Critical Reviews in Oncology / Hematology 138 (2019) 190–206

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Multidisciplinary expert opinion on the treatment consensus for patients with *EGFR* mutated NSCLC with brain metastases

Santiago Ponce[a], Jordi Bruna[b,c], Oscar Juan[d], Rafael López[e], Alejandro Navarro[f], Ana Laura Ortega[g], Javier Puente[h], Eugènia Verger[i], Adela Bartolomé[j], Ernest Nadal[c,k,*]

[a] *Lung Cancer Clinical Research Unit, Hospital Universitario 12 de Octubre, Av. Cordoba, s/n, 28041 Madrid, Spain*
[b] *Neuro-Oncology Unit, Bellvitge University Hospital-ICO, Carrer de la Feixa Llarga, s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain*
[c] *Clinical Research in Solid Tumors (CReST) and Neuro-Oncology Group. Oncobell, IDIBELL, Avda Gran Via 199-203, 08907, L'Hospitalet de Llobregat, Barcelona, Spain*
[d] *Medical Oncology Service, Hospital Universitario y Politécnico La Fe, Valencia, Avda. de Fernando Abril Martorell, nº 106, 46026, Valencia, Spain*
[e] *Medical Oncology Unit. Hospital Clínico Universitario de Valladolid, Av. Ramón y Cajal, 3, 47003, Valladolid, Spain*
[f] *Medical Oncology. Hospital Vall d'Hebron, Passeig de la Vall d'Hebron, 119-129, 08035, Barcelona, Spain*
[g] *Oncology Research Unit, Complejo Hospitalario de Jaén, Av. del Ejército Español, 10, 23007, Jaén, Spain*
[h] *GU, Thoracic and Melanoma Cancer Unit, Medical Oncology Department, Assistant Professor of Medicine, Complutense University. Hospital Clinico Universitario San Carlos, Calle del Prof Martín Lagos, s/n, 28040, Madrid, Spain*
[i] *Radiation Oncology Department, Hospital Clínic de Barcelona, Carrer de Villarroel, 170, 08036, Barcelona, Spain*
[j] *Radiotherapy Oncology Department. Hospital Universitario 12 de Octubre, Av. Cordoba, s/n, 28041, Madrid, Spain*
[k] *Thoracic Oncology Unit, Department of Medical Oncology, Catalan Institute of Oncology. Avda Gran Via 199-203, 08907, L'Hospitalet de Llobregat, Barcelona, Spain*

ARTICLE INFO

Keywords:
NSCLC
EGFR mutation
Brain metastases
Consensus
Management
Recommendation
Diagnosis
Treatment

ABSTRACT

The presence of an epidermal growth factor receptor (*EGFR*) mutation is associated with higher incidence of brain metastases in patients with non-small cell lung cancer (NSCLC); however, patients with synchronous brain metastases at diagnosis have generally been excluded from clinical trials. As there is limited clinical evidence for managing this patient population, a multidisciplinary group of Spanish medical and radiation oncologists, and neuro-oncologist with expertise treating brain metastases in lung cancer patients met with the aim of reaching and developing an expert opinion consensus on the management of patients with *EGFR* mutated NSCLC with brain metastases. This consensus contains 26 recommendations and 20 conclusion statements across 21 questions in 7 areas, as well as a first-line treatment algorithm.

1. Introduction

Significant advances have been made in the management of non-small-cell lung cancer (NSCLC) in recent years; however, the prognosis for patients with brain metastasis is still poor. Brain metastases occur in 20–40% of patients with NSCLC, and are associated with short survival, reduced quality of life, increased healthcare utilization and increased cost of care (Barnholtz-Sloan et al., 2019; Guerin et al., 2016; Lassman and DeAngelis, 2003; Mujoomdar et al., 2007; Patchell et al., 1998; Wong et al., 2008). Approximately 10% of patients with NSCLC have brain metastases at diagnosis (Schuette, 2004) and a further 25%–40% will develop brain metastases during the course of their disease (Dempke et al., 2015). The common approach to the treatment of brain metastases has historically been whole-brain radiation therapy (WBRT), alone or in combination with surgery and stereotactic radiosurgery (SRS) (Morin-Ben Abdallah and Wong, 2018). However, in the population of patients with brain metastasis, including patients with NSCLC, WBRT increases intracranial control, but does not improve overall survival (OS) (Pechoux et al., 2016), all at the expenses of increased cognitive decline (Brown et al., 2017, 2016; Mulvenna et al., 2016). Overall, there is a lack of evidence-based management of this patient group. The lack of effective treatment options is certainly a major issue.

* Corresponding author at: Thoracic Oncology Unit, Department of Medical Oncology, Catalan Institute of Oncology, AvdaGran Via 199-203, 08907, L'Hospitalet de Llobregat, Barcelona, Spain.
E-mail addresses: sponceaix@gmail.com (S. Ponce), jbruna@bellvitgehospital.cat (J. Bruna), juan_osc@gva.es (O. Juan), rafalopezcastro@yahoo.es (R. López), alexnavarro84@gmail.com (A. Navarro), analauraortega@gmail.com (A.L. Ortega), javierpuente.hcsc@gmail.com (J. Puente), everger@clinic.cat (E. Verger), adelabartolome@gmail.com (A. Bartolomé), esnadal@iconcologia.net (E. Nadal).

https://doi.org/10.1016/j.critrevonc.2019.03.017
Received 19 November 2018; Received in revised form 9 February 2019; Accepted 26 March 2019

Yet despite the high incidence of brain metastasis in NSCLC, patients with such metastases are commonly underrepresented in clinical trials of systemic therapies (Langer and Mehta, 2005; Nguyen and Deangelis, 2004; Eichler and Loeffler, 2007).

On the other hand, there is growing evidence to suggest that epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) might allow patients with brain metastases and *EGFR* mutations to forego local treatment to the brain (Morin-Ben Abdallah and Wong, 2018). In this subpopulation of NSCLC patients, brain metastases occur in approximately 30% of patients during treatment with an EGFR TKI (Mujoomdar et al., 2007; Heon et al., 2010). NSCLC patients with *EGFR* mutations have a high incidence of brain metastases (Ge et al., 2017; Tomasini et al., 2016; Baek et al., 2018), probably due to the poor penetration of the blood brain barrier of first- and second-generation EGFR TKIs that were extensively used to treat patients with *EGFR* mutations, along with the long survival of these patients. Recently, the Young Investigators of the EORTC Lung Cancer Group conducted a survey on screening and treatment of NSCLC patients with brain metastases with 462 participating physicians from 394 institutions with high experience in treating NSCLC (Levy et al., 2018). The preferred treatment for asymptomatic brain metastases with more than 5 lesions was systemic chemotherapy in patients without an oncogenic driver and a TKI (85%) in patients with an oncogenic driver. However, the evidence about the efficacy of systemic treatments for patients with brain metastases remains scarce (Arvold et al., 2016).

Overall, there is limited evidence-based data about the management of NSCLC patients with *EGFR* mutations with brain metastases (Levy et al., 2018). To address this, our key objective was to develop a document based on a formal consensus process with recommendations on the diagnosis and treatment of brain metastases in patients with sensitizing *EGFR* mutated NSCLC. These recommendations have been formulated for any healthcare provider involved in the management of NSCLC patients with brain metastases.

2. Methods

This consensus document was developed out by a panel of 8 experts (5 medical oncologists [OJ, RL, AN, ALO, JP], 2 radiotherapy oncologists [AB, EV], and 1 neuro-oncologist [JB]), overseen by a coordinating committee of 2 medical oncologists (EN and SP) (Expert Panel). Methodological assessment was provided by GOC Networking (Spain). Further details of the methodology can be found in the Supplementary Appendix.

This consensus was developed using different methods, including those presented in the document on "Preparation of Clinical Practice Guidelines in the National Health System. Methodological manual" (Grupo de trabajo para la actualización del Manual de Elaboración de GPC, 2016). Development of the consensus followed these steps: Start-up, development of the protocol and formulation of clinical questions; Kick-off meeting: initial meeting, revision of the methodology and preparation of the thematic index; Non-exhaustive systematic review of literature; Critical reading and synthesis of available evidence; Preparation of recommendations by the Expert Panel; Online validation with a Delphi questionnaire of the recommendations and conclusions proposed by the Expert Panel; Final consensus meeting; and Final report, review and validation by the authors. This publication summarizes the recommendations and conclusions reached by consensus within the Expert panel. These recommendations are intended to provide guidance for the treatment of NSCLC patients with *EGFR* mutations and brain metastases; however, they should not be a substitute for the advice of the treating physician.

Seven areas to explore were defined to be included in the consensus and were grouped into 4 categories: *Pretreatment:* "Definitions", "Diagnosis", "Prognostic factors"; *On treatment:* "Treatment under different clinical scenarios", "First-line treatment algorithm", *Post-treatment:* "Patient follow-up"; and *Leptomeningeal carcinomatosis*: "Treatment of leptomeningeal carcinomatosis". Within these 7 areas, 21 clinical questions were posed (Supplementary Table S1).

The degree of agreement for each recommendation and conclusion was assessed as follows: (1) Recommendation or conclusion accepted unanimously: When the entire panel of experts agreed (100%); (2) Recommendation or conclusion accepted by consensus: When at least 80% of the panel of experts agreed, without reaching unanimity; (3) Recommendation or conclusion in discrepancy: When less than 80% of the panel of experts agreed with the recommendation.

A PubMed search was conducted for each question. Additionally, information on drug interactions was also sought in the database www.drugs.com. The search strategy focused on patients with *EGFR* mutated NSCLC with brain metastases and included multiple terms, as described in the Appendix. The aim of the search strategy was to generate recommendations that were useful and applicable to routine clinical practice. The treatment options that were included as search terms were restricted to what was available in the clinical practice at the time of the analysis. For example, for systemic treatment, the search focused on the EGFR TKIs that were approved for first-line treatment in Spain (gefitinib, erlotinib, and afatinib); however, it did not exclude dacomitinib (as a search criteria) or osimertinib (included in the bibliographic review according to author criteria). The search was limited to publications in English or Spanish language for the last 10 years. No exclusion criteria were established by type of publication. A total of 49 publications were identified (Supplementary Figure S1). The following clinical practice guidelines were included in the 49 publications analyzed: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines Oncology Non-small cell lung cancer. Version 2.2017 – October 26, 2016 (this version was used during the publication synthesis phase; however, during the recommendation development phase the updated version of Version 2.2018 (National Comprehensive Cancer Network, 2017) was included), 2016 European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up of metastatic NSCLC (Novello et al., 2016) (this version was originally used, but all recommendations and the manuscript were updated with the 2018 version (Planchard et al., 2018)), and the 2017 guidelines from the European Association of Neuro-Oncology (EANO) for the diagnosis and treatment of brain metastases from solid tumors (Soffietti et al., 2017). During the drafting of this article, additional publications were identified and have been incorporated as part of the literature review; however, the consensus recommendations remained as validated by the Expert Panel. This project was sponsored by Boehringer Ingelheim, Spain, but the company was not involved in any decision regarding the manuscript or in the approval of the last version of the manuscript.

3. Results

3.1. Consensus recommendations

Consensus-reached recommendations are listed in Box 1.

