Treatment of brain metastases of lung cancer in the era of precision medicine

Michael E. Haughton[1], Michael D. Chan[2], Kounosuke Watabe[3], Marcelo Bonomi[1], Waldemar Debinski[4], Glenn J. Lesser[1], Jimmy Ruiz[1,5]

[1]Department of Medicine, Hematology and Oncology, Wake Forest School of Medicine, Winston-Salem, NC, USA, [2]Department of Radiation Oncology, Wake Forest School of Medicine, Winston-Salem, NC, USA, [3]W.G. (Bill) Hefner Veteran Administration Medical Center, Cancer Center, Salisbury, NC, USA, [4]Brain Tumor Center of Excellence, Wake Forest School of Medicine, Winston-Salem, NC, USA, [5]Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, NC, USA

TABLE OF CONTENTS

1. ABSTRACT

Common and deadly complications of non-small cell lung cancer (NSCLC) are brain metastases (BM). BM portends a poorer prognosis with limited effective treatment options and current management strategies present several challenges from iatrogenic complications of supportive medications, optimal delivery of drug across the blood-brain barrier, and preservation of neurocognitive function. Long term side effects and survivorship issues have become more evident in the era of targeted therapy where a systemic disease is much better controlled. Targeted therapies and immunotherapy are beginning to provide improvements in responses and survival rates. With further advancements and experience, our knowledge in this era of precision medicine will likely lead to strides in improving the quality of life and overall survival of patients with BM from NSCLC. In this review, we present the most recent updates in treatment of BM in NSCLC in regards to targeted and immunotherapy.

2. INTRODUCTION

The development of brain metastases (BM) represents the most common cause of neurologic demise experienced by patients with lung cancer leading to dramatically increased morbidity and mortality. Metastatic disease in the brain is present in 10-25% of lung cancer patients at diagnosis and may develop in up to 40% at some time during their disease course (1). Median survival following metastatic spread to the brain can be as short as 3-6 months but can be up to 12 months depending on the patients prognostic index and treatment modalities implemented (2,3). NSCLC is the most common tumor to cause BM and adenocarcinoma subtype is present in over 50% of the patients with NSCLC and BM (4). The incidence of BM is rising in part due to advances in imaging techniques that can detect smaller lesions earlier as well as improved survival following newer systemic treatments (5,6). It poses an enormous treatment problem and calls for improvements in the treatment strategies of lung cancer BM (LC-BM).

Several prognostic scoring systems for BM have been developed including the recursive partitioning analysis which utilized the common parameters of performance status, age, extent of extracranial disease and primary diagnosis, all of which delineate prognostic

groups with differing, but poor prognoses (7–13). This has changed, to a certain degree, how patients are treated with brain metastases.

Standard local therapeutic strategies for the treatment of newly diagnosed LC-BM include whole brain radiation therapy, surgical resection, stereotactic radiosurgery, and combinations of these modalities (2,14,15). Systemic chemotherapy has played a limited role in first line therapy for BM largely because of its inability to penetrate across the blood-brain barrier (BBB) (16). However, data revealing at least partial BBB disruption in BM suggests a potential role for effective systemic therapeutics including those with limited or no penetration across an intact BBB (17). In fact, published data describes response rates of up to 40-50% following standard systemically administered cytotoxic chemotherapy in patients with BM from NSCLC (18–20).

In the new era of precision medicine and whole genome sequencing of tumors, driver mutations including EGFR, ALK and ROS-1 translocations now define important subsets of patients with NSCLC and improve outcomes with the use of novel targeted therapies. Anti-PD-1 inhibitors and immunotherapeutic approaches to NSCLC have also emerged as effective anticancer strategies (21,22). The purpose of this review is to highlight the role of these promising new systemic treatment options in patients with NSCLC and BM.

3. CHEMOTHERAPY IN NSCLC

Traditional cytotoxic chemotherapy has had a limited role in the treatment of LC-BM. There is no level 1 evidence supporting its use over local radiation and surgical therapies. Concerns about BBB penetration of systemically administered chemotherapy have limited its use in the primary treatment of BM. Pharmacologic data support this concern as high molecular weight, hydrophilic and protein-bound drugs are typically excluded from the CNS due to tight-junctions and highly regulated protein transporters of the endothelial vasculature (23). However, growing published evidence suggests that the BBB is compromised in BM. Decreased expression of P-glycoprotein, an efflux pump, which is thought to remove chemotherapy agents from the CNS, is one potential mechanism underlying BBB dysfunction in BM (17). Supporting this is an analysis by Ortuzar *et al*, of 2296 patients in two phase III trials which demonstrated a reduced incidence of CNS failure, 3.2% (95% CI 2.1%-4.6%) versus 6.6% (95% CI, 5.0%-8.6%) with P=0.002 for pemetrexed versus non-pemetrexed regimens (24). There are several active clinical trials trying to further evaluate the effectiveness of various combination therapies in patients with NSCLC and BM, including Cisplatin/Pemetrexed/Bevacizumab (ClinicalTrials.gov Identifier: NCT02162537) and a phase II trial of temozolomide with topotecan (ClinicalTrials.gov Identifier: NCT01736800).

4. LOCAL THERAPY

4.1. Surgery

Surgery is a useful modality for LC-BM. The advantages of surgery include the ability to acquire a pathologic tissue sample, the rapid decompression of symptoms, and a survival advantage in some patients. However, as surgery delays systemic therapy for a period of time for wound healing and recovery of health status, patients should be properly selected. Patients with large or symptomatic metastases tend to benefit most from surgery. Patchell *et al* published a randomized study for patients with predominantly symptomatic brain metastases and found that patients who received surgery followed by whole brain radiotherapy (WBRT) had improved overall survival over those patients who received WBRT alone (2). Moreover, patients with a new diagnosis of brain metastasis after a disease free interval from the original lung cancer will benefit from surgical sampling because up to 10% of patients in this scenario will have pathology consistent with something other than a brain metastasis (25).

Contraindications to surgery include patients with tumors in surgically inaccessible (deep brain) regions or eloquent regions. Patients with poor prognosis are also not good surgical candidates because recovery from brain surgery may take a large portion of the remaining life expectancy. Finally patients with multifocal brain metastases may benefit more from a radiotherapeutic modality since radiation can treat all lesions simultaneously. However, if a dominant lesion exists in a setting of multifocal brain disease, surgical intervention may have a role.

Of note, surgical resection of a brain metastasis is not considered an oncologic surgery, and local recurrence after surgery is a common occurrence. Surgery alone for a brain metastasis has local failure rates as high as 50% (26). Post-operative radiotherapy either as WBRT or stereotactic radiosurgery (SRS) directed to the resection cavity can improve local control rates and decrease the likelihood of neurologic death (26,27).

4.2. Radiation therapy

For many years, WBRT had been the mainstay of treatment for patients with brain metastases from NSCLC. The advantage of WBRT includes the high response rate (50-75%) with regards to both tumor size on imaging as well as patient symptoms caused by BM (28). WBRT has significant toxicities both in the acute and late setting. The major acute toxicities include hair loss, fatigue, headaches, and decline in performance status (29,30). Despite performance status being a fairly subjective clinical judgment, it is often one of the most important tools used to determine whether a patient is an appropriate candidate for chemotherapy. Thus, toxicities

related to upfront WBRT can significantly delay the start of chemotherapy for patients' extracranial disease. The major late toxicity of WBRT is cognitive decline for which few treatments are effective (30,31). The advent of better systemic therapies along with improved technology have changed the landscape of LC-BM management for patients over the past 2 decades. With SRS, there is now a technology that allows for sparing of the toxicities associated with WBRT, while still controlling brain metastases. Multiple randomized trials have now shown that SRS is at least as effective as WBRT, and patient's survival is not affected by withholding WBRT as long as there are 4 or fewer brain metastases (32–34).

