analysis of leptomeningeal activity of lorlatinib derives from an international early/expanded access program of 95 previously TKI-treated patients, in which 11 evaluable patients with LM (9 ALK+ and 2 ROS1+) achieved an intracranial ORR of 45% (95% CI 17–77) and DCR of 91% (95% CI 59–100) [97]. The median PFS was 9.3 months (95% CI 1.0–NR) for the entire

LM cohort of 13 patients, suggestive of durable leptomeningeal responses. Survival data was not included. A German early access program of 52 previously TKI-treated patients included 9 with LM and reported a partial response rate of 77.8% in this cohort, without further comment on duration of disease control or patient survival [98]. While encouraging, cognitive and mood disturbances, such as depression, agitation, mania, and hallucinations, occur in approximately 20% of patients treated with lorlatinib in a dose-dependent manner [99]. This toxicity is likely more frequent among patients with pre-existing CNS metastases and steroid use, and therefore the therapeutic consequence of lorlatinib dose reductions in this population is uncertain. Further prospective, controlled data are needed to better understand how lorlatinib dose influences CSF penetration and LM response rates.

2.4 KRAS Inhibitors

The Kirsten rat sarcoma viral oncogene homologue (KRAS) gene encodes KRAS, a small intracellular guanosine triphosphatase (GTPase) and integral component of the RAS/MAPK pathway [100]. KRAS, together with other RAS isoforms (HRAS and NRAS), are among the most commonly mutated proteins in cancer biology, present in 90% of pancreatic cancers, 42% of colon cancers, 20% of lung cancers, and 20% of melanoma [100, 101]. Despite its prevalence, KRAS has been notoriously challenging to target due to the protein's smooth, shallow surface impeding small molecule binding as well as the extremely high affinity of KRAS for GTP. Sotorasib, a selective irreversible inhibitor of KRAS-G12C, overcomes this challenge by covalently bonding to a pocket of the protein that is only present in the guanosine diphosphate (GDP)–bound state, trapping KRAS in an inactive form and earning its place as the first FDA-approved KRAS inhibitor in 2021 [102, 103]. The intracranial activity of sotorasib was demonstrated in a post-hoc analysis of patients with *KRAS* G12C mutant NSCLC and stable brain metastases in the phase I/II CodeBreaK100 study [104]. Forty patients with asymptomatic, treated brain metastases achieved a median PFS of 5.3 months and OS of 8.3 months following initiation of sotorasib, compared with 6.7 months and 13.6 months, respectively, in 132 patients without baseline brain metastases. Adagrasib, a second covalent inhibitor of KRAS-G12C, offers a longer half-life than sotorasib and demonstrated a comparable intracranial PFS of 5.4 months in patients with stable brain metastases [105]. The intracranial activity of sotorasib and adagrasib against untreated, active brain metastases is also suggested in case reports and preliminary findings from the KRYSTAL-1 study (NCT03785249) [106, 107].

To date, there are no published case reports or prospective studies highlighting the leptomeningeal activity of sotorasib or adagrasib. CSF penetration is confirmed, however, with 2 patients treated with adagrasib in the KRYSTAL-1 study achieving CSF concentrations of 24.2 nM and 34.6 nM at steady state and with correlative regression of their untreated brain metastases [108].

2.5 HER2 Inhibitors

The overexpression of HER2 is present in approximately 30% of patients with breast cancer, propagating cancer cell progression via RTK-mediated PI3K/Akt and MAPK pathway activation [109]. HER2 is also implicated in a number of other primary malignancies, including lung, esophageal, colon, ovarian, and endometrial cancer [110]. Patients with HER2+ breast cancer have high rates of intracranial metastases, likely owing to both intrinsic neurotropism of HER2+ malignancies and the poor BBB penetrance of trastuzumab and pertuzumab, two first-line HER2-targeting monoclonal antibodies [111].The rate of LM in patients with HER2+ breast cancer is estimated between 6-7% [112].