Box 1
Consensus recommendations

	Recommendation	LOE/ GOR	% agree (N)*
	Pretreatment consensus		
1	Given that patients with EGFR-mutated tumors may be more likely to develop brain metastases, it is advisable to perform an MRI in asymptomatic patients at the time of diagnosis [EP].	5/D	87.5 (9)
2	Lung-Mol DS-GPA index is a useful tool to assess the prognosis of patients with lung cancer and brain metastases (Sperduto et al., 2008, 2010)	1/A	87.5 (9)
	On treatment consensus		
3	In clinical trials with patients in advanced stages, the recommended endpoint could be OS or PFS, and patients should be stratified according to the presence of brain metastases (Lin et al., 2015; Pazdur, 2008)	5/D	100 (9)
4	It is advisable to avoid the use of local techniques with high toxicity (such as WBRT) in a patient that is EGFR-TKI naïve and asymptomatic [EP].	5/D	100 (8)
5	EGFR TKI is a reasonable option for those patients with asymptomatic brain metastases who will not receive local ablative therapies (surgery, radiosurgery, etc) (NCCN, 2016; Novello et al., 2016; Planchard et al., 2018; Khalifa et al., 2016; Zhang et al., 2016; Tan et al., 2016).	3/C	100 (8)
6	In patients with treatment naïve, EGFR-mutated NSCLC, with multiple asymptomatic brain metastases, it is advisable to start treatment with an EGFR TKI and postpone RT (NCCN, 2016; Novello et al., 2016; Planchard et al., 2018; Khalifa et al., 2016; Zhang et al., 2016; Tan et al., 2016).	3/C	100 (8)
7	For patients with asymptomatic brain metastases, it is advisable to begin systemic treatment with the best BBB-penetrating EGFR TKI available and delay the start of WBRT in order to minimize potential undesirable neurological adverse effects (Chen et al., 2016).	3/C	100 (9)
8	It is advisable to consider local treatments in case of symptoms associated with brain metastases (National Comprehensive Cancer Network, 2017).	3/B	88.9 (9)
9	In patients with symptomatic metastases that remain asymptomatic after treatment with corticosteroids, local treatment may be delayed [EP].	5/D	100 (9)
10	Surgery is indicated in patients with lung carcinoma with a brain metastasis $>$ 3 cm and/or with a significant mass effect (displacement of the median line greater than 1 cm) (Chi and Komaki, 2010; NCCN, 2016).	3/C	100 (9)
11	Surgery is indicated in patients with EGFR-positive lung carcinoma with a single brain metastasis and with good general condition, and controlled extracerebral disease (Pollock et al., 2003).	3/C	100 (8)
12	Radiosurgery is the treatment of choice in patients with lung carcinoma with 1-3 brain metastases without a significant mass effect that do not cause obstructive hydrocephalus (Schoggl et al., 2000; O'Neill et al., 2003; Sahgal et al., 2015).	2/B	100 (9)
13	In patients with more than 3 brain metastases, in which none exceed 3 cm or a volume $>$ 10 ml and the cumulative volume of all metastases is $<$ 15 ml, radiosurgery can be considered (Novello et al., 2016; Planchard et al., 2018; NCCN, 2016; Bhatnagar et al., 2006; Yamamoto et al., 2014).	3/C	100 (9)
14	In patients with EGFR mutations, radiosurgery should be considered when the only place of progression is the brain and there are 1-3 brain metastases (Na et al., 2017).	3/C	100 (8)
15	For patients with symptomatic brain metastases and steroid-controlled symptoms, the first recommended treatment is an EGFR TKI together with the appropriate supportive treatment (Jiang et al., 2016a).	3/B	88.9 (9)
16	For patients with uncontrolled symptomatic brain metastases, depending on the number of metastases and the patient's PS, it is recommended to consider surgery, radiosurgery or WBRT (National Comprehensive Cancer Network, 2017).	3/B	100 (9)
17	In case of intracranial disease progression that is sensitive to RT, an interruption of the EGFR TKI should be considered for a time that is equivalent to at least 4 or 5 half-lives of the drug before starting the RT. The EGFR TKI should be restarted from the second or third day after finishing RT (Hendriks et al., 2015).	3/C	100 (9)
18	There is not enough evidence to support the concurrent use of RT with EGFR TKI. However, in those patients with significant extracranial tumor burden, concurrence could be considered, but should be aware of a potential increase in toxicity (Tan et al., 2016; Proto et al., 2016).	2/C	100 (9)
19	When using an enzyme-inducing anticonvulsant, close monitoring of plasma pharmacological levels is recommended and the use of afatinib should be evaluated, instead of erlotinib or gefitinib given its absence of metabolism at the cytochrome P450 level (Grenader et al., 2007; Thomas-Schoemann et al., 2014).	NA	†
20	If continuous treatment with corticosteroid is required, concurrent with erlotinib or gefitinib, prednisone or methylprednisone should be considered as alternatives to dexamethasone (https://www.drugs.com/drug_interactions.html).	NA	†
	Post-treatment consensus		
21	In patients with good ECOG PS, especially in those who received only EGFR TKI and/or SRS, cranial imaging tests (ideally brain MRI) should be performed during follow-up (NCCN, 2017).	3/C	100 (8)
22	The advisable frequency of performing the cranial imaging tests would be every 3 months for 24-30 months, and subsequently every six months (NCCN, 2017; Magnuson et al., 2017).	5/D	87.5 (8)
	Treatment of patients with leptomeningeal carcinomatosis		
23	Depending on the treatments that have been previously received, intrathecal treatment and systemic pharmacotherapy could be considered for patients with leptomeningeal carcinomatosis with acceptable prognostic factors (Bruna et al., 2009).	4/C	100 (9)
24	Patients with leptomeningeal carcinomatosis diagnosed by neuroimaging without neoplastic cells in the CSF, can be considered for systemic therapy (EGFR TKI or chemotherapy) (Subira et al., 2015, 2012). ‡	5/D	100 (8)
25	Intrathecal chemotherapy plus systemic EGFR TKI can be considered in leptomeningeal carcinomatosis progression with systemic control of the disease (Glantz et al., 1999; Cole et al., 2017).	4/C	100 (9)
26	In patients with parenchymal brain metastases and leptomeningeal carcinomatosis, the first treatment choice should be based on the identification of the lesion causing the neurological symptoms, prioritizing RT and delaying intrathecal treatment for at least 2-3 weeks, to avoid neurological toxicity in the case of symptomatic brain metastases (Bruna et al., 2012).	5/C	87.5 (8)

3.2. First-line treatment algorithm

The algorithm of the first-line of treatment validated by the Expert Panel is detailed in Fig. 1.

1 **Asymptomatic:** does not exhibit neurological symptoms or alterations during neurological exploration (**C1**). **Oligosymptomatic:** presents alterations during neurological exploration that might be referred to in the medical history, but these do not impede a correct function considering basal state, or that disappear with medical treatment (steroids, analgesics, anticonvulsants) (**C2**).
2 **C16:** Concomitant WBRT plus EGFR TKI is the treatment of choice for patients with *EGFR*-mutated NSCLC and multiple BMs ($>$ 3) and symptoms derived from BMs.
3 **R15**: For patients with symptomatic BMs and symptom control with steroids, the first recommended treatment is an EGFR TKI with best supportive care. LOE/GOR:3/B.
4 **R18**: There is not enough evidence to support the use of concurrent

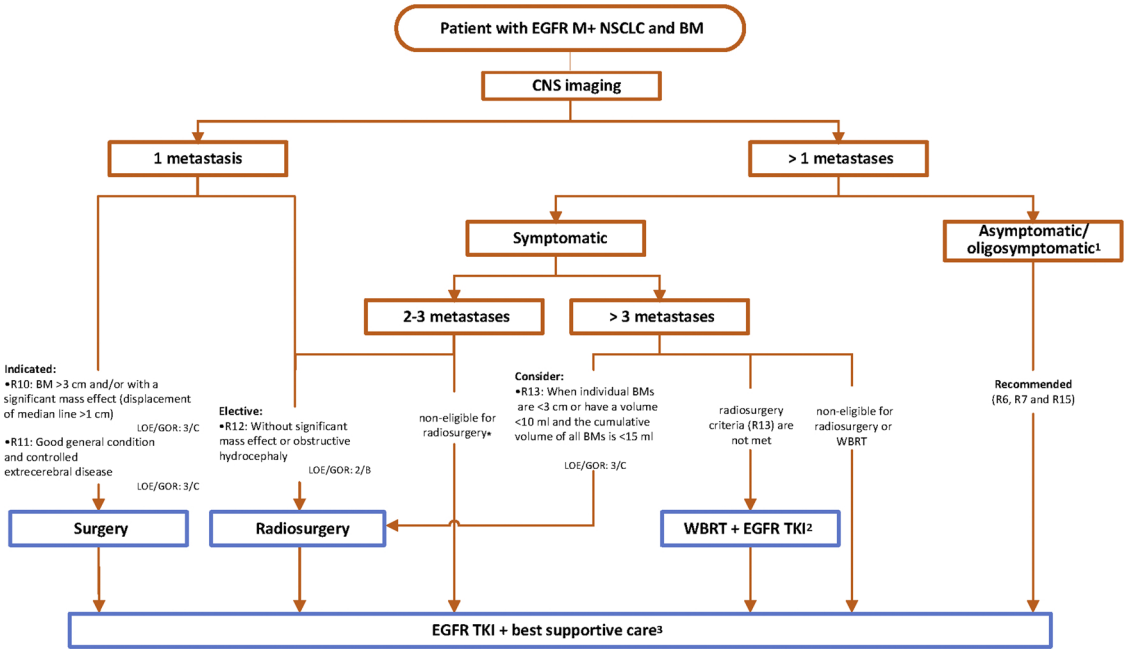

Fig. 1. First-line of treatment algorithm.

RT with EGFR TKI. However, in those patients with significant extracranial tumor burden, concurrent treatment could be considered; but, should be aware of a potential increase in toxicity. LOE/GOR:2/C.

*That have become asymptomatic after steroid treatment.

BM, brain metastases; EGFR, epidermal growth factor receptor; EGFR M+, mutated EGFR gene; EGFR TKI*, EGFR tyrosine kinase inhibitor; GOR, grades of recommendation; LOE, level of evidence; NSCLC, non-small cell lung cancer; RT, radiotherapy; WBRT, whole brain radiotherapy.*

4. pretreatment considerations for the management of patients with *EGFR* mutated NSCLC with brain metastases

4.1. Definition of asymptomatic/oligosymptomatic

The following definitions of asymptomatic or oligosymptomatic patients were formulated and validated by the Expert Panel.

	LOE/ GOR	% agree (N)
DEFINITION OF ASYMPTOMATIC / OLIGOSYMPTOMATIC		
What criteria define the asymptomatic and the oligosymptomatic patient?		
C1. A patient who is asymptomatic is considered to have imaging tests compatible with brain metastases but does not exhibit any symptoms or alteration in the neurological examination [EP].	NA	100 (9)
C2. A patient who is oligosymptomatic is considered to have alterations in the neurological examination, even they are noted or not in the medical history, that do not prevent appropriate functioning according to the patients' basal state, or that disappear with medical treatment (corticosteroids, analgesics, anticonvulsants) [EP].	NA	100 (9)

EP, Expert Panel; GOR, grades of recommendation; LOE, level of evidence, NA, not applicable.

4.2. Diagnosis by imaging and pattern of metastases

The extension of brain metastases can be assessed during the diagnosis of NSCLC with computerized axial tomography (CT), or by magnetic resonance imaging (MRI). Although the superiority of brain staging using MRI with gadolinium contrast over CT with iodinated contrast was not formally proven to improve OS in this clinical setting, brain MRI is the preferred method for its greater sensitivity (NCCN, 2016; Novello et al., 2016; Planchard et al., 2018). Consequently, the NCCN and the ESMO guidelines recommend MRI. If this is not possible, CT is recommended (Kuhn et al., 1994). Positron emission tomography (PET) is not recommended for the diagnosis of brain metastases (NCCN, 2016). Moreover, a prospective study and a meta-analysis both supported the use of MRI. A prospective study of 83 patients comparing the sensitivity of PET and MRI to detect a total of 39 brain lesions in 15 patients found that MRI detected 100% of the metastases, while PET only detected 38.5% of them with a sensitivity that was dependent upon the size of the metastases (Deuschl et al., 2017). A meta-analysis of 56 studies with a total of 8699 patients comparing 18F-fluorodeoxyglucose (FDG) PET/CT and CT showed higher sensitivity and specificity of PET/CT for the detection of all metastases except brain metastases (Wu et al., 2013).

The cumulative risk of developing brain metastases in patients with NSCLC is approximately 25%, with some studies indicating that the frequency may be higher in *EGFR* mutated tumors (Tan et al., 2016; Shin et al., 2014). In a retrospective study the cumulative risk of brain metastases over time in patients with *EGFR* mutated NSCLC was 34.2% at 1 year, 38.4% at 2 years, and 46.7% at 3 years. By 5 years more than half (52.9%) of the still living patients had brain metastases (Rangachari et al., 2015). Patients with *EGFR*-mutated brain metastases may have higher frequencies of multiple metastases than patients who do not harbor an *EGFR* mutation (Takamori et al., 2018). In addition, brain metastases harboring *EGFR* mutations were more frequently observed distant to cortico-subcortical areas compared to those without mutations in *EGFR*. Furthermore,

Table 1
Prognostic scales for patients with brain metastases.