The use of SRS has increased over the recent years due to improved access to radiotherapy technology such as linear accelerator-based SRS and gamma knife radiosurgery in the community. As the role of SRS has expanded for lung cancer patients with brain metastases, it has become paramount to better define the populations that will benefit from SRS as this is a much more expensive modality (35). Multiple factors play a role in this decision including prognosis, performance status, status of extracranial disease, and histopathology. Patients with prolonged survival after WBRT are more likely to suffer from the cognitive toxicities of WBRT (30). As such, a greater life expectancy leads to a greater incentive for the use of SRS. There is evidence that patients with brain metastases are living longer than ever before (27). Moreover, lung cancer patients, even those with BM, have a high rate of dying of their disease in the chest (36). As such, because SRS does not cause a delay in therapy directed towards systemic disease, it is often seen as a favorable treatment option by medical oncologists. Finally, there is emerging data that there are differences in outcomes based on histology of lung cancer, and that these differences may even translate to how patients respond to SRS and WBRT(37,38).

There are some differences between management of lung cancer patients with brain metastases as compared to some other histologies. First of all, lung cancer patients who receive WBRT are thought to benefit more from a SRS boost. A randomized study published by Andrews *et al* showed that while the overall population of patients with brain metastases did not benefit from an SRS after WBRT, the lung cancer subpopulation had an improvement in overall survival (5.9 vs 3.9 months, p=0.05) (39). Kuremsky *et al* demonstrated that the likelihood of development of new metastases after SRS alone is greater in patients with squamous cell rather than adenocarcinoma (38). This in turn caused a greater need for future WBRT in patients with squamous cell cancer. Finally, recent data suggests that the appropriate use of systemic targeted agents in lung cancer patients can not only alter survival, but also affect the development of new metastases after SRS (40).

The current standard of care, while controversial, is for SRS to be used in the upfront setting for patients with four or fewer brain metastases, while WBRT is reserved for patients who have greater number of metastases. It has been suggested that the current standard may over treat a number of patients with WBRT that otherwise would have been good candidates for SRS (41). This "over-irradiated" population includes patients with greater than 4 brain metastases that respond well to systemic chemotherapy and do not develop new brain metastases for a prolonged period. A recent large prospective Phase II clinical trial from Japan suggested that treating up to 10 metastases with SRS alone may be a reasonable option (25).

In the future, it is likely that predictive models will be used to help triage lung cancer patients with brain metastases to the proper management algorithm. The disease specific Graded Prognostic Assessment is the modern prognostic model of LC-BM. A statistical nomogram has been developed to help predict which patients may rapidly fail SRS and may be more appropriately triaged to WBRT (41). Advances in molecular profiling may also help to identify the proper treatment option for patients.

5. MOLECULAR TARGETED THERAPY

5.1. EGFR mutation

Epidermal growth factor receptor (EGFR) tyrosine kinase is a multiple domain glycoprotein that is made up of an extracellular ligand-binding domain and an intracellular tyrosine kinase domain separated by a transmembrane region. Ligand binding leads to receptor dimerization on the cell surface and leads to autophosphorylation of the intracellular tyrosine kinase domain which stimulates signal transduction pathways regulating various pathobiological functions from proliferation to angiogenesis (42). Mutations in EGFR are noted in 10-15% of NSCLC adenocarcinomas in the US, and are sensitive to EGFR tyrosine kinase inhibitors (TKIs) (43). A meta-analysis by Lee *et al* evaluating EGFR TKI versus platinum-based regimens demonstrated progression-free survival was significantly prolonged with hazard ratio of 0.43 (95% CI 0.38-0.49) (44). Of note, increased EGFR gene amplification has been demonstrated to be associated with improved survival and response both in the Southwest Oncology Group 0126 trial and by Cappuzzo *et al* (45–47). Researchers in China reported 72 of 136 NSCLC patients were found to be EGFR mutant according to resected BM specimens, which demonstrated a concordance of 93.3% between the primary tumor and BM (48). In the US, there are three currently approved EGFR TKIs, erlotinib and gefitinib which are first generation agents and afatinib a second generation irreversible TKI. Studies evaluating the efficacy of these agents against BM come from retrospective analyses and small prospective studies.

Table 1. Summary of trails studying targeted therapy for LC-BM

Treatment	Patients	RR (%)	PFS (months)	OS (months)	References
Gefitinib	41	10	3.0	5.0	49
Gefitinib	76	33	5.0	9.9	50
Gefitinib/erlotinib	41	NR	NR	14.5	54
Erlotinib/WBRT	40	86	8.0	19.1	87
WBRT/SRS/erlotinib	41	NR	4.8	6.1	55
Erlotinib	63	NR	16	26	56
Afatinib	100	35	NR	9.8	60
Crizotinib	22	18	NR	NR	69
Ceritinib	124	54	NR	NR	73
Alectinib	21	52	NR	NR	75

RR: Response rate; PFS: Progression free survival; OS: Overall survival; WBRT: Whole brain radiation therapy; SRS: Stereotactic radiation surgery; NR: Not reported

5.1.1. First generation EGFR TKI

In 2004, Ceresoli *et al* demonstrated the efficacy of gefitinib in 41 heavily pretreated NSCLC patients with BM and an unknown EGFR status (49). Patients were candidates if they had failed previous whole brain radiation therapy (WBRT) or did not receive WBRT because of asymptomatic BM or it they had declined radiotherapy. Thirty-nine percent of patients had two or more previous chemotherapies and 43% received prior WBRT. Overall, disease control rate (DCR) in BM was 27%, with 10% having partial response (Table 1). Further prospective studies appeared to validate these results with DCR of 63.2% [95% CI, 52.1-74.3%] and a median overall survival (OS) of 9.9 months [95% CI, 4,9-14.8] in patients treated with gefitinib for BM (50). Eighty one percent of these patients showed comparable tumor response in intracranial and extracranial lesions. To further back these findings, Eichler *et al* performed a retrospective analysis and found 93 patients with BM, of which 44% had EGFR mutations, and noted median survival was 14.5 vs 7.6 months in the EGFR mutated patient with a P=0.09 (51). Multivariable analysis further demonstrated that EGFR mutation was independently associated with survival. Of note a majority of these patients were initially treated with WBRT +/- surgical resection.

Several retrospective analysis and small prospective studies have demonstrated some benefit in treating BM with gefitinib or erlotinib. A review in 2012 examined 8 phase II studies evaluating either gefitinib or erlotinib and their efficacy in treating NSCLC BM, with a total number of 411 patients (52). In all comers, gefitinib had an intracranial response rate (RR) of 27-32%, but with patients selected for an EGFR mutation a RR 43-89%. Studies evaluating Erlotinib only demonstrated an intracranial RR 56-82% with patients selected for known EGRF mutations. Further supporting that EGFR TKIs have activity against BM, a more robust response noted in the studies enriched with patients with known EGFR mutations.