Several small molecule HER2 inhibitors have been developed in attempts to improve outcomes and CNS control, primarily in HER2+ breast cancer. Lapatinib and neratinib represent second-generation HER2-targeting agents that are FDA-approved for the treatment of recurrent HER2+ breast cancer. Lapatinib reversibly targets both HER2 and EGFR, whereas neratinib is an irreversible pan-HER inhibitor [113]. Despite their small molecular weight (suggestive of BBB penetration), the intracranial benefit afforded these agents has been poor as monotherapies, with heterogenous uptake in brain metastasis pharmacokinetic studies [114–119]. Lapatinib and neratinib both demonstrate improved intracranial control in prospective studies when in combination with capecitabine, with CNS ORR of 20–66% in trials [114–117]. The CSF penetration rates of lapatinib (1250 mg single dose, 0.9–1.3%) and neratinib (250 mg for 7–21 days, undetectable < 1.50 ng/mL in CSF) are low in a few pharmacokinetic studies [120, 121]. Case reports of these agents suggest leptomeningeal control lasting for 1–7 months for combination neratinib/capecitabine [117] and 6–12 months for lapatinib/capecitabine [118, 122]; however, attribution is challenging as capecitabine monotherapy is also associated with case-reportable leptomeningeal activity [123–126].

Tucatinib, a third-generation reversible and highly selective HER2 inhibitor, gained FDA approval in April 2020 after its use was associated with improvements in both CNS-PFS (9.9 vs 4.2 months) and OS (18.1 vs 12.0 months), when used in combination with trastuzumab and capecitabine in those with stable or active brain metastases [35, 127]. While this study excluded patients with LM, a subsequent case report suggested leptomeningeal disease control lasting 10 months with whole brain radiotherapy (WBRT) followed by combination tucatinib and capecitabine in a patient with

HER2-activating variant breast cancer [128]. To appropriately investigate this question, a phase II study is currently underway investigating combination tucatinib, trastuzumab, and capecitabine in patients with HER2+ breast cancer and LM (NCT03501979), with encouraging preliminary results supportive of durable leptomeningeal activity [129]. Paired CSF and plasma samples in 15 patients demonstrate detectable tucatinib (range 0.57–25 ng/mL, IC50 3.3 ng/mL) and its metabolite, ONT-993 (range 0.28–4.7 ng/mL), in the CSF as early as 2 hours following tucatinib administration [130], with steady state CSF levels of tucatinib approaching that of unbound plasma levels.

HER2-targeted treatments in breast cancer continue to evolve. Two HER2 antibody-drug conjugates, trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), have gained FDA approval in recent years and have shown potent intracranial activity [131–137]. As bulky molecules with large molecular weights (> 100 kDa), the extent to which either agent penetrates the blood–CSF barrier remains to be determined. While these agents are not small molecule inhibitors and therefore beyond the scope of this review, they are worth mentioning as their leptomeningeal activity is an emerging topic of future study (NCT04420598). Additional non-small molecule inhibitor HER2-targeting agents, such as intrathecal trastuzumab [138, 139] and investigational intrathecal HER2 chimeric antigen receptor (CAR) T cells (NCT03696030), have been used in the HER2+ LM arena.

2.6 PARP Inhibitors

The poly(ADP-ribose) polymerase (PARP) family of proteins are involved in the base-excision repair system of DNA single-stranded breaks (SSBs) [140]. The accumulation of SSBs leads to the development of double-stranded DNA breaks, which necessitate different DNA repair pathways such as homologous recombination and nonhomologous end joining. Certain malignancies, namely breast cancer susceptibility proteins 1 (*BRCA1*) or *BRCA2*-mutated breast and ovarian cancer, have defective homologous recombination repair enzymes and therefore are more dependent on an intact SSB repair pathway to propagate [141]. The use of PARP inhibitors in this scenario invokes the concept of synthetic lethality, whereby combinatorial disruption of both DNA pathways results in cell death [142].