	Developed from	Classification	Considers
RPA (Gaspar et al., 1997)	3 RTOG randomized studies 1200 patients with BMs	3 functional groups: Class I, II, III	Age, extracranial metastases, controlled primary tumor, KPS
GPA (Sperduto et al., 2014).	1 RTOG randomized study 211 patients with BM and lung cancer	3 scores: 0, 0.5 or 1.0	Age, KPS, number of BMs, extracranial metastases
DS-GPA (Sperduto et al., 2008, 2010).	Retrospective data on 5067 patients with BMs	Scores: 0-4	Disease-specific prognostic factors: KPS, age, extracranial metastases, number of BMs
Lung-Mol GPA (Sperduto et al., 2017).	1521 patients with lung adenocarcinoma and BMs	Scores 0-4	Oncogenic drivers

BMs, brain metastases; DS-GPA, disease specific graded prognostic assessment; GPA, graded prognostic assessment; KPS, Karnofsky performance status; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group.

survival in patients with asymptomatic brain metastases is higher than in symptomatic patients, independent of the treatment that was administered (Sanchez de Cos et al., 2009). This highlights the relevance of an early diagnostic that can be provided by baseline MRI screening and proper frequency of neuroimaging assessment during the treatment follow-up.

Based on this evidence, the following conclusions and **recommendation** regarding the imaging technique for detecting brain metastases were formulated and validated.

	LOE/ GOR	% agree (N)*
DIAGNOSIS BY IMAGING AND PATTERN OF METASTASES		
What is the preferred imaging technique to diagnose brain metastases?		
C3. Based on published data in the scientific literature and in clinical guidelines, the preferred technique for the diagnosis of brain metastases is MRI, preferably with gadolinium (Novello et al., 2016; Planchard et al., 2018; NCCN, 2016)	NA	100 (8)
C4. When an MRI test is not available or there is a technical impossibility to perform it, a contrast CT would be the alternative technique, although suboptimal (Kuhn et al., 1994)	NA	100 (9)
C5. PET/CT have low sensitivity to diagnose brain metastases (Wu et al., 2013).	NA	100 (9)
Should imaging tests be performed on asymptomatic patients to identify brain metastases?		
C6. The data found in the literature are based on retrospective series and are not specific to patients with *EGFR* mutation; however, the frequency of silent brain metastases in patients with lung cancer is considerable (Sanchez de Cos et al., 2009; Jena et al., 2008; Na et al., 2008)	NA	100 (8)
R1. Given that patients with *EGFR*-mutated tumors may be more likely to develop brain metastases, it is advisable to perform an MRI in asymptomatic patients at the time of diagnosis [EP].	**5/D**	**87.5 (9)**

CT, computerized axial tomography; *EGFR*, epidermal growth factor receptor; GOR, grades of recommendation; LOE, level of evidence; EP, Expert Panel; MRI, magnetic resonance imaging; NA, not applicable; PET, positron emission tomography.
*Not all participants were able to complete the first online round of validation (n = 8), while all participants attended the final meeting (n = 9) and an additional round of validation (n = 9).
The recommendations are in bold and the conclusions not bolded.

4.3. Prognostic factors

There are several assessments (Table 1) for estimating a patient's prognosis: recursive partitioning analysis (RPA) (Gaspar et al., 1997), the most currently used for brain metastases and validated in Phase III clinical studies, graded prognostic assessment (GPA) (Sperduto et al., 2014), the disease-specific graded prognostic assessment (DS-GPA) (Sperduto et al., 2008, 2010), the graded prognostic assessment for lung cancer using molecular markers (Lung-Mol GPA) (Sperduto et al., 2017), and the Barnholtz-Sloan nomogram (Barnholtz-Sloan et al., 2012). In patients with NSCLC harboring actionable genomic alterations and brain metastases, the Lung-Mol GPA index can help clinical decisions and patients' stratification in future clinical trials. These scales have some limitations and cannot precisely establish which is the best treatment option for each individual patient.

Regarding the prognostic role of specific *EGFR* mutations, the evidence is inconclusive, mostly due to the retrospective nature of the studies, the unknown power of the studies, and the lack of randomization between study groups. *EGFR* mutations generally occur between exons 18-21. Deletions in exon 19 (LREA) and mutations in exon 21 (L858R) account for about 90% of *EGFR* mutations (Porta et al., 2011; Sekine et al., 2014).

In a retrospective study of 817 patients with NSCLC and brain metastases undergoing radiosurgery with gamma knife surgery (GKS), mutations in *EGFR* (exon 18–21) was a positive prognostic factor associated with improved OS (Lee et al., 2017). Even though EGFR TKIs were more frequently prescribed to patients with *EGFR* mutations, multivariable analysis showed that the presence of *EGFR* mutations was a strong independent prognostic factor. In a study examining the significance of *EGFR* mutations on the incidence of brain metastases in patients with stage I to III lung cancer, there was a higher cumulative incidence of brain metastases in patients with *EGFR* mutations than in patients with wild-type *EGFR* (Chang et al., 2018). In patients with *EGFR* mutations there is a preferential pattern of primary disease progressing through lung metastases to the brain, as compared with *EGFR* wild type (Gino et al., 2017).

Another study showed no statistical improvement in survival; however, patients with *EGFR* exon 19 deletion tended to have a longer survival. Along the same direction other studies have shown that patients with *EGFR* deletions in exon 19, but not patients with mutations in exon 21 treated with EGFR TKI plus WBRT or SRS had higher PFS

and OS than patients treated only with EGFR TKI (Zhu et al., 2017). Differences in outcome between the two *EGFR* mutation subtypes in patients with brain metastases and treated with *EGFR*-TKI monotherapy have also been observed in terms of overall response rate (ORR) (Sekine et al., 2014; Iuchi et al., 2013; Lee et al., 2013) and in terms of PFS and OS (Iuchi et al., 2013). Several retrospective analyses have confirmed the efficacy of EGFR TKI for brain metastases, particularly in patients with *EGFR* mutated NSCLC (Porta et al., 2011; Hotta et al., 2004; Kim et al., 2009).

The following conclusions and **recommendation** regarding clinical and radiological variables impacting patients' prognosis, including the type of *EGFR* mutation, were formulated and validated.

	LOE/ GOR	% agree (N)*
PROGNOSTIC FACTORS		
What clinical and radiological variables have an impact on the patient's prognosis?† What is the value of the prognostic scales?†		
C7. In NSCLC, significant prognostic factors are KPS, age, presence of extracranial metastases and the number of brain metastases, confirming the original GPA for this diagnosis (Sperduto et al., 2008, 2010)	NA	100 (8)
C8. The molecular aspects included in the previous scale add a new tool to manage patients with lung cancer and brain metastases and define the Lung-Mol DS-GPA index (Sperduto et al., 2017).	NA	100 (9)
R2. Lung-Mol DS-GPA index is a useful tool to assess the prognosis of patients with lung cancer and brain metastases (Sperduto et al., 2008, 2010).	**1/A**	**87.5 (9)**
Do patients with brain metastases have a different prognosis depending on the type of mutation?		
C9. The influence exon 19 deletions (LREA) or exon 21 mutations (L858R) on the outcome of patients with *EGFR* mutated NSCLC with brain metastases, regardless of therapy, has not yet been established (Tsao et al., 2005)	NA	89 (9)
C10. *EGFR* mutations predict benefit of treatment with EGFR TKI. The predicted response of treatment sensitive *EGFR* mutations (exon 19 [LREA deletion] and exon 21 [L858-R]) is well defined. Patients with these mutations have a significantly better response to EGFR TKI (Langer, 2013).	NA	100 (9)

DS-GPA, Diagnosis-Specific Graded Prognostic Assessment; *EGFR*, epidermal growth factor receptor; EP, Expert Panel; GPA, graded prognostic assessment; GOR, grades of recommendation; LOE, level of evidence; NA, not applicable; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

*Not all participants were able to complete the first online round of validation (n = 8), while all participants attended the final meeting (n = 9) and an additional round of validation (n = 9).

† These two questions are closely related, and it was agreed to unify and evaluate them as one.

The recommendations are in bold and the conclusions not bolded.

5. On treatment considerations for the management of patients with *EGFR* mutated NSCLC with brain metastases

5.1. Recommended endpoint for clinical studies

Most clinical trials evaluating systemic treatments have not included patients with brain metastases; however, time to treatment failure and high-grade toxicities might be similar to those observed in patients without brain metastases (Tsimberidou et al., 2011). The response to systemic treatment may differ between intra-CNS and extra-CNS diseases due to the limited capacity of most drugs to cross the blood-brain barrier (BBB) (Suh et al., 2006). On the whole, there are no data to indicate that the inclusion of patients with brain metastases should lead to a modification of the recommended primary endpoints in clinical studies; however, additional endpoints could be included to specifically asses the efficacy of a specific treatment in brain metastases.

The RANO working group has proposed a series of criteria to objectively measure intracranial disease and evaluate the response in patients with brain metastases (Lin et al., 2015). Although not yet validated, these criteria, include the size of the lesions, clinical status and the use of corticosteroids, providing information on the antitumor effect and the clinical benefit of the treatment (Table S2).

The RANO Expert Panel recommends Phase II and III trials protocols to specify and allow local treatment with surgery, WBRT or SRS to rescue patients with isolated intracranial progression, allowing patients to remain on trial if they are presenting clinical benefit or stabilization of extracranial disease.

Based on this evidence, it was recommended, that in clinical trials with patients in advanced stages, the recommended primary endpoint could be OS or PFS, and patients should be stratified according to the presence of brain metastases (Lin et al., 2015; Pazdur, 2008; European Medicine Agency, 2012 (**Recommendation 3**).

5.2. Asymptomatic/oligosymptomatic brain metastases

There are conflicting data on the timing of radiation for patients with asymptomatic or oligosymptomatic brain metastases. Disease control can be achieved with RT in patients with *EGFR*-mutated tumors and newer techniques such as WBRT with hippocampal avoidance could reduce the neurotoxicity of these treatments (Khalifa et al., 2016; Tan et al., 2016). However, these novel techniques have not been specifically evaluated in patients with *EGFR*-mutated NSCLC.

Although the low molecular weight and nonpolar nature of EGFR TKIs favor passive diffusion across the BBB, most EGFR TKIs are substrates for P-glycoprotein or other efflux transporter proteins (Chamberlain et al., 2017). The cerebrospinal fluid (CSF) concentrations achieved by erlotinib, gefitinib and afatinib are above those required to inhibit cell proliferation in vitro in cell models with *EGFR* mutations.

WBRT might have a detrimental impact on cognitive function and quality of life. EGFR TKI have high antitumor activity at the CNS level (Soon et al., 2015; Schuler et al., 2016); although it is rare to obtain a complete radiologic response in the brain. Treatment with EGFR TKI followed by RT at the time of clinical or radiological intracranial progression resulted in a similar in OS among patients receiving RT or not receiving RT (23.6 vs. 18.7 months; p = 0.317) (Zhang et al., 2016). In a retrospective study of patients with *EGFR* mutated NSCLC there was a lack of survival benefit when RT was administered at the start of treatment with EGFR TKI and there was no benefit compared with EGFR TKI alone in terms of intracranial progression (Liu et al., 2015). On the other hand, the delay to administering RT in combination with an EGFR TKI was associated with worse survival in patients with *EGFR* mutation in another retrospective study (Magnuson et al., 2017). Randomized trials comparing WBRT followed by EGFR TKI with concurrent administration of WBRT and EGFR TKI have not been completed, with one study closed prematurely due to low recruitment (NCT01518621). The Phase III trials of afatinib (LUX-Lung 3, LUX-Lung 6), and osimertinib (FLAURA) are large sets of prospective data from

Table 2
Rates of tumor response in patients with or without BM, and common *EGFR* mutations in LUX-Lung 3 and 6 (Schuler et al., 2016) and in FLAURA (Soria et al., 2018) Phase III studies.