Current data does not favor one EGFR TKI over another; however studies have evaluated the concentration of drugs in the CSF, trying to determine which TKI is more efficacious. Fifteen patients from Japan with NSCLC and BM had CSF tested during therapy with gefitinib or erlotinib and showed drug concentration of 3.7 +/- 1.9 ng/mL versus 28.7 +/- 16.8 ng/mL (53). This difference was found to be highly significant with a P value of 0.0008 and thus proposing that erlotinib might be more efficacious but larger controlled trials need to be performed to truly validate this hypothesis.

5.1.2. Concurrent therapy

We now know that EGFR TKIs have activity in BM from NSCLC, so combination treatment with radiation therapy could potentiate these responses. A phase II study with 40 patients with BM from NSCLC treated with concurrent erlotinib and WBRT had RR 86% and median OS 12 months, but when taking this idea to a large randomized control trial, the phase III RTOG 0302 showed worse OS and increased toxicity in the concurrent arms (54,55). Grade 3 to 5 toxicities occurred in 11% in the radiation arm versus 41-49% in the concurrent arms and OS was 13.6 vs 6.1 months. At this time there is insufficient safety data to recommend concurrent erlotinib and radiation therapy, but there are current clinical trials trying to further evaluate the role of this combination, ClinicalTrials.gov Identifier: NCT01887795.

Radiation therapy is the most effective modality in the treatment of patients with brain metastases, but given the data EGFR TKIs are appealing as first line treatment for BM. A recent retrospective analysis with 110 patients with BM and known EGFR mutations evaluated which treatment modality, EGFR TKIs or WBRT, was better

in front line treatment (56). Patients were treated with erlotinib, stereotactic radiosurgery (SRS), or WBRT and although it was noted there was no significant difference in OS with erlotinib versus WBRT with a P value of 0.62. However, there was a shorter time to intracranial progression with erlotinib (16 vs 24 months; P value 0.04) and a higher incidence of intracranial failure as site of first progression with erlotinib. This demonstrates that radiation therapy appears to still be the advantageous treatment modality.

5.1.3. Second generation EGFR TKI

As mentioned previously, afatinib is a second generation irreversible EGFR TKI with demonstrated clinical activity in patients with NSCLC in the LUX-Lung trials (57,58). In LUX-Lung 4, a phase II trial of afatinib in patients who had progressed during prior treatment with first generation EGFR TKIs, afatinib showed modest efficacy in this setting. A pre-planned sub group analysis of the LUX-Lung 3 trial, which evaluated Afatinib versus pemetrexed and cisplatin which allowed patients with stable BM, demonstrated a progression free survival (PFS) of 11.1 months with afatinib versus 5.4 months with chemotherapy (HR, 0.52; p value 0.13) (59). A retrospective study from earlier this year evaluated the efficacy of afatinib in the pretreated NSCLC patient with BM who had received at least one prior chemotherapy and one line of EGFR TKI (60). Of one hundred patients with BM or leptomeningeal disease, 74% having documented EGFR mutations, 35% of evaluable patients had cerebral response with 16% responding exclusively in the brain. Afatinib has demonstrated benefit in the heavily pretreated patients, even in those with previous EGFR TKIs, but we will have to await further well designed clinical trials to assess if there is definitive benefit in the front line setting. The newest addition to this class of medications is the third generation irreversible EGFR TKIs, which overcome T790M mutation, an acquired resistant EGFR mutation found in 50-60% of patients on current first or second generation TKIs. AZD9291 and Rociletinib (previously CO-1686) are two of these medications with publications from phase I-II studies demonstrating efficacy in the systemic setting, future studies will hopefully better ascertain their potential role in CNS diseases (61,62).

5.2. ALK inhibitors
5.2.1. First generation ALK inhibitors

Anaplastic lymphoma kinase (ALK) gene rearrangements which form fusion oncogenes have been found to be driver mutations in NSCLC. There are multiple variants of this oncogene rearrangement but the first described was EML4-ALK which encodes for a cytoplasmic chimeric protein with constitutive kinase activity and has an incidence of 2-7% of patients with NSCLC (63). ALK oncogenes are associated with younger age, never/light smoker, adenocarcinomas and are responsive to inhibition with ALK TKIs (64). BM are frequently found in ALK-rearranged NSCLC, reported

in 35% of patients in the phase III PROFILE 1007 trial (65). In addition, it is one of the most common sites of relapse, even in systemic responders, as reported in an update of the phase I PROFILE 1001 trial (66,67). A recent retrospective analysis reviewing patients with BM enrolled in the PROFILE 1005 and 1007 studies indicated limited long term efficacy in regards to treatment of BM (68). There were 31% of patients who had asymptomatic BM at time of entry and median duration of response was 8 weeks for intracranial disease versus 58 weeks for systemic disease. In addition, median time to progression (TTP) was 7.0 months for intracranial disease versus 12.5 months for systemic. The possible mechanisms underlying this high propensity to develop BM are uncertain but include secondary resistance or low concentration of drug in the CSF leading to inadequate exposure of drug to BM. Low CSF concentrations have been documented and a case report has demonstrated response to high dose crizotinib providing some support for this hypothesis (69,70). Brain-only progression is clearly not uncommon in this cohort of patients and thus treatment strategies have been developed to manage this. Potential strategies include brain directed therapy (WBRT or SRS) while continuing crizotinib in order to maintain systemic response and this appears to provide clinical benefit (71). Future studies, including PROFILE 1014, will evaluate crizotinib's effect on the rate of CNS disease control and brain only progression compared to chemotherapy and provide better insight on its effect on CNS disease.

5.2.2. Second generation ALK inhibitors

Second generation ALK inhibitors have been developed as a result of resistance to crizotinib. They are more potent, with potential to overcome secondary acquired resistant mechanisms. Ceritinib is reported to be 20 times more potent than crizotinib and is approved for patients who have progressed on or are intolerant to crizotinib (72). Reports from ASCEND-1, a phase 1 single arm study evaluating efficacy of ceritinib in pretreated ALK-positive NSCLC patients, showed that 124 of 255 patients had known BM at initiation of study and achieved an overall response rate of 54% and tumor shrinkage was noted in 50% of those with BM who had previous ALK inhibitor treatment (73). Thus indicating activity of this agent in treatment of CNS disease but further updates on these and other studies will help us to confirm these dramatic responses in these heavily pretreated patients.

Alectinib is another highly selective ALK inhibitor that has demonstrated promising clinical activity against BM and overcomes crizotinib resistance. In a phase I/II trial in patients who were ALK inhibitor naïve and treated with alectinib, an initial objective response rate of 52% in BM (74). A second phase I/II trial evaluating alectinib in patients with resistance to crizotinib found 21 patients with BM at baseline and demonstrated that in regards

to the BM there was a 29% complete response, 24% a partial response and 38% with stable disease in addition it has been reported that a linear correlation exists between the concentrations of free alectinib in the CSF and in the serum, suggestive of a high degree of penetration (75). These are more promising results using the next generation ALK inhibitors and the updated results of the phase II portion of this trial will help to further delineate the clinical activity within the CNS. Current studies comparing alectinib and crizotinib, with time to CNS progression as a secondary endpoint (NCT02075840), in the ALK inhibitor-naïve patients will help decide whether these newer agents can be moved in the front line setting. Several promising newer agents are in the pipeline that have the potential to further target CNS disease, including PF-06463922 which was designed to increase potential CNS penetration and act as a more potent ALK inhibitor, as well as X-396 which has demonstrated CNS responsiveness in phase I studies (76,77).