There are currently four FDA-approved PARP inhibitors (olaparib, rucaparib, niraparib, and talazoparib), with others in development (veliparib), for the treatment of homologous recombination-deficient (HRD) cancers. Breast cancer brain metastases have been shown to contain a higher HRD mutational burden relative to matched primary tumor [143], raising the question of enhanced sensitivity of brain metastases to PARP inhibitors and with activity suggested in small studies and case reports [144–147]. The use of PARP inhibition is of particular value to patients with triple negative breast cancer, who are enriched in the *BRCA1* subtype and oftentimes lack additional targetable therapies [148, 149]. Data regarding the CSF penetration of these agents is lacking, with preclinical suggestion of superior brain and/or CSF penetration of veliparib and niraparib compared with other PARP inhibitors [150, 151]. Veliparib's CSF penetration rate is calculated to be 57% that of plasma in non-human primates [152]. Case reports have hinted at durable LM responses with olaparib lasting 12–14 months for *BRCA* -mutated ovarian cancer [153, 154] and 19 months in *BRCA* -mutated breast cancer patients [155]. Further investigation of both CSF penetration and leptomeningeal activity of PARP inhibitors is warranted.

2.7 Combinatorial Endocrine Therapy and CDK4/6 Inhibition

The addition of cyclin-dependent kinase (CDK)4 and CDK6 inhibitors, such as ribociclib, abemaciclib, and palbociclib, to endocrine therapy (ET) has significantly improved outcomes in patients with hormone receptor (HR)-positive breast cancer. As LM most commonly represents a late stage of advanced cancer, the use of such agents in a heavily pretreated patient population is challenging due to prior exposure to CDK4/6 inhibitors and acquired endocrine resistance.

ET is the therapeutic backbone of HR+ breast cancer patients, with data to suggest BBB penetrability of tamoxifen, letrozole, and anastrozole [156, 157]. Tamoxifen can also be detected in trace amounts in the CSF, with a CSF-to-serum ratio < 0.2 [158]. A few case reports of durable leptomeningeal control with various ET monotherapies have been published (neurologic PFS of 16 months with letrozole, 12 months with exemestane, 10 months for tamoxifen), consistent with CSF penetration [159–163]. The largest study of ET in patients with HR+ brain and leptomeningeal metastases found a retrospective survival benefit among LM patients that received ET (7 vs 3 months), which on multivariate analysis was independent of the use of aromatase inhibitors, tamoxifen, or fulvestrant [164]. Significantly fewer patients with LM received ET compared with those with only parenchymal metastases (26.7% vs 47.6%), likely a consequence of acquired endocrine resistance at later stages of disease. As a result, hormonal therapy is likely insufficient in isolation for most patients with LM and should be used as combinatorial treatment with other agents when possible.

Justification for combinatorial ET and CDK4/6 inhibition strategies arises from the observation that cell dysregulation is a common cause of endocrine resistance [165]. The efficacy of combination ET and CDK4/6 inhibition in patients with HR+ breast, brain and leptomeningeal metastases has been studied in one prospective phase II study, in which 10

patients with HR+ breast cancer LM (HR+ HER2− $n = 7$; HR+ HER2+ $n = 3$) received either abemaciclib with or without ET or trastuzumab [166]. CSF was collected at steady state, with roughly equivalent CSF-to-plasma concentrations which exceeded the IC50 for both CDK4 and CDK6 inhibition. The best intracranial response in the HER2− LM cohort was stable disease in 2 of 7 patients, with a combined PFS of 5.9 months (95% CI 0.7–8.6) and a median OS of 8.4 months (95% CI 3.3–23.5). In the HER2+ LM cohort, the best intracranial response was stable disease in 1 patient lasting < 6 months. Of note, cytologic data was only available in 20% of the LM patients on this study at study entry, limiting interpretation of the leptomeningeal burden of disease. Currently, there are no published case reports of the efficacy of ribociclib or palbociclib in LM, despite reports of intracranial activity for parenchymal metastases [167–169]. However, the CSF concentration of ribociclib in a phase 0 glioblastoma study at the time of surgery was equal to 0.374 μmol/L, with a CSF-to-plasma unbound ratio of 1.8 (0.6–4.4) [170]. Drug concentration in the CSF was less than that in enhancing and non-enhancing tumor, but still greater than the in vitro CDK4/6 IC50.