	With brain metastases			Without brain metastases		
LUX-Lung 3	Afatinib n = 20	Cisplatin-pemetrexed n = 15	p-value	Afatinib n = 166	Cisplatin-pemetrexed n = 82	p-value
ORR, n (%)	14 (70.0)	3 (20.0)	0.0058	100 (60.2)	19 (23.2)	< 0.0001
DCR, n (%)	19 (95.0)	12 (80.0)	0.1986	157 (94.6)	65 (79.3)	0.0005
LUX-Lung 6	Afatinib n = 28	Cisplatin-gemcitabine n = 18	p-value	Afatinib n = 185	Cisplatin-gemcitabine n = 86	p-value
ORR, n (%)	21 (75.0)	5 (27.8)	0.0027	124 (67.0)	19 (22.1)	< 0.0001
DCR, n (%)	25 (89.3)	13 (72.2)	0.1486	171 (92.4)	66 (76.7)	0.0005
FLAURA*	Osimertinib n = 53	EGFR TKI n = 63	p-value	Osimertinib n = 226	EGFR TKI n = 214	p-value
ORR, n (%)	40 (75.5)	54 (85.7)	0.16	183 (81.0)	156 (72.9)	0.04
DCR, n (%)	53 (100)	62 (98.4)	NR	217 (96.0)	194 (90.7)	NR

BM, brain metastases; DCR: disease control rate; *EGFR*: epidermal growth factor receptor; CI: confidence interval; LUX-Lung 3: Phase III study of Afatinib or Cisplatin and Pemetrexed in patients with metastatic lung adenocarcinoma with mutated *EGFR*; LUX-Lung 6: a randomized, open-label Phase III study of BIBW 2992 compared to QT as the first line of treatment for patients with stage IIIB or IV lung adenocarcinoma with active *EGFR* mutation; NR, not reported; ORR: overall response rate. *Unconfirmed objective response rate (with response assessed by the investigator).

patients with *EGFR* mutated NSCLC and brain metastases treated with EGFR TKIs (Schuler et al., 2016; Soria et al., 2018). These trials allowed the participation of patients with stable and clinically asymptomatic brain metastases. Baseline brain imaging was mandatory only in patients with known or suspected CNS metastases, and follow-up imaging was performed only in patients with confirmed CNS metastases. In both LUX-Lung trials, ORR was significantly higher in patients with *EGFR* mutated NSCLC and brain metastases treated with afatinib than with chemotherapy (Table 2). In both afatinib trials, ORR with afatinib was 82.1% in patients with deletion in exon 19 and 60.0% in carriers of mutation in exon 21 (L858R) (Schuler et al., 2016). Approximately 20% of patients in the FLAURA trial had neurologically stable brain metastases at baseline. Overall, the outcomes of patients with brain metastases were lower than patients without brain metastases. However, patients with brain metastases treated with osimertinib had a longer median PFS (15.2 vs 9.6 months, HR 0.47 [95% CI, 0.30–0.74]) and a longer CNS PFS in patients with measurable and nonmeasurable CNS lesions (not reached vs 13.9 months, HR 0.48 [95% CI 0.26-0.86]). In patients with at least one measurable brain metastasis, CNS response rate was 91% vs 68% for osimertinib vs standard treatment, respectively (Reungwetwattana et al., 2018). In patients with measurable and nonmeasurable CNS lesions, CNS response rate was 66% and 43% respectively. In addition, osimertinib had a more favorable tolerability profile than first-generation EGFR TKIs (gefitinib or erlotinib). Patients treated with osimertinib experienced fewer events of central nervous system (CNS) progression (6%) than those treated with first-generation EGFR TKI (15%), but only patients with brain metastases were required to have radiological follow-up throughout the study. Afatinib appears to reduce the risk of CNS metastases based on a recent competing risk analysis of the LUX-Lung 3, 6, and 7 studies (Yang et al., 2018a). In this analysis, the risk of CNS progression vs non-CNS progression or death was calculated based on the cumulative frequency of the event of interest versus the competing risk event. The risk of new CNS progression was very low (6.4%) compared with non-CNS progression (78.4%) in patients without baseline brain metastases who received afatinib (N = 485; median follow-up 13.0 months). The cumulative incidence of CNS progression was 5.3% at 24 months.

Given the high rate of responses with EGFR TKIs, EANO guidelines recommend it as a treatment option for *EGFR*-mutated NSCLC patients with asymptomatic brain metastases (Soffietti et al., 2017). An alternative is the use of cranial RT (stereotactic or holocranial) in combination with an EGFR TKI, with the aim of achieving better survival outcomes. With the use of EGFR TKI alone, it is possible to delay the need for WBRT, thus delaying its adverse events (Schuler et al., 2016).

Based on this evidence, the following conclusions and **recommendations** regarding local treatment of asymptomatic patients were formulated and validated.

	LOE/ GOR	% agree (N)*
TREATMENT IN DIFFERENT CLINICAL SCENARIOS		
Should brain metastases be treated locally in asymptomatic patients?		
C11. Not enough evidence has been found to answer this question. The use of therapies associated with less neurological toxicity seems the most reasonable option in patients with asymptomatic and oligosymptomatic brain metastases [EP].	NA	87.5 (9)
R4. It is advisable to avoid the use of local techniques with high toxicity (such as WBRT) in a patient that is EGFR-TKI naïve and asymptomatic [EP].	5/D	100 (8)
R5. EGFR TKI is a reasonable option for those patients with asymptomatic brain metastases who will not receive local ablative therapies (surgery, radiosurgery) (NCCN, 2016; Novello et al., 2016; Khalifa et al., 2016; Zhang et al., 2016; Tan et al., 2016).	3/C	100 (8)
R6. In patients with treatment naïve, *EGFR*-mutated NSCLC, with multiple asymptomatic brain metastases, it is advisable to start treatment with an EGFR TKI and postpone RT (NCCN, 2016; Novello et al., 2016; Khalifa et al., 2016; Zhang et al., 2016; Tan et al., 2016).	3/C	100 (8)
What is the first treatment that should be used in the patient with asymptomatic brain metastases?		
C12. There is not enough evidence to establish which should be the first treatment for patients with *EGFR*-mutated NSCLC with asymptomatic brain metastases [EP].	NA	87.5 (8)
C13. There was not enough evidence to answer this question. However, given the potential neurocognitive impairment of WBRT, the use of less aggressive therapies seems the most reasonable option in patients with asymptomatic brain metastases [EP].	NA	100 (8)
R7. For patients with asymptomatic brain metastases, it is advisable to begin systemic treatment with the best BBB-penetrating EGFR TKI available and delay the start of WBRT in order to minimize potential undesirable neurological adverse effects.	3/C	100 (9)

BBB, blood-brain barrier; *EGFR*, epidermal growth factor receptor; EP, Expert Panel; GOR, grades of recommendation; LOE, level of evidence; MRI, magnetic resonance imaging; NA, not applicable; RT, radiotherapy; TKI, tyrosine kinase inhibitor; WRBT, whole brain radiation therapy.
*Not all participants were able to complete the first online round of validation (n = 8), while all participants attended the final meeting (n = 9) and an additional round of validation (n = 9).
The conclusions are not in bold and the recommendations are in bold.

Table 3
Results of comparative studies (WBRT, SRS, and EGFR TKI).

Ref	Study design	Treatment	Time to intracranial progression (months)	OS (months)
(Doherty et al., 2017)	Retrospective	WBRT (n = 120)	NR	21.6
	Patients with NSCLC and BMs (*EGFR*+/*ALK*+)	SRS (n = 37)	12.0 p = 0.0064	23.9 p = 0.67
	N = 184 (163 *EGFR*+ and 21 *ALK*+)	EGFR TKI (n = 27)	16.2	22.6
(Magnuson et al., 2017)	Retrospective	WBRT followed by EGFR TKI (n = 120)	24 (95% CI 21–30)	30 (95% CI 27–38)
	Patients with NSCLC and BMs (*EGFR*+) without prior EGFR TKI treatment	SRS followed by EGFR TKI (n = 120)	23 (95% CI 18–28); p = 0.025	46 (95% CI 37–57); p < 0.001
	N = 351	EGFR TKI followed by WBRT or SRS (n = 131)	17 (95% CI 14–30)	25 (95% CI 20–22)
(Yang et al., 2017)	Phase III study	WBRT (n = 91)	4.8 (95% CI 2.4–7.2)	20.5 (17.0–24.1)
	Patients with NSCLC and ≥ 3 BMs (*EGFR*+) without prior EGFR TKI or RT	EGFR TKI (icotinib) (n = 85)	10.0 (95% CI 5.6–14.4)	18.0 (15.1–20.9)
	N = 176		HR 0.56 (95% CI 0.36–0.90), favoring EGFR TKI; p = 0.014	HR 0.93 (95% CI 0.60–1.44); p = 0.734

ALK, anaplastic lymphoma kinase; BM, brain metastases; CI, confidence interval; *EGFR*, epidermal growth factor receptor; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WRBT, whole brain radiation therapy.

5.3. Symptomatic brain metastases

5.3.1. Surgery

Currently, there are no randomized trials aimed at evaluating surgery, or radiosurgery for brain metastases exclusively in patients with NSCLC, regardless of mutations in *EGFR*. Surgery would be indicated in the case of single symptomatic metastasis and in patients with multiple metastases on the dominant and symptomatic lesion (NCCN, 2016; Chi and Komaki, 2010). In patients with a single brain metastasis, limited extracranial disease and good general condition, surgery with WBRT is superior to WBRT alone (Patchell et al., 1998; Vecht et al., 1993; Mintz et al., 1996). In selected patients with multiple brain metastases (2 to 3), with good general condition and controlled systemic disease, complete surgical resection has results similar to those obtained in patients with a single brain metastasis (median OS of 19 months) (Pollock et al., 2003). Four retrospective studies compared surgery and radiosurgery, suggesting that surgery offers better results in the control of symptoms in patients with lesions > 3 cm or that cause a significant mass effect (displacement > 1 cm from the median line) (Schoggl et al., 2000; O'Neill et al., 2003; Bindal et al., 1996; Garell et al., 1999). The addition of WBRT to surgery or to SRS is associated with a decrease in intracranial relapse, with no impact on OS, although with an increase in neurological toxicity (Patchell et al., 1998; Aoyama et al., 2006; Chang et al., 2009; Tsao et al., 2012; Churilla et al., 2017). Conversely, SRS to the surgical cavity presents a better safety profile with less cognitive decline and similar OS with regard the addition of WBRT. However, the intracranial relapse still is higher than with WBRT.

5.3.2. Radiosurgery

Most studies set a limited size of the lesions at 3–4 cm for radiosurgery, due to side effects secondary to the RT in larger lesions (Sneed et al., 2015). In contrast with the studies mentioned in the previous section, two retrospective studies of patients with single brain metastasis, radiosurgery was equal to or superior to surgery in terms of OS and local control (Schoggl et al., 2000; O'Neill et al., 2003). A prospective study with 1194 patients with multiple brain metastases (1, 2–4 or 5–10) with an accumulated volume of all metastases < 15 ml, treated with radiosurgery, showed similar OS (10.8 months) and toxicity in the 2–4 and 5–10 metastases groups (HR 0.97 [95% CI 0.81–1.18]; p = 0.78) (Yamamoto et al., 2014). In a retrospective study, patients with 1–3 brain metastases, radiosurgery plus WBRT was superior to surgery with WBRT in terms of OS (56% vs 47%; p = 0.034), intracranial control (66% vs 50%; p = 0.003) and local control at one year (82% vs 66%; p = 0.006) (Rades et al., 2009). In patients with more than 3 metastases, WBRT has classically been the standard treatment, although radiosurgery may be considered in some patients (NCCN, 2016; Novello et al., 2016). As previously commented, in patients with a limited number of metastases, adding WBRT to radiosurgery results in an increased risk of cognitive impairment without benefit in OS (Chang et al., 2009; Aoyama et al., 2007; Trifiletti et al., 2016) In patients with *EGFR* mutations, radiosurgery can be considered when the brain is the only place of progression and the number of brain metastases is ≤ 3, whereas WBRT can be considered in more extensive brain disease (Na et al., 2017; Doherty et al., 2017). Moreover, in a retrospective study in patients with *EGFR* mutated NSCLC, early radiosurgery achieved better OS (46 months) than WBRT (30 months) or EGFR TKI without local treatment (25 months) (Magnuson et al., 2017). However, the retrospective nature of this study might have contributed to some potential biases, since patients were not randomly assigned to SRS, WBRT or EGFR TKI. In addition, the authors did not compare the toxicity and cognitive impairment associated with those therapeutic approaches.

5.3.3. WBRT

Longer time to intracranial progression was observed with WBRT compared with initial treatment with radiosurgery and EGFR TKI in two

Table 4
Comparative studies of WBRT and EGFR TKI combinations vs EGFR TKI alone.