6. IMMUNOTHERAPY

An immune system that is intact can recognize and eliminate tumor cells through immune check-points but tumors have been able to adapt and escape this defense mechanism. One such mechanism is PD-1 (programmed cell death protein 1), an immunoinhibitory receptor that is expressed on T cells, B cell, monocytes, natural killer cells and many tumor infiltrating lymphocytes (78). There are two ligands that have been reported, PD-L1 and PD-L2, which are noted to be expressed on a range of cells from T and B cells to endothelial cells and certain tumors have high expression of these ligands inhibiting T-cell proliferation and cytokine production (79,80). By blocking this pathway in cancer cells one could modulate the antitumor immune response. An additional theoretical advantage with addition of radiation therapy is the abscopal effect, which is an immunologic mediated effect where radiation leads to antigen release and this stimulates immune cells to induce tumor cell death outside of the radiation field (81). This can be thought of as using radiation to prime the immune response by providing antigen stimulation with the hope of improving response rates at non-irradiated sites. This is an exciting area of interest and with more experience and use of these PD-1 inhibitors we can further understand and utilize the abscopal effect.

Nivolumab, a fully human, IgG4 immune checkpoint inhibitor antibody, binds PD-1 on activated immune cells to disrupt PD-1 interaction with its ligands and augment the antitumor response. In the CheckMate 063 trial, a phase 2, single arm trial evaluated the activity of nivolumab of advanced refractory squamous NSCLC and reported 17/117 had an objective response and 30/117 had stable disease with a median time to response of 3.3 months (22). It was noted that four patients had baseline BM and there were responses

noted, suggesting clinical activity, but no documentation of how many responded is noted in the study. Whether this will play a more prominent role in the management of BM will be answered with a large currently enrolling clinical trial (NCT01454102). One of the treatment arms in this study will be evaluating the activity of nivolumab in NSCLC patients with untreated, asymptomatic brain metastases with no evidence of cerebral edema. The estimated completion date is November 2017 at which time will find out if immunotherapy will add to our armamentarium against this difficult-to-treat process.

7. ANGIOGENESIS

Preclinical data from animal models support the potential role of antiangiogenic agents for the prevention and treatment of brain metastasis. Elevated VEGF expression has been linked to the development of brain metastasis in a murine model (82). The idea of targeting angiogenesis in metastatic lung cancer is supported by the idea that different tumor types have a different growth pattern, for example, lung carcinoma is highly dependent on angiogenesis and melanoma is less dependent on angiogenesis (83).

Bevacizumab is a recombinant monoclonal antibody targeting VEGF. Concern over the potential for cerebral hemorrhage generally prevented its use in patients with BM. The PASSPORT trial, phase II trial evaluating safety of bevacizumab in patients with NSCLC and previously treated BM, enrolled 115 patients and after a median of five cycles there were no reported episodes of grade ≥ 2 CNS hemorrhage (84). A retrospective analysis of bevacizumab safety in BM demonstrated a similar risk of develop of cerebral hemorrhage, with 3.3% of bevacizumab treated patients developing cerebral hemorrhage and only one control-arm patient developed cerebral hemorrhage (85). Thus from these limited studies, the use of bevacizumab in the treatment of NSCLC with treated BM seems to be safe and not predispose to a major risk of cerebral hemorrhage. The BRAIN trial, a phase II prospective study investigated the efficacy and safety of bevacizumab in chemotherapy naïve or pretreated patients with non-squamous NSCLC and asymptomatic untreated BM (86). This demonstrated acceptable safety in this population and a median overall survival of 16.0 months and PFS of 6.7 months. The data is continuing to build for the use of bevacizumab in NSCLC and BM and will await further data to support or refute this finding. Something to keep in mind is that when using bevacizumab to treat patients with glioblastoma, it's been noted that some patients are developing relapse with a more aggressive tumor. One retrospective analysis of 37 patients with glioblastoma multiforme treated with bevacizumab noted 35% of patients with increased nonenhancing tumor and this pattern of progression was associated with shorter OS (87). Whether this will be also seen in patients with LC-BM treated with bevacizumab is

not known but is something that we should be aware of as a possible outcome.

8. SUMMARY AND PRESPECTIVE

Precision medicine is upon us and the use and investigation of additional targeted agents will continue and provide viable options for selected patients in hopes of improvements to survival. BM will continue to be a problem, even in this population. Whether a patient has an EGFR mutation or ALK fusion protein, there appears to be some response in BM, but this occurs less when using the first generations of targeted agents. There have been improved responses with advancing generations of targeted agents, with new drugs better designed to overcome various mechanisms of resistance and/or overcoming barriers to get penetrate the CNS. We are in the beginnings of understanding of how to utilize and improve these targeted agents to treat BM in conjunction with local therapies. More clinical studies are warranted to see which treatment strategies work best in BM.

Currently, patients with an actionable mutation with asymptomatic BMs have a reasonable option to delay local therapy with close monitoring and treatment with the targeted agent. But patients with symptomatic BMs generally should be treated with standard therapies including radiation therapy or surgery. In these patients, it is preferred to use SRS to avoid the toxicities of WBRT upfront. Immunotherapy also has potential in the treatment of BM and hopefully with ongoing trials and we can gain sufficient experience to clarify its role in the treatment of BM in lung cancer patients. The use of concurrent therapies of targeted agents and local therapies like SRS to treat BM with stable systemic disease offers viable options to the armamentarium against this difficult to treat complication of NSCLC.

9. REFERENCES

1. C Kristensen, P Kristjansen, H Hansen: Systemic chemotherapy of brain metastases from small-cell lung cancer: a review. *J Clin Oncol* 10, 1498–502 (1992)

2. R Patchell, P Tibbs, J Walsh, R Dempsey, Y Maruyama, R Kryscio, W Markesbery, J Macdonald, B Young: A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 322, 494–500 (1990)
    DOI: 10.1056/NEJM199002223220802

3. P Sperduto, N Kased, D Roberge, Z Xu, R Shanley, X Luo, P Sneed, S Chao, R Weil, J Suh, A Bhatt, A Jensen, P Brown, H Shih, J Krikpatrick, L Gaspar, J Fiveash, V Chiang, J Knisely, C Sperduto, N Lin, M Mehta: Summary report on the graded prognostic assessment:

4. J Hubbs, J Boyd, D Hollis, J Chino, M Saynak, C Kelsey: Factors associated with the development of brain metastases: analysis of 975 patients with early stage nonsmall cell lung cancer. *Cancer* 116, 5038–5046 (2010)
    DOI: 10.1002/cncr.25254

5. L Nayak, E Lee, P Wen: Epidemiology of brain metastases. *Curr Oncol Rep* 14, 48–54 (2012)
    DOI: 10.1007/s11912-011-0203-y

6. R Patel, M Mehta: Targeted therapy for brain metastases: improving the therapeutic ratio. *Clin Cancer Res* 13, 1675–1683 (2007)
    DOI: 10.1158/1078-0432.CCR-06-2489