2.8 PI3K/Akt/mTOR Inhibitors

In addition to cell cycle dysregulation, resistance to endocrine therapies in breast cancer may also occur through upregulation of the PI3K/Akt/mTOR pathway [171]. In fact, aberrant activation of this pathway occurs in almost every human malignancy. Downstream signaling from the PI3K/Akt/mTOR pathway influences cellular proliferation, motility, metabolism, and angiogenesis [171]. Despite the ubiquitous nature of this master regulator, data supporting the use of any PI3K/Akt/mTOR inhibitor in LM from solid tumor malignancies has been largely disappointing.

Alpelisib, a selective PI3Kα inhibitor, has demonstrated activity in combination with ET for breast cancer brain metastases, with greater clinical activity among those harboring PI3Kα mutations [172–174]. Despite FDA approval in 2019 for advanced PIK3CA-mutated HR+HER2− breast cancer, to date there is no published literature on the CSF penetration or leptomeningeal activity of this agent. In clinical practice, the use of PI3K inhibitors is limited in patients with brain metastases due to toxicities of mood disturbances and hyperglycemia, which are both challenging (and often dose-limiting) side effects for patients requiring corticosteroids for cerebral edema [175]. Psychiatric side effects were of particular concern for buparlisib, a CNS-penetrant oral pan-PI3K inhibitor, ultimately leading to discontinuation of study in the breast cancer population [176]. Preliminary results of a dose-finding phase I study of paxalisib, a CNS-penetrant dual PI3K/mTOR inhibitor, in combination with WBRT for patients with brain or leptomeningeal metastases from PI3K-mutated malignancies showed this drug to be well tolerated [177]. The dose expansion arm of this study is currently recruiting (NCT04192981).

The combination of everolimus, a CNS-penetrant mTOR inhibitor, with exemestane is a long-accepted regimen for patients with metastatic HR+HER2− breast cancer following progression on aromatase inhibitors [178]. Despite known CNS activity of everolimus, the brain and leptomeningeal activity of this combination is not well characterized in the literature. The role of everolimus for breast cancer brain metastases has been studied in various chemotherapy-containing combinations [179, 180], with 3-month clinical benefit rate ranging approximately 65–90%, but again with exclusion of patients with LM.

While PI3K and mTOR inhibitors have been previously established as treatment strategies for HR+ breast cancer and with some CNS activity, Akt inhibitors are only recent additions to the investigational landscape. Two small molecule Akt inhibitors, capivasertib and ipatasertib, are under investigation for patients with metastatic HR+ breast cancer [181–183]. Further studies are required to determine the brain and leptomeningeal activity of these agents. Of note, preclinical studies suggest that ipatasertib may have CNS-active properties in breast cancer brain metastasis animal models [184] and is also currently under investigation for glioblastoma (NCT03673787).

2.9 BRAF/MEK Inhibitors

Approximately 40–60% of patients with melanoma harbor an activating *BRAF* mutation, which results in constitutively active cytoplasmic serine–threonine kinase and MAPK pathway [185]. Patients with *BRAF*-mutated melanoma tend to be younger and with a more aggressive phenotype, with a high frequency of brain metastases [186, 187]. The BRAF/MEK inhibitor combinations, dabrafenib/trametinib and encorafenib/binimetinib, in patients with *BRAF*-mutant melanoma brain metastases carry an intracranial clinical benefit rate of approximately 60–90% for a duration of 4–8 months [188, 189].

Despite ample data supporting BRAF/MEK inhibitor activity in parenchymal metastases, there are no prospective studies investigating these agents for patients with LM. CSF penetration of vemurafenib and dabrafenib are both predicted to be low based on available data. In an untimed analysis of 6 patients, mean vemurafenib CSF concentrations were 0.47 ± 0.37 mg/L with a CSF-to-plasma ratio of 0.98 ± 0.84% [190]. In non-human primates, CSF penetration of dabrafenib has been calculated as 0.57 ± 0.18% [191]. Nevertheless, case reports suggest leptomeningeal activity of these agents in small patient numbers. The largest retrospective review of this nature reported an OS of 7.2 months in 3 patients treated with BRAF/MEK inhibition alone, and 6.2