	WBRT plus EGFR TKI			EGFR TKI		
	Chen et al. (2016)	Zhu et al. (2017)	Jiang et al. (2016a)	Chen et al. (2016)	Zhu et al. (2017)	Jiang et al. (2016a)
N	53	67	51	75	60	116
EGFR mutations (%)	100	100	100	100	100	100
Asymptomatic (%)	30.2	NA	77.4	65.6	NA	87.9
Extracranial metastases (%)	NA	65,7	60,8	NA	65.2	59.5
> 3 BMs (%)	79.2	73.1	96	69.6	65.3	95.7
iPFS (months)	24.7	16	6.9	18.2	11.2	7.4
OS (months)	48	22	21.6	41.1	15	26.4

BM, brain metastases; *EGFR*, epidermal growth factor receptor; iPFS, intracranial progression-free survival; NA, not available; NSCLC, non-small cell lung cancer; OS, overall survival; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WRBT, whole brain radiation therapy.

retrospective studies (Magnuson et al., 2017; Doherty et al., 2017), but was longer with EGFR TKI alone in a Phase III study (Yang et al., 2017) (Table 3). However, there were no differences in OS between treatments in two studies (Doherty et al., 2017; Yang et al., 2017), while in the other, patients treated with radiosurgery had a longer survival (Magnuson et al., 2017). In the Phase III BRAIN study, the efficacy of the EGFR TKI icotinib was compared with WBRT with sequential or concurrent chemotherapy in Chinese patients with *EGFR* mutant NSCLC and multiple brain metastases (Yang et al., 2017). Icotinib yielded longer intracranial PFS than WBRT plus chemotherapy. Patients with exclusive intracranial progression receiving icotinib were switched to a combination of WBRT and icotinib or chemotherapy and patients receiving WBRT were switched to icotinib at disease progression. More patients in the WBRT group switched to icotinib compared with patients in the icotinib group who switched to icotinib plus WBRT, potentially explaining why OS was not improved in the icotinib arm.

The combination of WBRT and EGFR TKI is significantly superior to WBRT in intracranial response, time to intracranial progression and median OS (Magnuson et al., 2017; Luo et al., 2015; Jiang et al., 2016b). There is high heterogeneity among studies comparing the WBRT/EGFR TKI combination with EGFR TKI alone (Table 4).

A meta-analysis of 12 retrospective studies and 363 patients with *EGFR* mutated NSCLC and brain metastases concluded that the combination of WBRT and EGFR TKI had similar response rates (relative risk [RR] 0.93 [95% CI 0.82–1.06]; p = 0.53) as EGFR TKI alone, but had an increase in intracranial progression-free survival (PFS) at 4 months (RR 1.06 [95% CI 1.00–1.12]; p = 0.03) and OS at 2 years (RR 1.33 [95% CI 1.00–1.77]; p = 0.05); however, the WBRT/EGFR TKI combination was associated with an increase in neurological side effects (headache and dizziness) (Soon et al., 2015). Conversely, another meta-analysis of 4 retrospective studies in patients with *EGFR* mutated NSCLC and multiple brain metastases (> 3 lesions) showed similar survival between the combination of WBRT/EGFR TKI and EGFR TKI alone (HR 1.25 [95% CI 0.98–1.59]; p = 0.08). The intracranial PFS was higher with EGFR TKI alone (HR 1.30 [95% CI 1.03–1.65]; p = 0.03) (Zheng et al., 2017).

To complicate the interpretation, a third metanalysis has recently been published. This analysis of four other retrospective studies included 507 patients with *EGFR* mutated patients with synchronous brain metastases compared the treatment of front-line EGFR TKI with brain RT (generally WBRT) combined with EGFR TKI (Liang et al., 2018). There was no significant benefit in OS (HR 0.81 [95% CI 0.53–1.26]) or intracranial PFS (HR 0.84 [95% CI 0.55–1.27]) with combined EGFR TKI plus brain RT compared with EGFR TKI alone.

Based on the evidence reviewed of local treatment, the following conclusions and **recommendations** regarding treatment of

Table 5
Summary of the characteristics and results of the studies with EGFR TKI.

Ref	Study design	Primary objective	Patients with BM treated with EGFR TKIs	Intracranial activity
(Bai et al., 2017)	Retrospective study N = 148 patients	Response rate	Gefitinib (n = 95) and erlotinib (n = 53)	34.7% (gefitinib) vs. 39.6% (erlotinib)† p = 0.813
(Zhang et al., 2016)	Retrospective study N = 43 patients	Response rate	Gefitinib (n = 30) and erlotinib (n = 13)	57% (no significant differences between gefitinib and erlotinib)
(Kashima et al., 2016)	Retrospective study N = 205 patients (63 patients had brain metastases at initiation of EGFR TKI)	OS	Gefitinib (n = 52) and erlotinib (n = 11)	mOS: 25.0 months (erlotinib) vs 18.1 months (gefitinib); p = 0.45
(Hoffknecht et al., 2015)	Retrospective study* N = 100 patients	Response rate	Afatinib (N = 100)	35%‡
(Goss et al., 2018)	Pre-specified analyses of pooled Phase II studies	Response rate	Osimertinib (N = 50)	54%§
(Soria et al., 2018; Reungwetwattana et al., 2018)	Randomized Phase III clinical trial N = 556	Progression-free survival	Osimertinib (N = 61) versus erlotinib or gefitinib (N = 67)	66% (osimertinib) vs. 43% (erlotinib, gefitinib)¶

CNS, central nervous system; NR, not reported; (m)OS, (median) overall survival; TKI, tyrosine kinase inhibitor;
*Afatinib's compassionate use program.
†Partial response results.
‡ 19% (6 of 31) of the patients had a general response (defined as a systemic response and a response at the CNS level) and 16% (5 of 31) had an intracranial response only.
§18/50 patients (36%) had both a CNS and systemic response and 9/50 (18%) had an intracranial response only.
¶CNS objective response rate in patients with measurable and/or non-measurable CNS lesions.

symptomatic patients were formulated and validated.

	LOE/ GOR	% agree (N)
TREATMENT IN DIFFERENT CLINICAL SCENARIOS		
Should brain metastases be treated locally in symptomatic patients?		
R8. It is advisable to evaluate local treatments in case of symptoms associated with brain metastases (National Comprehensive Cancer Network, 2017).	3/B	88.9 (9)
R9. In patients with symptomatic metastases that remain asymptomatic after treatment with corticosteroids, local treatment may be delayed [EP].	5/D	100 (9)
Which patients should be considered to surgical treatment?		
R10. Surgery is indicated in patients with lung carcinoma with a brain metastasis > 3 cm and/or with a significant mass effect (displacement of the median line greater than 1 cm) (NCCN, 2016; Chi and Komaki, 2010).	3/C	100 (9)
R11. Surgery is indicated in patients with *EGFR* positive lung carcinoma with a single brain metastasis and with good general condition, and controlled extracerebral disease (Pollock et al., 2003).	3/C	100 (8)
Which patients should be considered for radiosurgery treatment?		
C14. The addition of WBRT to radiosurgery does not improve survival and has a negative effect on the survival of patients younger than 50 years [EP].	1/A	100 (8)
C15. The addition of WBRT to radiosurgery increases the risk of cognitive impairment [EP].	2/B	100 (8)
R12. Radiosurgery is the treatment of choice in patients with lung carcinoma with 1-3 brain metastases without a significant mass effect that do not cause obstructive hydrocephalus (Schoggl et al., 2000; O'Neill et al., 2003; Sahgal et al., 2015).	2/B	100 (9)
R13. In patients with more than 3 brain metastases, in which none exceed 3 cm or a volume > 10 ml and the cumulative volume of all metastases is < 15 ml, radiosurgery can be considered (NCCN, 2016; Novello et al., 2016; Planchard et al., 2018; Bhatnagar et al., 2006; Yamamoto et al., 2014).	3/C	100 (9)
R14. In patients with *EGFR* mutations, radiosurgery should be considered when the only place of progression is the brain and there are 1-3 brain metastases (Na et al., 2017).	3/C	100 (8)
Which patients should be considered for holocranial treatment?		
C16. Concomitant WRBT and EGFR TKIs is the treatment of choice in patients with *EGFR*-mutated NSCLC and multiple symptomatic brain metastases (> 3) (Soon et al., 2015).	NA	87.5 (8)
C17. WBRT may be postponed in patients with *EGFR*-mutated NSCLC, and multiple brain metastases that remain asymptomatic after administration of corticosteroids (Zheng et al., 2017) and [EP].	NA	87.5 (8)
C18. WBRT is not indicated after local treatment (radiosurgery or surgery) in patients with *EGFR*-mutated NSCLC and a limited number of brain metastases (Sahgal et al., 2015; Chang et al., 2009; Aoyama et al., 2007).	NA	100 (8)
What is the first treatment that should be used in the patient with symptomatic brain metastases?		
R15. For patients with symptomatic brain metastases and steroid-controlled symptoms, the first recommended treatment is an EGFR TKI together with the appropriate supportive treatment (Jiang et al., 2016a).	3/B	88.9 (9)
R16. For patients with uncontrolled symptomatic brain metastases, depending on the number of metastases and the patient's PS, it is recommended to consider surgery, radiosurgery or WBRT (National Comprehensive Cancer Network, 2017).	3/B	100 (9)

EGFR, epidermal growth factor receptor; EP, Expert Panel; GOR, grades of recommendation; LOE, level of evidence; NSCLC, non-small cell lung cancer; RT, radiotherapy; TKI, tyrosine kinase inhibitor; WRBT, whole brain radiation therapy.
*Not all participants were able to complete the first online round of validation (n = 8), while all participants attended the final meeting (n = 9) and an additional round of validation (n = 9).
The conclusions are not in bold and the recommendations are in bold.

5.3.4. Systemic treatment

Having an *EGFR* mutation is predictive of response to EGFR TKIs in patients with NSCLC and brain metastases (NCCN, 2016; Zhang et al., 2016). The brain penetration of first- and second-generation EGFR TKI is low compared with the concentration that is achieved in plasma (Khalifa et al., 2016). The limited brain exposure of EGFR TKI may explain the high incidence of brain metastases in patients with *EGFR*-mutated NSCLC, despite disease control of extracranial disease. However, the existence of brain metastases might make the BBB more permeable facilitating a greater penetration of the EGFR TKI (Lassman et al., 2005). Icotinib had similar brain penetration as erlotinib and gefitinib (Tan et al., 2017). On the other hand, osimertinib showed higher penetration in the blood-brain barrier of mouse models than gefitinib, rociletinib or afatinib (Ballard et al., 2016).

5.3.4.1. Different EGFR TKIs. No significant differences in intracranial activity have been reported between erlotinib and gefitinib (Zhang et al., 2016; Bai et al., 2017; Park et al., 2012; Kashima et al., 2016) (Table 5), or between afatinib and gefitinib (Park et al., 2016). In the Phase III FLAURA trial, the rate of CNS progression was 19% for those treated with osimertinib, compared with 43% for patients receiving gefitinib or erlotinib, indicating that osimertinib is effective in delaying tumor progression in the brain (Soria et al., 2018). This reduction in CNS progression may result from the better local control of the systemic disease that prevented metastases from developing in the brain, or from a direct effect of osimertinib on established brain metastases, or a combination of both mechanisms.

5.3.4.2. EGFR TKIs and radiotherapy. Data from retrospective studies and meta-analyses show a higher control of intracranial disease with concurrent of EGFR TKI and RT compared with the use of EGFR TKI only (Chen et al., 2016; Luo et al., 2015; Wang et al., 2018; Sung et al., 2018) (Table 6). Upfront radiotherapy and EGFR TKI showed better intracranial PFS as well as OS than EGFR TKI alone. Patients with limited brain metastases benefited most from concomitant upfront RT and EGFR TKI (Wang et al., 2018). Adequate safety and tolerability was reported for concurrent EGFR TKI plus WBRT (Tan et al., 2016; Hendriks et al., 2015; Proto et al., 2016), albeit a slight increase in neurological and non-neurological level toxicity (Chen et al., 2016; Mehta et al., 2010). Studies assessing the combination of EGFR TKI with cranial radiotherapy did not evaluate neurotoxicity as the primary objective and most studies only included a basic neuropsychological test. In daily practice, EGFR TKIs are often discontinued for 4–5 times the half-life of the drug before starting cranial radiotherapy and are reinitiated 2–3 days after completing cranial radiotherapy (Hendriks et al., 2015).Tumor flare has been reported when EGFR TKIs are discontinued in this clinical setting (Weickhardt et al., 2012).