7. S Owen, L Souhami: The management of brain metastases in non-small cell lung cancer. *Front Oncol* 4, 248 (2014)
    DOI: 10.3389/fonc.2014.00248

8. F Lagerwaard, P Levendag, P Nowak, W Eijkenboom, P Hanssens, P Schmitz: Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol* 43, 795–803 (1999)
    DOI: 10.1016/S0360-3016(98)00442-8

9. E Weltman, J Salvajoli, R Brandt, R de Morais Hanriot, F Prisco, J Cruz, S de Oliveira Borges, D Wajsbrot: Radiosurgery for brain metastases: a score index for predicting prognosis. *Int J Radiat Oncol Biol Phys* 46, 1155–1161 (2000)
    DOI: 10.1016/S0360-3016(99)00549-0

10. J Lorenzoni, D Devriendt, N Massager, P David, S Ruíz, B Vanderlinden, P Van Houtte, J Brotchi, M Levivier: Radiosurgery for treatment of brain metastases: estimation of patient eligibility using three stratification systems. *Int J Radiat Oncol Biol Phys* 60, 218–24 (2004)
    DOI: 10.1016/j.ijrobp.2004.02.017

11. P Sneed, J Suh, S Goetsch, S Sanghavi, R Chappell, J Buatti, W Regine, E Weltman, V King, J Breneman, P Sperduto, M Mehta: A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol*

Phys 53, 519–526 (2002)
DOI: 10.1016/S0360-3016(02)02770-0

12. J Barnholtz-Sloan, C Yu, A Sloan, J Vengoechea, M Wang, J Dignam, M Vogelbaum, P Sperduto, M Mehta, M Machtay, M Kattan: A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol* 14, 910–918. (2012)
DOI: 10.1093/neuonc/nos087

13. D Rades, J Dunst, S Schild: A new scoring system to predicting the survival of patients treated with whole-brain radiotherapy for brain metastases. *Strahlenther Onkol* 184, 251–255 (2008)
DOI: 10.1007/s00066-008-1831-5

14. J Cairncross, J Kim, J Posner: Radiation therapy for brain metastases. *Ann Neurol* 7, 529–541 (1980)
DOI: 10.1002/ana.410070606

15. C Vecht, H Haaxma-Reiche, E Noordijk, G Padberg, J Voormolen, F Hoekstra, J Tans, N Lambooij, J Metsaars, A Wattendorff: Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 33, 583–590 (1993)
DOI: 10.1002/ana.410330605

16. M Caffo, V Barresi, G Caruso, M Cutugno, G La Fata, M Venza, C Alafaci, F Tomasello: Innovative therapeutic strategies in the treatment of brain metastases. *Int J Mol Sci* 14, 2135–2174 (2013)
DOI: 10.3390/ijms14012135

17. E Gerstner, R Fine: Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. *J Clin Oncol* 25, 2306–2312 (2007)
DOI: 10.1200/JCO.2006.10.0677

18. E Rivera, C Meyers, M Groves, V Valero, D Francis, B Arun, K Broglio, G Yin, G Hortobagyi, T Buchholz: Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. *Cancer* 107, 1348–1354 (2006)
DOI: 10.1002/cncr.22127

19. V Franciosi, G Cocconi, M Michiara, F Di Costanzo, V Fosser, M Tonato, P Carlini, C Boni, S Di Sarra: Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study. *Cancer* 85, 1599–1605 (1999)
DOI: 10.1002/(SICI)1097-0142(19990401)85 :7<1599:AID-CNCR23>3.0.CO;2-#

20. C Christodoulou, D Bafaloukos, H Linardou, G Aravantinos, A Bamias, M Carina, G Klouvas, D Skarlos, Hellenic Cooperative Oncology Group: Temozolomide (TMZ) combined with cisplatin (CDDP) in patients with brain metastases from solid tumors: a Hellenic Cooperative Oncology Group (HeCOG) Phase II study. *J Neurooncol* 71, 61–65 (2005)
DOI: 10.1007/s11060-004-9176-0

21. D Ettinger, W Akerley, H Borghaei, A Chang, R Cheney, L Chirieac, T D'Amico, T Demmy, R Govindan, F Grannis Jr, S Grant, L Horn, T Jahan, R Komaki, F Kong, M Kris, L Krug, R Lackner, I Lennes, B Loo Jr, R Martins, G Otterson, J Patel, M Pinder-Schenck, K Pisters, K Reckamp, G Riely, E Rohren, T Shapiro, S Swanson, K Tauer, D Wood, S Yang, K Gregory, M Hughes, National comprehensive cancer network: Non-small cell lung cancer, version 2.2013. *J Natl Compr Canc Netw* 11, 645–653 (2013)

22. N Rizvi, J Mazières, D Planchard, T Stinchcombe, G Dy, S Antonia, L Horn, H Lena, E Minenza, B Mennecier, G Otterson, L Campos, D Gandara, B Levy, S Nair, G Zalcman, J Wolf, P Souquet, E Baldini, F Cappuzzo, C Chouaid, A Dowlati, R Sanborn, A Lopez-Chavez, C Grohe, R Huber, C Harbison, C Baudelet, B Lestini, S Ramalingam: Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* 16, 257–265 (2015)
DOI: 10.1016/S1470-2045(15)70054-9

23. T Walbert, M Gilbert: The role of chemotherapy in the treatment of patients with brain metastases from solid tumors. *Int J Clin Oncol* 14, 299–306 (2009)
DOI: 10.1007/s10147-009-0916-1

24. W Ortuzar, N Hanna, E Pennella, G Peng, C Langer, M Monberg, G Scagliotti: Brain metastases as the primary site of relapse in

two randomized phase III pemetrexed trials in advanced non-small-cell lung cancer. *Clin Lung Cancer* 13, 24–30 (2012)
DOI: 10.1016/j.cllc.2011.05.007

25. M Yamamoto, T Serizawa, T Shuto, A Akabane, Y Higuchi, J Kawagishi, K Yamanaka, Y Sato, H Jokura, S Yomo, O Nagano, H Kenai, A Moriki, S Suzuki, Y Kida, Y Iwai, M Hayashi, H Onishi, M Gondo, M Sato, T Akimitsu, K Kubo, Y Kikuchi, T Shibasaki, T Goto, M Takanashi, Y Mori, K Takakura, N Saeki, E Kunieda, H Aoyama, S Momoshima, K Tsuchiva: Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 15, 387–395 (2014)
DOI: 10.1016/S1470-2045(14)70061-0

26. R Patchell, P Tibbs, W Regine, R Dempsey, M Mohiuddin, R Kryscio, W Markesbery, K Foon, B Young: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 280, 1485–1489 (1998)
DOI: 10.1001/jama.280.17.1485

27. C Jensen, M Chan, T McCoy, J Bourland, A deGuzman, T Ellis, K Ekstrand, K McMullen, M Munley, E Shaw, J Urbanic, S Tatter: Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. *J Neurosurg* 114, 1585–1591 (2011)
DOI: 10.3171/2010.11.JNS10939

28. E McTyre, J Scott, P Chinnaiyan: Whole brain radiotherapy for brain metastasis. *Surg Neurol Int* 4(Suppl 4), S236–244 (2013)