and 12.5 months in 2 patients treated with BRAF/MEK inhibition plus immune checkpoint blockade [192]. Vemurafenib monotherapy has been associated with LM-symptom, radiographic and cytologic improvement lasting 4–16 months, with longer duration of control in combination with WBRT [193–195]. A similar rapid improvement in LM symptoms and imaging abnormalities was associated with dabrafenib monotherapy, lasting at least 3–4 months [196]. Dabrafenib and trametinib have induced LM disease control for at least 5–9 months in 2 patients [197, 198]. Extrapolation of such data to true LM control rates of BRAF/MEK inhibition is challenging to determine given the high variability in patient characteristics, use of radiation, and prior immunotherapy or BRAF/MEK exposure among these case reports.

Prospective studies of BRAF/MEK inhibition in patients with LM are currently underway, including a phase I investigation of PF-07284890 in combination with binimetinib in patients with intracranial *BRAF* V600 mutant solid tumors (NCT04543188), and a phase II study of encorafenib, binimetinib, and nivolumab versus ipilimumab and nivolumab in *BRAF* V600 mutant melanoma and CNS metastases (NCT04511013).

2.10 VEGF Inhibitors

Vascular Endothelial Growth Factor (VEGF) is a master regulator of angiogenesis in carcinogenesis, but also plays a key role in tumor environment immune modulation and cellular proliferation via the MAPK and PI3K/Akt pathways [199]. CSF levels of VEGF are elevated in the presence of LM, which has been associated with inferior response to therapy and poor patient outcomes [200–202].

Currently approved VEGF receptor small molecule inhibitors include sorafenib, sunitinib, and pazopanib. Subgroup analysis of the phase III TARGET study of sorafenib versus placebo in patients with renal cell carcinoma revealed a lower rate of brain metastasis development in those who received sorafenib versus placebo (3% vs 12%), suggesting CNS activity [203]. Sorafenib is also a radiosensitizer, and in patients with breast cancer brain metastases was shown to be well tolerated in combination with WBRT with a CNS-PFS of 12.8 months (95% CI 6.7–NR) [204]. There are no available data regarding the CSF penetration of this agent, however a case report of a patient with renal cell carcinoma revealed a sorafenib-induced radiographic LM response lasting at least 10 weeks [205]. Considering the impact of anti-VEGF therapy on gadolinium uptake on MRI, further investigations of VEGF small molecule inhibitors should incorporate both radiographic and cytologic changes to measure response.

2.11 NTRK Inhibitors

Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions are rare oncogenic driver mutations present in a wide variety of cancers [206]. The *NTRK1, NTRK2,* and *NTRK3* genes encode tropomyosin receptor kinase (TRK) receptors TRKA, TRKB, and TRKC, respectively. Under normal conditions, transmembrane TRK receptors are expressed primarily in neuronal tissues. Upon binding of neutrophin growth factors to the extracellular binding domain, TRK receptors dimerize to support neuronal function including neural development, cell growth, and synaptic plasticity. However, in cancer biology, activating fusion mutations of the *NTRK* gene with a 5′ fusion partner encoding a dimerization domain results in constitutive activation the TRK receptor, with downstream signaling through the MAPK, PI3K, and phospholipase C-ɣ1 pathways. In adults, *NTRK* gene fusions are enriched primarily in secretory carcinomas of the breast, secretory salivary gland carcinoma, and thyroid cancer, but can also be detected in a minority of patients with more common cancers such as melanoma, colon cancer, lung adenocarcinoma, and various sarcomas [207]. Larotrectinib, a highly selective TRKA/B/C inhibitor, and entrectinib, a multikinase inhibitor with activity against TRKA/B/C, are two CNS-active small molecule inhibitors with demonstrated clinical activity amongst cancers harboring NTRK fusion mutations, including durable responses in primary and metastatic brain tumors [208–210].