A prospective study showed that the addition of erlotinib to WBRT plus SRS was not feasible due to unacceptable toxicity (Sperduto et al., 2013). In a retrospective study comparing the clinical outcomes of patients with progressing brain metastases there was no difference in outcomes when treated with WBRT and osimertinib compared with those treated with osimertinib alone (Xie et al., 2018). The results of the ENTER study (NCT01887795) have been recently reported (Yang et al., 2018b). In this open label randomized Phase III clinical trial that compared WBRT plus concurrent erlotinib with frontline WBRT alone in patients with advanced NSCLC with multiple untreated synchronous brain metastases. After completing WBRT, patients received systemic treatment according to EGFR status and patients with *EGFR* mutations were treated with erlotinib. A total of 220 patients were included in the study and 109 harbored an activating *EGFR* mutation. There were no differences in the intracranial PFS among the intention-to-treat population neither in the EGFR mutated patients (HR = 0.74, 95% CI 0.49–1.13).

The pciAdenoINCAN clinical trial (NCT01603849) studied the role of prophylactic cranial irradiation (PCI) with hippocampal sparing

Table 6
Characteristics and results of EGFR TKI and RT studies.

Reference	Study design	Primary endpoints	EGFR TKI	Number of patients	Intracranial activity
(Chen et al., 2016)	Retrospective study N = 132 patients	Intracranial response rate and iPFS	Gefitinib and erlotinib	N = 53 WBRT/EGFR TKI N = 79 EGFR TKI	67.9% (concomitant WBRT/EGFR TKI) vs. 39.2% (EGFR TKI alone); p < 0.001
(Luo et al., 2015)	Meta-analysis N = 980 patients	Intracranial response rate, CNS-TTP, and OS	Gefitinib and erlotinib	N = 374 WBRT/EGFR TKI N = 376 WBRT	CNS-ORR (HR 1.56 [95% CI 1.20– 2.03] in favor of WBRT/EGFR TKI; p = 0.0008) CNS-TTP (HR 0.58 [95% CI 0.35, 0.96] in favor of WBRT/EGFR TKI; p = 0.03)
(Wang et al., 2018)	Meta-analysis N = 1068 patients	iPFS, and OS	Gefitinib, erlotinib, and icotinib	N = 534 RT N = 534 EGFR TKI	iPFS HR 0.72 (favoring RT, 95% CI 0.53–0.97; p = 0.028) OS HR 0.70 (favoring RT, 95% CI 0.53–0.93; p = 0.015).
(Sung et al., 2018)	N = 81 patients	Intracranial progression (ICP)	Gefitinib or erlotinib	N = 40 RT (WBRT or SRS)/EGFR TKI N = 41 EGFR TKI	36.5% in the TKI plus RT group and 62.2% in the TKI alone group (p = 0.006).
(Fan et al., 2017)	Retrospective study N = 97	iPFS, and OS	Icotinib	N = 56 RT (WBRT or SRS)/EGFR TKI N = 41 EGFR TKI	iPFS 22.4 months 13.9 months (p = 0.043)
(Xie et al., 2018)	Retrospective study N = 40	CNS response	Osimertinib	N = 11 EGFR TKI (progressing brain metastases) N = 9 RT/EGFR TKI (progressing brain metastases) N = 20 EGFR TKI (stable brain metastases)	CNS response: 32%
(Yang et al., 2018b)	Open label randomized Phase III (ENTER Study) N = 222	iPFS	Erlotinib	N = 115 WBRT N = 107 WBRT/EGFR TKI	All patients (both *EGFR* mutated and wild type NSCLC) Median iPFS: 11.2 months with WBRT/EGFR TKI vs 9.2 months with WBRT alone (HR 0.93 [95% CI 0.70–1.23; p = 0.601) *EGFR* mutated NSCLC Median iPFS: 14.6 months with WBRT/EGFR TKI vs 12.8 months with WBRT alone (HR 0.74 [95% CI 0.49–1.13; p = 0.164)

versus observation in 84 patients with advanced lung adenocarcinoma harboring EGFR or ALK alterations or with high levels of CEA in serum (Arrieta et al., 2018). PCI increased intracranial PFS in patients harboring EGFR and ALK alterations treated with first- and second-generation EGFR TKIs. PCI was not associated with early cognitive impairment measured by neurocognitive tests; however, these results should be confirmed in a larger randomized trial.

5.3.4.3. EGFR TKIs and anticonvulsants. Erlotinib and gefitinib are metabolized in the liver by the cytochrome P450 complex, mainly by CYP3A4, as well as CYP3A5 and CYP2D6 to a lesser extent. Osimertinib is also metabolized by CYP3A4 and CYP3A5. However, afatinib is not metabolized by the cytochrome P450 complex. In patients with NSCLC receiving an EGFR TKI, the use of anticonvulsant drugs that do not induce enzymes is recommended (Usery et al., 2010). When using an enzyme-inducing anticonvulsant, close monitoring of its plasma pharmacological levels is recommended (Grenader et al., 2007; Thomas-Schoemann et al., 2014), and the use of afatinib should be evaluated, instead of erlotinib or gefitinib given its absence of metabolism at the cytochrome P450 level.

5.3.4.4. EGFR TKIs and corticosteroids. The use of corticosteroids for anti-edema purposes is common in this clinical setting; however, there are potential drug interactions that could affect the blood levels of EGFR TKI. Dexamethasone is a CYP3A substrate and a CYP3A inducer that could reduce EGFR TKI plasma levels. There is a moderate interaction of dexamethasone with erlotinib, gefitinib and osimertinib, which could lead to a reduction in EGFR TKI levels in blood (https://www.drugs.com/drug_interactions.html). Other corticosteroids, such as prednisone or methylprednisone, do not interact with erlotinib and gefitinib; whereas afatinib does not interact with any corticosteroid (https://www.drugs.com/drug_interactions.html). Based on this evidence, if continuous treatment with corticosteroid is required, concurrent with erlotinib or gefitinib, prednisone or methylprednisone should be considered as alternatives to dexamethasone.

Based on this evidence, the following conclusions and **recommendations** regarding systemic treatment with EGFR TKIs of symptomatic patients were formulated and validated.

	LOE/ GOR	% agree (N)*
SYSTEMIC TREATMENT		
Are there differences in intracranial activity between the different EGFR TKIs?		
C19. There are no significant differences in intracranial activity between erlotinib and gefitinib; between afatinib and gefitinib was a difference (HR 0.76) that was not powered for significance (Zhang et al., 2016; Bai et al., 2017; Park et al., 2012; Park et al., 2016).	NA	100 (8)
Is it safe to co-administer EGFR TKIs with RT?		
C20. Studies evaluating treatment of concurrent EGFR TKI and cerebral RT have shown inconsistent results in terms of toxicity (Chen et al., 2016; Hendriks et al., 2015; Luo et al., 2015).	NA	100 (9)
R17. In case of intracranial disease progression in the brain that is sensitive to RT, an interruption of the EGFR TKI should be considered for a time that is equivalent to at least 4 or 5 half-lives of the drug before starting the RT. The EGFR TKI should be restarted from the second or third day after finishing RT (Hendriks et al., 2015)	3/C	100 (9)
R18. There is not enough evidence to support the concurrent use of RT with EGFR TKI. However, in patients with significant extracranial tumor burden, concurrence could be considered, but should be aware of a potential increase in toxicity (Tan et al., 2016; Proto et al., 2016).	2/C	100 (9)

Are there interactions between anticonvulsants and EGFR TKIs?		
R19. When using an enzyme-inducing anticonvulsant, close monitoring of plasma pharmacological levels is recommended and the use of afatinib should be evaluated, instead of erlotinib or gefitinib given its absence of metabolism at the cytochrome P450 level (Grenader et al., 2007; Thomas-Schoemann et al., 2014),	NA	†
Are there interactions between corticosteroids and EGFR TKIs?		
R20. If continuous treatment with corticosteroid is required, concurrent with erlotinib or gefitinib, prednisone or methylprednisone should be considered as alternatives to dexamethasone (https://www.drugs.com/drug_interactions.html).	NA	†

EGFR, epidermal growth factor receptor; EP, Expert Panel; GOR, grades of recommendation; LOE, level of evidence; NSCLC, non-small cell lung cancer; RT, radiotherapy; TKI, tyrosine kinase inhibitor; WRBT, whole brain radiation therapy.
*Not all participants were able to complete the first online round of validation (n = 8), while all participants attended the final meeting (n = 9) and an additional round of validation (n = 9).
†The recommendations of these questions were not voted in the online validation round, because they are widely accepted by the scientific community.
The conclusions are not in bold and the recommendations are in bold.

6. Post treatment considerations for the surveillance of patients with *EGFR* mutated NSCLC with brain metastases

Patients with *EGFR* mutations should be frequently monitored for the early detection of brain metastasis (Sadoyama et al., 2018). Neurological symptoms are not usually present when brain metastases are diagnosed by routine imaging (Shen et al., 2016). Cranial screening with neuro-imaging, preferably with brain MRI, every 2–3 months after treatment of brain metastases both in asymptomatic and symptomatic patients is highly beneficial (Koiso et al., 2016). The NCCN guidelines recommend performing cranial follow-up with MRI every 2–3 months for the first year and subsequently every 4–6 months (NCCN, 2017), regardless of the brain metastasis etiology or size/number. Other studies have recommended follow-up with biannual cranial MRI (Nishikawa et al., 2010) or cranial MRI every 3 months (Liu et al., 2015). In a multi-institutional retrospective study, the incidence of intracranial progression increased exponentially during the first 30 months of follow-up, until reaching stabilization (Magnuson et al., 2017).The most common image surveillance frequency employed is every 2–3 months (Rangachari et al., 2015).

Based on this evidence, the following **recommendations** regarding follow-up of patients were formulated and validated.

	LOE/ GOR	% agree (N)*
MONITORING RESPONSE		
How often should CNS lesions be evaluated in patients who have not received prior local treatment?†		
How often should CNS lesions be evaluated in patients who have received prior local treatment? †		
R21. In patients with good ECOG PS, especially in those who received only EGFR TKI and/or SRS, cranial imaging tests (ideally brain MRI) should be performed during follow-up (NCCN, 2017)	3/C	100 (8)
R22. The advisable frequency of performing the cranial imaging tests would be every 3 months for 24-30 months, and subsequently every six months (Magnuson et al., 2017; NCCN, 2017)	5/D	87.5 (8)

CNS, central nervous system; *EGFR*, epidermal growth factor receptor; GOR, grades of recommendation; LOE, level of evidence; MRI, magnetic resonance imaging; PS, performance status; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor.
*Not all participants were able to complete the first online round of validation (n = 8), while all participants attended the final meeting (n = 9) and an additional round of validation (n = 9).
†These two questions are closely related and were evaluated together.

7. Treatment of patients with leptomeningeal carcinomatosis

A complication in patients with pulmonary adenocarcinoma is the dissemination of neoplastic cells through CSF and leptomeninges, occurring in up to 9% of patients with *EGFR* mutations (Kuiper et al., 2015). Presence of malignant cells on CSF cytology provides the gold-standard for diagnosing leptomeningeal carcinomatosis. Brain metastases occur in 30.7–82% of patients with lung cancer and leptomeningeal carcinomatosis. Despite poor prognosis of patients with leptomeningeal carcinomatosis, outcomes can be improved (Bruna et al., 2009; Kuiper et al., 2015; Balm and Hammack, 1996; Wasserstrom et al., 1982; Morris et al., 2012), when specifically managed.

Due to the diffuse nature of leptomeningeal carcinomatosis, systemic administration and intrathecal administration are the preferred options because they encompass the entire subarachnoid space (Morris et al., 2012). Myelosuppression associated with whole neuroaxis irradiation may compromise chemotherapy treatments for the underlying cancer and is not considered an option for leptomeningeal carcinomatosis (Hermann et al., 2001). Likewise, the concomitant use of focal RT and intrathecal chemotherapy should be avoided due to severe toxicities (up to 20.3% grade 3–5 toxicities) (Pan et al., 2016).

Two studies comparing the addition of intrathecal chemotherapy to systemic treatment suggested that it does not improve the results in patients with leptomeningeal carcinomatosis and increases the rate of neurotoxic complications (Bokstein et al., 1998; Boogerd et al., 2004). On the other hand, in multivariate analyses from other studies, systemic treatment, intrathecal chemotherapy, and treatment with EGFR TKI were all independently associated with better survival (Bruna et al., 2009; Gwak et al., 2013).

There is high preservation of the *EGFR* mutation in CSF (92–95%) in patients with resistance to EGFR TKIs due to T790 M resistance (Liao et al., 2015; Seiji et al., 2017). However, the CSF penetration rate of EGFR TKIs such as gefitinib, erlotinib, and afatinib is less than 5% (Tamiya et al., 2017; Deng et al., 2014; Zhao et al., 2013; Togashi et al., 2012), but encouraging results have been observed with higher doses of gefitinib and erlotinib. Osimertinib, has also shown promising results in patients with leptomeningeal carcinomatosis achieving a leptomeningeal response in 43% of patients in the T790 M unselected cohort (JC-H et al., 2017; Nanjo et al., 2018; Hitchins et al., 1987).