29. R Soffietti, M Kocher, U Abacioglu, S Villa, F Fauchon, B Baumert, L Fariselli, T Tzuk-Shina, R Kortmann, C Carrie, M Ben Hassel, M Kouri, E Valeinis, D van den Berge, R Mueller, G Tridello, L Collette, A Bottomley: A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life. *J Clin Oncol* 31, 65–72 (2013)
DOI: 10.1200/JCO.2011.41.0639

30. D Greene-Schloesser, M Robbins: Radiation-induced cognitive impairment--from bench to bedside. *Neuro Oncol* 14 Suppl 4, iv37–44 (2012)
DOI: 10.1093/neuonc/nos196

31. A Attia, B Page, G Lesser, M Chan: Treatment of radiation-induced cognitive decline. *Curr Treat Options Oncol* 15, 539–550 (2014)
DOI: 10.1007/s11864-014-0307-3

32. M Kocher, R Soffietti, U Abacioglu, S Villà, F Fauchon, B Baumert, L Fariselli, T Tzuk-Shina, R Kortmann, C Carrie, M Ben Hassel, M Kouri, E Valeinis, D van den Berge, S Collette, L Collette, R Mueller: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 29, 134–141 (2011)
DOI: 10.1200/JCO.2010.30.1655

33. E Chang, J Wefel, K Hess, P Allen, F Lang, D Kornguth, R Arbuckle, J Swint, A Shiu, M Maor, C Meyers: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 10, 1037–1044 (2009)
DOI: 10.1016/S1470-2045(09)70263-3

34. H Aoyam, H Shirato, M Tago, K Nakagawa, T Toyoda, K Hatano, M Kenjyo, N Oya, S Hirota, H Shioura, E Kunjeda, T Inomata, K Hayakawa, N Katoh, G Kobashi: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 295, 2483–2491 (2006)
DOI: 10.1001/jama.295.21.2483

35. S Lester, G Taksler, J Kuremsky, J Lucas, D Ayala-Peacock, D Randolph, J Bourland, A Laxton, S Tatter, M Chan: Clinical and economic outcomes of patients with brain metastases based on symptoms: an argument for routine brain screening of those treated with upfront radiosurgery. *Cancer* 120, 433–441 (2014)
DOI: 10.1002/cncr.28422

36. J Lucas, H Colmer, L White, N Fitzgerald, S Isom, J Bourland, A Laxton, S Tatter, M Chan: Competing Risk Analysis of Neurologic versus Nonneurologic Death in Patients Undergoing Radiosurgical Salvage After Whole-Brain Radiation Therapy Failure: Who Actually Dies of Their Brain Metastases? *Int J Radiat Oncol* 92, 1008-1015 (2015)
DOI: 10.1016/j.ijrobp.2015.04.032

37. D Ayala-Peacock, A Peiffer, J Lucas, S Isom,

J Kuremsky, J Urbanic, J Bourland, A Laxton, S Tatter, E Shaw, M Chan: A nomogram for predicting distant brain failure in patients treated with gamma knife stereotactic radiosurgery without whole brain radiotherapy. *Neuro Oncol* 16, 1283–1288 (2014)
DOI: 10.1093/neuonc/nou018

38. J Kuremsky, J Urbanic, W Petty, J Lovato, J Bourland, S Tatter, T Ellis, K McMullen, E Shaw, M Chan: Tumor histology predicts patterns of failure and survival in patients with brain metastases from lung cancer treated with gamma knife radiosurgery. *Neurosurgery* 73, 641–647 (2013)
DOI: 10.1227/NEU.0000000000000072

39. D Andrews, C Scott, P Sperduto, A Flanders, L Gaspar, M Schell, M Werner-Wasik, W Demas, J Ryu, J Bahary, L Souhami, M Rotman, M Mehta, W Curran: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 363, 1665–1672 (2004)
DOI: 10.1016/S0140-6736(04)16250-8

40. A Johnson, J Ruiz, R Hughes, B Page, S Isom, J Lucas, E McTyre, K Houseknecht, D Ayala-Peacook, D Bourland, W Hinson, A Laxton, S Tatter, W Devinski, K Watabe, M Chan: Impact of systemic targeted agents on the clinical outcomes of patients with brain metastases. *Oncotarget* Epub ahead of print, (2015)

41. D Ayala-Peacock, A Attia, J Hepel, J Lucas, N Onyeuku, M Stavas, R Taylor, C Chung, J Fiveash, M Chan: A Multi-institutional Predictive Nomogram for Distant Brain Failure in Patients Treated with Upfront Stereotactic Radiosurgery Without Whole Brain Radiation Therapy. *Int J Radiat Oncol • Biol • Phys* 90, S126 (2014)

42. M Roengvoraphoj, G Tsongalis, K Dragnev, J Rigas: Epidermal growth factor receptor tyrosine kinase inhibitors as initial therapy for non-small cell lung cancer: Focus on epidermal growth factor receptor mutation testing and mutation-positive patients. *Cancer Treat Rev* 39, 839–850 (2013)
DOI: 10.1016/j.ctrv.2013.05.001

43. J Paez, P Jänne, J Lee, S Tracy, H Greulich, S Gabriel, P Herman, F Kaye, N Lindeman, T Boggon, K Naoki, H Sasaki, Y Fujii, M Eck, W Sellers, B Johnson, M Meyerson: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 304, 1497–1500 (2004)
DOI: 10.1126/science.1099314

44. C Lee, C Brown, R Gralla, V Hirsh, S Thongprasert, C-M Tsai, E Tan, J Ho, T Chu da, A Zaatar, J Osorio Sanchez, V Vu, J Au, A Inoue, S Lee, V Gebski, J Yang: Impact of EGFR Inhibitor in Non-Small Cell Lung Cancer on Progression-Free and Overall Survival: A Meta-Analysis. *JNCI J Natl Cancer Inst* 105, 595–605 (2013)
DOI: 10.1093/jnci/djt072

45. C Gridelli, M Bareschino, C Schettino, A Rossi, P Maione, F Ciardiello: Erlotinibin Non-Small Cell Lung Cancer Treatment: Current Status and Future Development. *Oncologist* 12, 840–849 (2007)
DOI: 10.1634/theoncologist.12-7-840

46. F Hirsch, M Varella-Garcia, J McCoy, H West, A Xavier, P Gumerlock, P Bunn, W Franklin, J Crowley, D Gandara: Increased epidermal growth factor receptor gene copy number detected by fluorescence *in situ* hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: A southwest oncology group study. *J Clin Oncol* 23, 6838–6845 (2005)
DOI: 10.1200/JCO.2005.01.2823

47. M-S Tsao, A Sakurada, J-C Cutz, C-Q Zhu, S Kamel-Reid, J Squire, I Lorimer, T Zhang, N Liu, M Daneshmand, P Marrano, G da Cunha Santos, A Lagarde, R Richardson, L Seymour, M Whitehead, K Ding, J Pater, F Shepherd: Erlotinib in lung cancer - molecular and clinical predictors of outcome. *N Engl J Med* 353, 133–144 (2005)
DOI: 10.1056/NEJMoa050736

48. D Luo, X Ye, Z Hu, K Peng, Y Song, X Yin, G Zhu, Q Ji, Y Peng: EGFR mutation status and its impact on survival of Chinese non-small cell lung cancer patients with brain metastases. *Tumour Biol* 35, 2437–2444 (2014)
DOI: 10.1007/s13277-013-1323-9