A few clinical cases and preclinical experiments highlight potential CSF activity of NTRK inhibitors, particularly entrectinib. Rat toxicology modeling suggests superior CSF-to-unbound plasma concentrations of entrectinib (0.22) compared with larotrectinib (0.03) following intravenous administration [211]. One case report outlines a patient with undifferentiated uterine sarcoma who developed widespread LM after treatment with larotrectinib for 3 years [212]. No drug resistance mutations were identified on meningeal biopsy. She subsequently received WBRT and transitioned to entrectinib, but unfortunately experienced neurologic deterioration after 1 month of treatment and transitioned to hospice. CNS progression on larotrectinib therapy was also demonstrated in a patient with NSCLC and an acquired *TPM3-NTRK1* fusion mutation, though the authors do not comment on whether the resistance mutation was present in the leptomeninges [213]. The clinical activity of entrectinib was, however, demonstrated in two pediatric patients with CSF-disseminated *ROS1/NTRK*-fusion high-grade gliomas [214]. A partial radiographic response was observed in 1 patient after initiation of entrectinib monotherapy, and combination of entrectinib with other treatments (including radiation and intrathecal therapy) appeared to be well tolerated with controlled leptomeningeal tumors for at least 5–8 months. Entrectinib concentration in the CSF steadily

increased over time, approaching approximately 25 nM after 40 days of treatment in 1 patient. In summary, CSF penetration and activity of entrectinib is suggested in gliomas in small patient numbers, but the performance of either agent in patients with LM from extracranial malignancies remains to be determined.

3 Immune Checkpoint Inhibitors

The immune checkpoint pathways, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1), are two signaling pathways integral to T-cell maturation and the downregulation of T cells reactive to self-antigens. These two molecules compete with costimulatory signals upon T-cell receptor (TCR) binding to the antigen-presenting major histocompatibility complex (MHC). By blocking the costimulatory signal from activating the maturing T-lymphocyte, the CTLA-4 and PD-1 pathways induce T-cell anergy either in the priming phase of T-lymphocyte development within the lymph nodes (for CTLA-4) or in the effector stage in the peripheral tissues (for PD-1). Cancer cells evade this system by downregulating MHC expression and by upregulating the CTLA-4 and PD ligand-1 (PD-L1) molecules. The use of monoclonal antibodies directed against CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab, cemiplimab), and PD-L1 (atezolizumab, durvalumab, avelumab) inhibitors remove the cancer-expressing "brakes" on the immune system and result in increased T-lymphocyte-mediated destruction. Immune checkpoint inhibitors have confirmed intracranial activity in patients with brain metastases from a wide variety of malignancies, including melanoma [215, 216], NSCLC [217–219], renal cell carcinoma [220–222], and breast cancer [223, 224]. The combination of intracranial radiation with immunotherapy may augment this response, in part through the radiation-mediated release of cancer antigens [225–227].

Despite demonstrable activity of immunotherapy for parenchymal brain metastases, the efficacy of these agents in LM has been slower to crystalize. A few retrospective reviews and prospective studies do provide a suggestion of potential benefit in select patients.

Three phase II studies treated patients with LM with various immune checkpoint blockade regimens. One study for patients with melanoma brain metastases investigated combination ipilimumab/nivolumab versus nivolumab monotherapy for intracranial control, and included a cohort C designed for those with poor prognosis (brain metastasis recurrent after local therapy, neurologic symptoms, and/or presence of LM) to receive nivolumab monotherapy [228]. Four of the 16 patients in this cohort had LM; none of them responded intracranially to nivolumab monotherapy, and the best intracranial response was progressive disease in 81% of the entire cohort. A second phase II study studied pembrolizumab monotherapy in patients with solid tumor LM, which included predominantly breast cancer patients [229]. The median OS was 3.6 months (90% CI 2.2–5.2), with a trend for higher pre-treatment CSF lymphocyte percentage among those surviving longer than 3 months. No difference in survival was observed on the basis of HR or HER2 status. The best intracranial response to pembrolizumab was stable disease in 11 of 16 evaluable patients. A third study investigated combination ipilimumab and nivolumab in 18 patients with LM from solid tumor malignancies, with breast cancer representing 44% of the study population [230]. The median OS was 2.9 months (90% CI 1.6–5.0) with a median intracranial PFS of 1.93 months (90% CI 1.28–2.66 months).