Regarding exclusive intrathecal chemotherapy treatment for patients with leptomeningeal carcinomatosis, only non-controlled studies have established its benefit over the supportive treatment (Bruna et al., 2009; Balm and Hammack, 1996). There are three randomized trials, two of them with methodological limitations, which did not show advantages in OS between the most commonly used drugs (methotrexate, cytarabine, liposomal cytarabine, and Thio-TEPA) (Glantz et al., 1999; Grossman et al., 1993; Hitchins et al., 2016). Only liposomal cytarabine increased the time to neurological progression with better quality of life compared with intrathecal methotrexate (Glantz et al., 1999; Cole et al., 2017). If intrathecal chemotherapy is considered, the administration through the Ommaya reservoir is more comfortable for the patients and the distribution of the drug is more uniform than with a lumbar puncture (Glantz et al., 2010). When administered through the lumbar route, it is advisable that the patient remain in a prone position for at least one hour after administration to facilitate the distribution of the drug (Blaney et al., 1995).

Based on this evidence, the following **recommendations** regarding treatment of patients with leptomeningeal carcinomatosis were formulated and validated.

	LOE/ GOR	% agree (N)*
MONITORING RESPONSE		
In patients with leptomeningeal carcinomatosis, should intrathecal treatment or local treatment be performed?		
R23. Depending on the treatments that have been previously received, intrathecal treatment and systemic pharmacotherapy could be considered for patients with leptomeningeal carcinomatosis with acceptable prognostic factors (Bruna et al., 2009).	4/C	100 (9)
R24. Patients with leptomeningeal carcinomatosis diagnosed by neuroimaging, without neoplastic cells in the CSF, can be considered for systemic therapy (EGFR TKI or chemotherapy)† (Subira et al., 2015, 2012).	5/D	100 (8)
R25. Intrathecal chemotherapy plus systemic EGFR TKI can be considered in leptomeningeal carcinomatosis progression with systemic control of the disease (Glantz et al., 1999; Cole et al., 2017).	4/C	100 (9)
R26. In patients with parenchymal brain metastases and leptomeningeal carcinomatosis, the first treatment choice should be based on the identification of the lesion causing the neurological symptoms, prioritizing RT and delaying intrathecal treatment for at least 2-3 weeks, to avoid neurological toxicity in the case of symptomatic brain metastases (Bruna et al., 2012).	5/C	87,5 (8)

CSF, cerebrospinal fluid; *EGFR*, epidermal growth factor receptor; GOR, grades of recommendation; LOE, level of evidence; TKI, tyrosine kinase inhibitor.

*Not all participants were able to complete the first online round of validation (n = 8), while all participants attended the final meeting (n = 9) and an additional round of validation (n = 9).

†It is important to consider that most procedures in cytological diagnosis may underestimate the burden of the disease, as has been shown in the use of flow cytometry.

8. Future perspectives

Unfortunately, overall outcome of patients with *EGFR* mutated NSCLC and brain metastases is still worse than patients without brain metastases. However, it is important to note that in general these patients have a favorable long-term prognosis in comparison with patients with wild type *EGFR* NSCLC and brain metastases, and this should be considered with making decisions on how to manage these patients. To improve outcomes, better diagnosis and effective management strategies are needed. In this sense, it is important to correctly diagnose the presence of brain metastases in patients with *EGFR* mutations, by screening at diagnosis even in asymptomatic patients. There is limited scientific evidence from clinical trials that must be considered when trying to implement effective management strategies. Patients with NSCLC and brain metastases have been generally excluded from prospective clinical trials (Ali et al., 2013) and brain metastases are the most frequent reason for ineligibility to participate in a clinical trial (Kawachi et al., 2018). In this expert consensus many recommendations are based on expert experience due to lack of evidence-based clinical data. There are no randomized clinical trials and frequently there has been contradictory data from smaller studies and patient series. Further studies exploring the effects of EGFR TKIs in patients with NSCLC and *EGFR* mutations and brain metastases are warranted. A couple of clinical trials (NCT02714010 and NCT02338011) are ongoing and will compare the efficacy and safety of upfront EGFR TKI versus WBRT.

Newer EGFR TKIs are being specifically assessed in patients with brain or leptomeningeal metastases such as AZD3759, which was designed to achieve high levels in plasma and CSF (Ahn et al., 2017). Early data with tesevatinib in patients who had progressed with erlotinib, gefitinib, or afatinib, and had received prior radiotherapy showed rapid improvement of CNS symptoms (Berz et al., 2017). Phase II data of nazartinib showed promising efficacy in patients with NSCLC and *EGFR* mutations despite a high number of patients with brain metastases (40%) (Kim et al., 2018). The ORR in patients with brain metastases was 50%, with a 90% DCR.

In AURA3, a Phase III randomized clinical trial that compared osimertinib with platinum-pemetrexed in patients with *EGFR* T790M-positive advanced NSCLC who progressed to prior EGFR TKI, patients with asymptomatic, stable CNS metastases were eligible for enrollment (Mok et al., 2017). Osimertinib demonstrated superior CNS efficacy versus platinum-pemetrexed in T790M-positive advanced NSCLC in terms of CNS response and PFS (Wu et al., 2018). FLAURA, a Phase III clinical trial that compared frontline osimertinib with first-generation EGFR TKIs in patients with *EGFR* mutated advanced NSCLC enrolled patients with asymptomatic, stable CNS metastases (Soria et al., 2018). Osimertinib prolonged PFS compared with standard EGFR TKIs in patients with CNS metastases (HR = 0.47 [95% CI 0.30-0.74]; $p < 0.001$). CNS progression was also lower in patients who did not have brain metastases and received osimertinib vs standard TKIs (5 vs 17 patients). Overall survival results of both trials are not yet mature, but management of patients with *EGFR* mutated NSCLC and asymptomatic synchronous brain metastases will rapidly change with the uptake of osimertinib.

9. Conclusion

Although NSCLC patients harboring *EGFR* mutations have significant high risk of brain metastases, these patients have generally been excluded from clinical trials. Due to the limited clinical evidence and clinical guidelines for managing this patient population, a multidisciplinary group of Spanish medical and radiation oncologists, and neuro-oncologist with expertise in treating brain metastases in lung cancer patients developed an expert opinion consensus on the management of patients with *EGFR* mutated NSCLC with brain metastases. Although, there are limitations to this project, including the fact that most literature is obtained from non-randomized clinical trials or retrospective series, and the small size of the expert panel. The data that emerged since this project started, especially the results from osimertinib studies, may limit the clinical relevance of this consensus. However, availability of first-line osimertinib is not yet widespread and this consensus provides important treatment recommendations for clinical practice; particularly for patients with symptomatic brain metastases. As new therapeutic advances as well as new data for currently approved EGFR TKIs become available, the consensus will most likely require a future update. Importantly, the methodology used to create this consensus document was very robust and followed international guidelines. We have provided 24 consensus recommendations and 20 conclusion statements on the clinical definition and management of brain metastases in patients with *EGFR* mutated NSCLC, as well as a first-line treatment algorithm.

Conflict of interest

Santiago Ponce: Consulting fees from Boehringer Ingelheim

Jordi Bruna: Consulting fees from Boehringer Ingelheim

Oscar Juan: Consulting fees from Boehringer Ingelheim

Rafael López: Financing to attending meetings and congresses: ELCC 2018 from Pfizer and ASCO 2018 from Boehringer Ingelheim. Speaker honorarium from Roche. Consulting fees from Boehringer Ingelheim and Roche

Alejandro Navarro: Consulting fees from Boehringer Ingelheim

Ana Laura Ortega: Financing to attending meetings and congresses: WCLC 2018 from Roche

Javier Puente: Grants/research fees from Astellas. Consulting fees from Roche, Pfizer, Astellas, Sanofi, Janssen, Bayer, MSD, BMS, Boehringer-Ingelheim.

Eugènia Verger: Consulting fees from Boehringer Ingelheim

Adela Bartolomé: Consulting fees from Boehringer Ingelheim

Ernest Nadal: Consulting fees from Boehringer Ingelheim, Astra Zeneca and Roche.

Funding

This project was sponsored by Boehringer Ingelheim, Spain.

Acknowledgments

Ernest Nadal received support from the SLT006/17/00127 grant, funded by the Department of Health of the Generalitat de Catalunya by the call “Acció instrumental d'intensificació de professionals de la salut”. We thank CERCA Programme / Generalitat de Catalunya for institutional support. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Aurora O’Brate. Boehringer Ingelheim was given the opportunity to check the data used in the manuscript for factual accuracy only. Methodological support was provided by GOC Networking (Spain), supported financially by Boehringer Ingelheim.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.03.017.

References

Ahn, M.-J., Kim, D.-W., Cho, B.C., Kim, S.-W., Lee, J.-S., Ahn, J.S., et al., 2017. Phase I study (BLOOM) of AZD3759, a BBB penetrable EGFR inhibitor, in patients with TKI-naïve, EGFRm NSCLC with CNS metastases. J. Clin. Oncol. 35 abstr 2006.

Ali, A., Goffin, J.R., Arnold, A., Ellis, P.M., 2013. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Curr. Oncol. 20, e300–6.

Aoyama, H., Shirato, H., Tago, M., Nakagawa, K., Toyoda, T., Hatano, K., et al., 2006. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295, 2483–2491.

Aoyama, H., Tago, M., Kato, N., Toyoda, T., Kenjyo, M., Hirota, S., et al., 2007. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int. J. Radiat. Oncol. Biol. Phys. 68, 1388–1395.

Arrieta, O., Maldonado, F., Ramírez-Tirado, L., Barron, F., Campos-Salgado, Y., Blake, M., et al., 2018. MA08.02 prophylactic cranial irradiation reduces the risk of brain metastases in HIGH-RISK Lung Cancer Patients: EGFR and ALK mutations. J. Thorac. Oncol. 13 abstr MA08.2.

Arvold, N.D., Lee, E.Q., Mehta, M.P., Margolin, K., Alexander, B.M., Lin, N.U., et al., 2016. Updates in the management of brain metastases. Neuro Oncol. 18, 1043–1065.

Baek, M.Y., Ahn, H.K., Park, K.R., Park, H.S., Kang, S.M., Park, I., et al., 2018. Epidermal growth factor receptor mutation and pattern of brain metastasis in patients with non-small cell lung cancer. Korean J. Intern. Med. 33, 168–175.

Bai, H., Xiong, L., Han, B., 2017. The effectiveness of EGFR-TKIs against brain metastases in EGFR mutation-positive non-small-cell lung cancer. Onco. Ther. 10, 2335–2340 PubMed PMID: 28490892. PMCID: PMC5415007. Epub 2017/05/12. eng.

Ballard, P., Yates, J.W., Yang, Z., Kim, D.W., Yang, J.C., Cantarini, M., et al., 2016. Preclinical comparison of Osimertinib with other EGFR-TKIs in EGFR-Mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin. Cancer Res. 22, 5130–5140.

Balm, M., Hammack, J., 1996. Leptomeningeal carcinomatosis. Presenting features and prognostic factors. Arch. Neurol. 53, 626–632.

Barnholtz-Sloan, J.S., Yu, C., Sloan, A.E., Vengoechea, J., Wang, M., Dignam, J.J., et al., 2012. A nomogram for individualized estimation of survival among patients with brain metastasis. Neuro Oncol. 14, 910–918.

Barnholtz-Sloan, J.S., Sloan, A.E., Davis, F.G., Vigneau, F.D., Lai, P., Sawaya, R.E., 2004. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer surveillance System. J. Clin. Oncol. (22), 2865–2872.

Berz, D., Subrananiam, D., Tonra, J., Berger, M., Camidge, D.R., 2017. P2.03b-016 tesevatinib in NSCLC patients with EGFR activating mutations and brain metastases (BM) or leptomeningeal metastases (LM). J. Thorac. Oncol. 12 S942-S3. abstr P2.03b-016.

Bhatnagar, A.K., Flickinger, J.C., Kondziolka, D., Lunsford, L.D., 2006. Stereotactic radiosurgery for four or more intracranial metastases. Int. J. Radiat. Oncol. Biol. Phys. 64, 898–903.