49. G Ceresoli, F Cappuzzo, V Gregorc, S Bartolini, L Crinò, E Villa: Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol* 15, 1042–1047 (2004)
DOI: 10.1093/annonc/mdh276

50. C Chiu, C Tsai, Y Chen, S Chiang, J Liou, R Perng: Gefitinib is active in patients with brain metastases from non-small cell lung cancer and response is related to skin toxicity. *Lung Cancer* 47, 129–138 (2005)
DOI: 10.1016/j.lungcan.2004.05.014

51. A Eichler, K Kahle, D Wang, V Joshi, H Willers, J Engelman, T Lynch, L Sequist. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. *Neuro Oncol* 12, 1193–1199 (2010)
DOI: 10.1093/neuonc/noq076

52. M Jamal-Hanjani, J Spicer: Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor-mutant non-small cell lung cancer metastatic to the brain. *Clin Cancer Res* 18, 938–944 (2012)
DOI: 10.1158/1078-0432.CCR-11-2529

53. Y Togashi, K Masago, M Fukudo, Y Tsuchido, C Okuda, Y Kim, Y Ikemi, Y Sakamori, T.Mio, T Katsura, M Mishima: Efficacy of increased-dose erlotinib for central nervous system metastases in non-small cell lung cancer patients with epidermal growth factor receptor mutation. *Cancer Chemother Pharmacol* 68, 1089–1092 (2011)
DOI: 10.1007/s00280-011-1691-z

54. J Welsh, R Komaki, A Amini, M Munsell, W Unger, P Allen, J Chang, J Wefel, S McGovern, L Garland, S Chen, J Holt, Z Liao, P Brown, E Sulman, J Heymach, E Kim, B Stea: Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol* 31, 895–902 (2013)
DOI: 10.1200/JCO.2011.40.1174

55. P Sperduto, M Wang, H Robins, M Schell, M Werner-Wasik, R Komaki, L Souhami, M Buyyounouski, D Khuntia, W Demas, S Shah, L Nedzi, G Perry, J Suh, M Mehta: A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys* 85, 1312–1318 (2013)
DOI: 10.1016/j.ijrobp.2012.11.042

56. N Gerber, Y Yamada, A Rimner, W Shi, G Riely, K Beal, H Yu, T Chan, Z Zhang, A. Wu: Erlotinib versus radiation therapy for brain metastases in patients with EGFR-mutant lung adenocarcinoma. *Int J Radiat Oncol Biol Phys* 89, 322–329 (2014)
DOI: 10.1016/j.ijrobp.2014.02.022

57. L Sequist, J Yang, N Yamamoto, K O'Byrne, V Hirsh, T Mok, S Geater, S Orlov, C Tsai, M Boyer, W Su, J Bennouna, T Kato, V Gorbunova, K Lee, R Shah, D Massey, V Zazulina, M Shahidi, M Schuler: Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 31, 3327–3334 (2013)
DOI: 10.1200/JCO.2012.44.2806

58. N Katakami, S Atagi, K Goto, T Hida, T Horai, A Inoue, Y Ichinose, K Koboyashi, K Takeda, K Kiura, K Nishio, Y Seki, R Ebisawa, M Shahidi, N Yamamoto: LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol* 31, 3335–3341 (2013)
DOI: 10.1200/JCO.2012.45.0981

59. M Schuler: Efficacy of afatinib versus chemotherapy in treatment-naive patients with non-small cell lung cancer (NSCLC) harbouring activating EGFR mutations with or without metastatic brain disease. Mini-Oral presentation at World Congress on Lung Cancer (2013)

60. P Hoffknecht, A Tufman, T Wehler, T Pelzer, R Wiewrodt, M Schütz, M Serke, J Stohlmacher-Williams, A Marten, R Maria Huber, N Dickgreber: Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol* 10, 156–163 (2015).
DOI: 10.1097/JTO.0000000000000380

61. L Sequist, J Soria, J Goldman, H Wakelee, S Gadgeel, A Varga, V Papadimitrakopoulou, B Solomon, G Oxnard, R Dziadziusko, D Aisner, R Doebele, C Galasso, E Garon, R Heist, J Logan, J Neal, M Mendenhall, S Nichols, Z Piotrowska, A Wozniak, M Raponi, C Karlovich, S Jaw-Tsai, J Isaacson, D Despain, S Matheny, L Rolfe, A Allen, D Camidge: Rociletinib in EGFR-Mutated

Non-Small-Cell Lung Cancer. *N Engl J Med* 372, 1700–1709 (2015)
DOI: 10.1056/NEJMoa1413654

62. P Jänne, J Yang, D Kim, D Planchard, Y Ohe, S Ramalingam, M Ahn, S Kim, W Su, L Horn, D Haggstrom, E Felip, J Kim, P Frewer, M Cantarini, K Brown, P Dickinson, S Ghiorghiu, M Ranson: AZD9291 in EGFR Inhibitor-Resistant Non-Small-Cell Lung Cancer. *N Engl J Med* 372, 1689–1699 (2015)
DOI: 10.1056/NEJMoa1411817

63. E Kwak, Y Bang, D Camidge, A Shaw, B Solomon, R Maki, S Ou, B Dezube, P Janne, D Costa, M Varella-Garcia, W Kim, T Lynch, P Fidias, H Stubbs, J Engelman, L Sequist, W Tan, L Gandhi, M Mino-Kenudson, G Wei, S Shreeve, M Ratain, J Settleman, J Christensen, D Haber, K Wilner, R Salgia, G Shapiro, J Clark, A Iafrate: Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 363, 1693–1703 (2010)
DOI: 10.1056/NEJMoa1006448

64. A Shaw, B Yeap, M Mino-Kenudson, S Digumarthy, D Costa, R Heist, B Solomon, H Stubbs, S Admane, U McDermott, J Settleman, S Kobayashi, E Mark, S Rodig, L Chirieac, E Kwak, T Lynch, A Iafrate: Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 27, 4247–4253 (2009)
DOI: 10.1200/JCO.2009.22.6993

65. A Shaw, D Kim, K Nakagawa, T Seto, L Crinó, M Ahn, T De Pas, B Besse, B Solomon, F Blackhall, Y Wu, M Thomas, K O'Byrne, D Moro-Sibilot, D Camidge, T Mok, V Hirsh, G Riely, S Iyer, V Tassell, A Polli, K Wilner, P Janne: Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 368, 2385–2394 (2013)
DOI: 10.1056/NEJMoa1214886

66. D Camidge, Y Bang, E Kwak, A Iafrate, M Varella-Garcia, S Fox, G Riely, B Solomon, S Ou, D Kim, R Salgia, P Fidias, J Engelman, L Gandhi, P Janne, D Costa, G Shapiro, P Lorusso, K Ruffner, P Stephenson, Y Tang, K Wilner, J Clark, A Shaw: Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 13, 1011–1019 (2012)
DOI: 10.1016/S1470-2045(12)70344-3

67. J Gainor, S Ou, J Logan, L Borges, A Shaw: The central nervous system as a sanctuary site in ALK-positive non-small-cell lung cancer. *J Thorac Oncol* 8, 1570–1573 (2013)
DOI: 10.1097/JTO.0000000000000029