Given the lack of lung cancer representation in the available prospective studies, a retrospective review of 19 patients with NSCLC LM treated with immune checkpoint inhibitors was performed across seven European institutions [231]. Lung cancer patients obtained a median PFS of 2.0 months (range 1.8–2.2) and a median OS of 3.7 months (range 0.9–6.6) with immune checkpoint blockade. Patients classified as 'good risk' by the National Comprehensive Cancer Center Network LM prognostic classification had a longer 6-month PFS compared with those considered 'poor risk' (40% vs 0%), however without a significant difference in 6- and 12-month survival rates between the two groups. Neurologic symptoms only improved in 1 patient, with all others with stable or worsening condition while on treatment. Combining immunotherapy with other agents might yield a more robust response in this patient population. A case report of the IMpower150 (IMP150) regimen (atezolizumab, bevacizumab, paclitaxel, carboplatin) in a patient with 'good risk' PD-L1-positive NSCLC suggests improvement in clinical, radiographic, and cytologic abnormalities lasting for at least 6 cycles with ongoing response [232]. The leptomeningeal activity of IMP150 is further supported by a multi-institutional retrospective review including 21 patients with NSCLC LM: ORR was 43%, DCR was 81%, PFS was 4.3 months (95% CI 3.5–9.9), and median OS was 7.1 months (95% CI 4.6–14.0) [233]. The authors refrain from commenting on the rate of CSF conversion, owing to the logistical challenge of measuring leptomeningeal responses in an uncontrolled retrospective review; however, the durable OS when employing combination therapy is encouraging and suggests superiority over regimens using immunotherapy alone.

Certain trends have emerged in a systematic review of 61 patients with solid tumor LM across 14 published studies treated with immune checkpoint inhibitors, alone or in combination with other treatments [234]. Median PFS and OS were 5.1 and 6.3 months, respectively, but with significantly lower survival among patients treated with steroids. There were no statistically significant differences in survival

outcomes between tumor types. Immunotherapy adverse events were found in 68.7% of patients, however the majority of these toxicities were mild and self-limited.

Intravenous administration of immune checkpoint inhibitors results in some penetration of drug into the CSF. Paired CSF and serum levels of steady-state pembrolizumab suggests a mean CSF-to-plasma ratio of only 0.009 (95% CI 0.004–0.014) in patients with glioblastoma [235]. However, this small concentration of drug remained capable of reducing PD-1-expressing T-lymphocyte percentage in the leptomeninges from 39.3% to 3.8%, suggestive of biochemical activity in the CSF. In patients with solid tumor CNS metastases receiving nivolumab, the CSF nivolumab concentration ranged from 14.5 ng/mL to 304 ng/mL, with again low corresponding CSF-to-plasma ratios [236]. Given the lack of more robust responses in prospective studies, intrathecal delivery of immune checkpoint inhibitors to increase CSF drug concentration is one potential strategy to improve patient outcomes. The concept of direct CSF T-lymphocyte activation is also not a unique concept; previous investigations of intrathecal IL-2 in patients with melanoma LM resulted in a median survival of 7.8 months (range 0.4–90.8) but with transient intracranial pressure complications [237]. Intrathecal nivolumab is currently being investigated in patients with solid tumor LM (NCT05112549) and in combination with intravenous nivolumab for melanoma LM (NCT03025256). Preliminary data suggests intrathecal nivolumab to be well tolerated with potential clinical benefit by current survival analysis [238]. The compassionate use of intrathecal pembrolizumab in a patient with triple negative breast cancer LM demonstrated tolerability without acute infusion reactions after two cycles of intrathecal drug administration, however the patient died 3 weeks later due to progressive neurologic symptoms [239].