68. D Costa, A Shaw, S Ou, B Solomon, G Riely, M Ahn, C Zhou, S Shreeve, P Selaru, A Polli, P Schnell, K Wilner, R Wiltshire, D Camidge, L Crino: Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. *J Clin Oncol* 33, 1881-1888 (2015)
DOI: 10.1200/JCO.2014.59.0539

69. D Costa, S Kobayashi, S Pandya, W Yeo, Z Shen, W Tan, K Wilner: CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 29, e443–5 (2011)
DOI: 10.1093/neuonc/noq076

70. Y Kim, H Ozasa, H Nagai, Y Sakamori, H Yoshida, Y Yagi, T Nakaoku, M Mishima: High-dose crizotinib for brain metastases refractory to standard-dose crizotinib. *J Thorac Oncol* 8, e85–6 (2013)
DOI: 10.1097/JTO.0b013e31829cebbb

71. S Ou, P Jänne, C Bartlett, Y Tang, D Kim, G Otterson, L Crino, P Selaru, D Cohen, J Clark, G Riely: Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann Oncol* 25, 415–422 (2014)
DOI: 10.1093/annonc/mdt572

72. A Shaw, D Kim, R Mehra, D Tan, E Felip, L Chow, D Camidge, J Vansteenkiste, S Sharma, T De Pas, G Riely, B Solomon, J Wolf, M Thomas, M Schuler, G Liu, A Santoro, Y Lau, M Goldwasser, A Boral, J Engelman: Ceritinib in ALK -Rearranged Non–Small-Cell Lung Cancer. *N Engl J Med* 370, 1189–1197 (2014)
DOI: 10.1056/NEJMoa1311107

73. D Kim, R Mehra, D Tan, E Felip, L Chow, D Camidge, J Vansteenkiste, S Sharma, T De Pas, G Riely, B Solomon, J Wolf, M Thomas, M Schuler, G Liu, A Santoro, M Geraldes, A Boral, A Yovine, A Shaw: Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial. *J Clin Oncol* 32, abstr 8003^ (2014)

74. T Seto, K Kiura, M Nishio, K Nakagawa, M

Maemondo, A Inoue, T Hida, N Yamamoto, H Yoshioka, M Harada, Y Ohe, N Nogami, K Takeuchi, T Shimada, T Tanaka, T Tamura: CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. *Lancet Oncol* 14, 590–598 (2013)
DOI: 10.1016/S1470-2045(13)70142-6

75. S Gadgeel, L Gandhi, G Riely, A Chiappori, H West, M Azada, P Morcos, R Lee, L FGarcia, L Yu, F Boisserie, L Di Laurenzio, S Golding, J Sato, S Yokoyama, T Tanaka, S Ou: Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol* 15, 1119–1128 (2014)
DOI: 10.1016/S1470-2045(14)70362-6

76. T Johnson, P Richardson, S Bailey, A Brooun, B Burke, M Collins, J Cui, J Deal, Y Deng, D Dinh, L Engstrom, M He, J Hoffman, R Hoffman, Q Huang, R Kania, J Kath, H Lam, J Lam, P Le, L Lingardo, W Liu, M McTigue, C Palmer, N Sach, T Smeal, G Smith, A Stewart, S Timofeevski, H Zhu, J Zhu, H Zou, M Edwards: Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *J Med Chem* 57, 4720–4744 (2014)
DOI: 10.1021/jm500261q

77. L Horn, J Infante, G Blumenschein, H Wakelee, H Arkenau, G Dukart, C Liang, K Harrow, J Gibbons, C Lovly, W Pao: A phase I trial of X-396, a novel ALK inhibitor, in patients with advanced solid tumors. 2014 ASCO Annual Meeting o Title. *J Clin Oncol* 32, abstr 8030^ (2014)

78. M Keir, M Butte, G Freeman, A Sharpe: PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol* 26, 677–704 2008
DOI: 10.1146/annurev.immunol.26.021607.090331

79. T Gajewski, J Louahed, V Brichard: Gene signature in melanoma associated with clinical activity: a potential clue to unlock cancer immunotherapy. *Cancer J* 16, 399–403 (2010)
DOI: 10.1097/PPO.0b013e3181eacbd8

80. M Ghiotto, L Gauthier, N Serriari, S Pastor, A Truneh, J Nunès, D Olive: PD-L1 and PD-L2 differ in their molecular mechanisms of interaction with PD-1. *Int Immunol* 22, 651–660 (2010)
DOI: 10.1093/intimm/dxq049

81. E Massarelli, V Papadimitrakopoulou, J Welsh, C Tang, A Tsao: Immunotherapy in lung cancer. *Transl lung cancer Res* 3, 53–63 (2014)

82. S Yano, H Shinohara, R Herbst, H Kuniyasu, C Bucana, L Ellis, D Davis, D McConkey, I Fidler: Expression of vascular endothelial growth factor is necessary but not sufficient for production and growth of brain metastasis. *Cancer Res* 60, 4959–4967 (2000)

83. Y Kienast, L von Baumgarten, M Fuhrmann, W Klinkert, R Goldbrunner, J Herms, F Winkler: Real-time imaging reveals the single steps of brain metastasis formation. *Nat Med* 16, 116–122 (2010)
DOI: 10.1038/nm.2072

84. M Socinski, C Langer, J Huang, M Kolb, P Compton, L Wang, W Akerley: Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. *J Clin Oncol* 27, 5255–5261 (2009)
DOI: 10.1200/JCO.2009.22.0616

85. B Besse, S Lasserre, P Compton, J Huang, S Augustus, U Rohr: Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res* 16, 269–278 (2010)
DOI: 10.1158/1078-0432.CCR-09-2439

86. B Besse, S Le Moulec, J Mazières, H Senellart, F Barlesi, C Chouaid, E Dansin, H Berard, L Falchero, R Gervais, G Robinet, A Ruppert, R Schott, H Lena, C Clement-Dchene, X Quantin, P Souquet, J Tredaniel, D Moro-Sibilot, M Perol, A Madroszyk, J Soria: Bevacizumab in Patients with Nonsquamous Non-Small Cell Lung Cancer and Asymptomatic, Untreated Brain Metastases (BRAIN): A Nonrandomized, Phase II Study. *Clin Cancer Res* 21, 1896–1903 (2015)
DOI: 10.1158/1078-0432.CCR-14-2082

87. F Iwamoto, L Abrey, K Beal, P Gutin, M

Rosenblum, V Reuter, L DeAngelis, A Lassman: Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. *Neurology* 73, 1200–1206 (2009)
DOI: 10.1212/WNL.0b013e3181bc0184

Abbreviations: NSCLC: non-small cell lung cancer; BM: brain metastasis; BBB: blood-brain barrier; LC-BM: lung cancer brain metastasis; WBRT: whole brain radiation therapy; SRS: stereotactic radiation surgery; TKI: tyrosine kinase inhibitor; EGFR: epidermal growth factor receptor; CNS: central nervous system; DCR: disease control rate; RR: response rate; OS: overall survival; ALK: anaplastic lymphoma kinase; TTP: time to progression; PD-1: programmed cell death protein 1; VEGF: vascular endothelial growth factor

Send correspondence to: Jimmy Ruiz, Medical Center Blvd, Winston-Salem, NC 27103 Tel: 336-716-0230, Fax: 336-716-5687, E-mail: jruiz@wakehealth.edu