In addition to the drug penetration and durability issues faced by all leptomeningeal-directed therapies, the activity of immune checkpoint blockade in LM also requires a functional immune system within the CSF, a topic of much debate. The presence of cancer cells in the leptomeninges certainly invokes an inflammatory response of both lymphoid and myeloid lineage [240], hence the historical term 'neoplastic meningitis' to describe this clinical syndrome. However, single cell sequencing of melanoma-containing skin, brain, and CSF samples reveals three immunologically distinct microenvironments, with the leptomeninges generally harboring a more immunosuppressive phenotype enriched with exhausted or inactivated CD4 and CD8 cells [241]. Immune checkpoint inhibition is associated with an abundance of CSF CD8+ T-lymphocytes with a proliferating phenotype compared with pre-treatment baseline [242]. These CD8+ T-lymphocytes demonstrate heightened gene expression related to antitumoral IFN-γ signaling and effector function, correlating with IFN-γ response within the tumor cells at equivalent time points. Further investigation into anatomic site-specific leptomeningeal immune responses to immune checkpoint blockade is warranted, with particular attention on to what degree this therapy can 'revitalize' exhausted T-lymphocytes in the intrathecal space and achieve leptomeningeal responses.

In conclusion, a wide spectrum of clinical outcomes is evident when comparing the relatively shorter survival in the prospective studies with superior outcomes in larger retrospective reviews, leading to several hypotheses. Survival estimates of 2–4 months in prospective studies with intravenous immune checkpoint blockade mirrors the historical survival benchmarks in the pre-immunotherapy era and underperforms relative to targeted therapy with small molecule inhibitors. While this suggests leptomeningeal bioactivity, it also raises questions regarding the potency of this strategy in isolation. Patient selection is also critically important. The retrospective reviews tended to be enriched in patients with known immunotherapy-responsive tumors and saw higher rates of immune checkpoint combinations with chemotherapy, anti-angiogenic agents, or immediately following radiation therapy. The relatively low CSF penetrability of immune checkpoint inhibitors into the CSF, compounded by dysfunctional and paucicellular immune repertoire in the leptomeninges, underscores the need for innovative strategies to amplify immunotherapeutic responses in the spinal fluid. In addition to intrathecal immune checkpoint inhibitor approaches (NCT05112549, NCT03025256), several other immunotherapy combinatorial strategies are under investigation for patients with LM, such as combination with WBRT (NCT03719768), the multi-kinase VEGFR inhibitor lenvatinib (NCT04729348), encorafenib and binimetinib (NCT04511013), and EGFR inhibition (NCT04833205).

4 Conclusion

Modern cancer therapeutics have evolved tremendously in the last two decades since the FDA approval of several small molecule inhibitors and immune checkpoint inhibitors for several malignancies, primarily lung, breast, and melanoma. A number of these agents have demonstrable activity in the leptomeningeal space based on retrospective series and select clinical trials designed specifically for patients with LM, providing a glimmer of hope for patients with historically poor outcomes and high unmet need. This benefit is most impressively demonstrated in patients with solid tumors harboring targetable driver mutations, such as EGFR-mutant and ALK/ROS1-positive NSCLC, with robust improvements in clinical performance status and unprecedented survival benefits for select patients with LM. Ongoing studies will hopefully soon illustrate whether this benefit may also be seen using modern HER2-targeting

strategies in patients with HER2+ breast cancer. Considering the high penetrance of TKIs into the leptomeningeal space as demonstrated in a few pharmacokinetic studies, the incorporation of such treatment strategies in patients with LM should be prioritized whenever possible. The extrapolation of immunotherapeutic approaches in patients with LM have been slower to crystalize, likely due to the relatively lower penetrance of immune checkpoint inhibitors into the CSF, the dysfunctional immune microenvironment in the leptomeninges, the need for optimal patient selection with immunotherapy-responsive tumors, and consideration of combinatorial strategies for this patient population.

As the neuro-oncologic community continues to develop clinical trials dedicated to patients with CNS metastases, further prospective studies of both existing and emerging oncogene- and immune-targeted therapies will soon illuminate the efficacy of these modern therapeutics in the leptomeningeal space. Pharmacokinetic sampling of matched CSF, plasma, and, when appropriate, brain metastasis tissue should always be considered in clinical trial design in order to define drug permeability through the unique blood–brain and blood–CSF barriers. Investigation of these agents in combination with our currently available therapies for LM, such as intrathecal chemotherapy and radiation, is also essential to devise the optimal sequential treatment strategy in this subset of patients and determine when potentially neurotoxic standard therapies might even be delayed or deferred in favor of modern CNS-active therapies.

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