Bindal, A.K., Bindal, R.K., Hess, K.R., Shiu, A., Hassenbusch, S.J., Shi, W.M., et al., 1996. Surgery versus radiosurgery in the treatment of brain metastasis. J. Neurosurg. 84, 748–754.

Blaney, S.M., Poplack, D.G., Godwin, K., McCully, C.L., Murphy, R., Balis, F.M., 1995. Effect of body position on ventricular CSF methotrexate concentration following intralumbar administration. J. Clin. Oncol. 13, 177–179.

Bokstein, F., Lossos, A., Siegal, T., 1998. Leptomeningeal metastases from solid tumors: a comparison of two prospective series treated with and without intra-cerebrospinal fluid chemotherapy. Cancer 82, 1756–1763.

Boogerd, W., van den Bent, M.J., Koehler, P.J., Heimans, J.J., van der Sande, J.J., Aaronson, N.K., et al., 2004. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. Eur. J. Cancer 40, 2726–2733.

Brown, P.D., Jaeckle, K., Ballman, K.V., Farace, E., Cerhan, J.H., Anderson, S.K., et al., 2016. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA 316, 401–409.

Brown, P.D., Ballman, K.V., Cerhan, J.H., Anderson, S.K., Carrero, X.W., Whitton, A.C., et al., 2017. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 18, 1049–1060.

Bruna, J., Gonzalez, L., Miro, J., Velasco, R., Gil, M., Tortosa, A., 2009. Leptomeningeal carcinomatosis: prognostic implications of clinical and cerebrospinal fluid features. Cancer 115, 381–389.

Bruna, J., Simo, M., Velasco, R., 2012. Leptomeningeal metastases. Curr. Treat. Options Neurol. 14, 402–415.

Chamberlain, M.C., Baik, C.S., Gadi, V.K., Bhatia, S., Chow, L.Q., 2017. Systemic therapy of brain metastases: non-small cell lung cancer, breast cancer, and melanoma. Neuro Oncol. 19 i1-i24.

Chang, E.L., Wefel, J.S., Hess, K.R., Allen, P.K., Lang, F.F., Kornguth, D.G., et al., 2009. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 10, 1037–1044.

Chang, W.Y., Wu, Y.L., Su, P.L., Yang, S.C., Lin, C.C., Su, W.C., 2018. The impact of EGFR mutations on the incidence and survival of stages I to III NSCLC patients with subsequent brain metastasis. PLoS One 13, e0192161.

Chen, Y., Yang, J., Li, X., Hao, D., Wu, X., Yang, Y., et al., 2016. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor alone or with whole-brain radiotherapy for brain metastases in patients with EGFR-mutated lung adenocarcinoma. Cancer Sci. 107, 1800–1805.

Chi, A., Komaki, R., 2010. Treatment of brain metastasis from lung cancer. Cancers (Basel). 2, 2100–2137.

Churilla, T.M., Ballman, K.V., Brown, P.D., Twohy, E.L., Jaeckle, K., Farace, E., et al., 2017. Stereotactic radiosurgery with or without whole-brain radiation therapy for limited brain metastases: a secondary analysis of the north central Cancer treatment group N0574 (Alliance) randomized controlled trial. Int. J. Radiat. Oncol. Biol. Phys. 99, 1173–1178.

Cole, B.F., 2017. Department of Community and Family Medicine DMS, Lebanon, New Hampshire, Glantz MJ, Department of Medicine BUSoM, Providence, Rhode Island, Jaeckle KA. Department of Neuro-Oncology TUoTMDACC, Houston, Texas et al. Quality-of-life–adjusted survival comparison of sustained-release cytosine arabinoside versus intrathecal methotrexate for treatment of solid tumor neoplastic meningitis. Cancer.97:3053-3060.

Dempke, W.C., Edvardsen, K., Lu, S., Reinmuth, N., Reck, M., Inoue, A., 2015. Brain Metastases in NSCLC - are TKIs Changing the Treatment Strategy? Anticancer Res. 35, 5797–5806.

Deng, Y., Feng, W., Wu, J., Chen, Z., Tang, Y., Zhang, H., et al., 2014. The concentration of erlotinib in the cerebrospinal fluid of patients with brain metastasis from non-small-cell lung cancer. Mol. Clin. Oncol. 2, 116–120.

Deuschl, C., Nensa, F., Grueneisen, J., Poeppel, T.D., Sawicki, L.M., Heusch, P., et al., 2017. Diagnostic impact of integrated 18F-FDG PET/MRI in cerebral staging of patients with non-small cell lung cancer. Acta radiol. 58, 991–996.

Doherty, M.K., Korpanty, G.J., Tomasini, P., Alizadeh, M., Jao, K., Labbe, C., et al., 2017. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. Radiother. Oncol. 123, 195–202.

Eichler, A.F., Loeffler, J.S., 2007. Multidisciplinary management of brain metastases. Oncologist 12, 884–898.

European Medicine Agency. Guideline on the evaluation of anticancer medicinal products in man13 December 2012 EMA/CHMP/205/95/Rev.4 Oncology Working Party https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-4_en.pdf.

Fan, Y., Xu, Y., Gong, L., Fang, L., Lu, H., Qin, J., et al., 2017. Effects of icotinib with and without radiation therapy on patients with EGFR mutant non-small cell lung cancer and brain metastases. Sci. Rep. 7, 45193.

Garell, P.C., Hitchon, P.W., Wen, B.C., Mellenberg, D.E., Torner, J., 1999. Stereotactic radiosurgery versus microsurgical resection for the initial treatment of metastatic cancer to the brain. J. Radiosurgery 2, 1–5.

Gaspar, L., Scott, C., Rotman, M., Asbell, S., Phillips, T., Wasserman, T., et al., 1997. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int. J. Radiat. Oncol. Biol. Phys. 37, 745–751.

Ge, M., Zhuang, Y., Zhou, X., Huang, R., Liang, X., Zhan, Q., 2017. High probability and frequency of EGFR mutations in non-small cell lung cancer with brain metastases. J. Neurooncol. 135, 413–418.

Gino, K.I., Jeremy, M., Sonia, L., Paul, K.N., Peter, K., Jorge, N., 2017. Development of metastatic brain disease involves progression through lung metastases in EGFR mutated non-small cell lung cancer. Converg. Sci. Phys. Oncol. 3, 035002.

Glantz, M.J., Jaeckle, K.A., Chamberlain, M.C., Phuphanich, S., Recht, L., Swinnen, L.J., et al., 1999. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin. Cancer Res. 5, 3394–3402.

Glantz, M.J., Van Horn, A., Fisher, R., Chamberlain, M.C., 2010. Route of intracerebrospinal fluid chemotherapy administration and efficacy of therapy in neoplastic meningitis. Cancer 116, 1947–1952.

Goss, G., Tsai, C.M., Shepherd, F.A., Ahn, M.J., Bazhenova, L., Crino, L., et al., 2018. CNS

response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. Ann. Oncol. 29, 687–693.
Grenader, T., Gipps, M., Shavit, L., Gabizon, A., 2007. Significant drug interaction: phenytoin toxicity due to erlotinib. Lung Cancer 57, 404–406.
Grossman, S.A., Finkelstein, D.M., Ruckdeschel, J.C., Trump, D.L., Moynihan, T., Ettinger, D.S., 1993. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. J Clin Oncol. 11, 561–569.
Grupo de trabajo para la actualización del Manual de Elaboración de GPC. Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud. Actualización del Manual Metodológico [Internet]. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; Zaragoza: Instituto Aragonés de Ciencias de la Salud (IACS); 2016 [Febrero 2018]. Disponible en: [http://portal.guiasalud.es/emanuales/elaboracion_2/?capitulo].
Guerin, A., Sasane, M., Dea, K., Zhang, J., Culver, K., Nitulescu, R., et al., 2016. The economic burden of brain metastasis among lung cancer patients in the United States. J. Med. Econ. 19, 526–536.
Gwak, H.S., Joo, J., Kim, S., Yoo, H., Shin, S.H., Han, J.Y., et al., 2013. Analysis of treatment outcomes of intraventricular chemotherapy in 105 patients for leptomeningeal carcinomatosis from non-small-cell lung cancer. J. Thorac. Oncol. 8, 599–605.
Hendriks, L.E., Schoenmaekers, J., Zindler, J.D., Eekers, D.B., Hoeben, A., De Ruysscher, D.K., et al., 2015. Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: a systematic review. Cancer Treat. Rev. 41, 634–645.
Heon, S., Yeap, B.Y., Britt, G.J., Costa, D.B., Rabin, M.S., Jackman, D.M., et al., 2010. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. Clin. Cancer Res. 16, 5873–5882.
Hermann, B., Hultenschmidt, B., Sautter-Bihl, M.L., 2001. Radiotherapy of the neuroaxis for palliative treatment of leptomeningeal carcinomatosis. Strahlenther. Onkol. 177, 195–199.
Hitchins, R.N., Bell, D.R., Woods, R.L., Levi, J.A., 1987. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J. Clin. Oncol. 5, 1655–1662.
Hitchins, R.N., Bell, D.R., Woods, R.L., Levi, J.A., 2016. A Prospective Randomized Trial of Single-agent Versus Combination Chemotherapy in Meningeal Carcinomatosis. http://dxdoiorg/101200/JCO19875101655.
Hoffknecht, P., Tufman, A., Wehler, T., Pelzer, T., Wiewrodt, R., Schütz, M., et al., 2015. 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.
Hotta, K., Kiura, K., Ueoka, H., Tabata, M., Fujiwara, K., Kozuki, T., et al., 2004. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. Lung Cancer 46, 255–261.
Iuchi, T., Shingyoji, M., Sakaida, T., Hatano, K., Nagano, O., Itakura, M., et al., 2013. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. Lung Cancer 82, 282–287.
JC-H, Yang, Cho, B.C., Kim, D.-W., Kim, S.-W., Lee, J.-S., Su, W.-C., et al., 2017. Osimertinib for patients (pts) with leptomeningeal metastases (LM) from EGFR-mutant non-small cell lung cancer (NSCLC): updated results from the BLOOM study. J. Clin. Oncol. 35 abstr 2020.
Jena, A., Taneja, S., Talwar, V., Sharma, J.B., 2008. Magnetic resonance (MR) patterns of brain metastasis in lung cancer patients: correlation of imaging findings with symptom. J. Thorac. Oncol. 3, 140–144.
Jiang, T., Su, C., Li, X., Zhao, C., Zhou, F., Ren, S., et al., 2016a. EGFR TKIs plus WBRT demonstrated No survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases. J. Thorac. Oncol. 11, 1718–1728.
Jiang, T., Min, W., Li, Y., Yue, Z., Wu, C., Zhou, C., 2016b. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. Cancer Med. 5, 1055–1065.
Kashima, J., Okuma, Y., Miwa, M., Hosomi, Y., 2016. Survival of patients with brain metastases from non-small cell lung cancer harboring EGFR mutations treated with epidermal growth factor receptor tyrosine kinase inhibitors. Med. Oncol. 33, 129.
Kawachi, H., Fujimoto, D., Morimoto, T., Ito, M., Teraoka, S., Sato, Y., et al., 2018. Clinical characteristics and prognosis of patients with advanced non-small-cell lung Cancer Who are ineligible for clinical trials. Clin. Lung Cancer.
Khalifa, J., Amini, A., Popat, S., Gaspar, L.E., Faivre-Finn, C., 2016. Brain metastases from NSCLC: radiation therapy in the era of targeted therapies. J. Thorac. Oncol. 11, 1627–1643.
Kim, J.E., Lee, D.H., Choi, Y., Yoon, D.H., Kim, S.W., Suh, C., et al., 2009. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer. 65, 351–354.
Kim, D.-W., DS-W, Tan, Ponce Aix, S., Sequist, L.V., Smit, E.F., Hida, T., et al., 2018. Preliminary Phase II results of a multicenter, open-label study of nazartinib (EGF816) in adult patients with treatment-naïve EGFR-mutant non-small cell lung cancer (NSCLC). J. Clin. Oncol. 35 abstr 2020.
Koiso, T., Yamamoto, M., Kawabe, T., Watanabe, S., Sato, Y., Higuchi, Y., et al., 2016. A case-matched study of stereotactic radiosurgery for patients with brain metastases: comparing treatment results for those with versus without neurological symptoms. J. Neurooncol. 130, 581–590.
Kuhn, M.J., Hammer, G.M., Swenson, L.C., Youssef, H.T., Gleason, T.J., 1994. MRI evaluation of "solitary" brain metastases with triple-dose gadoteridol: comparison with contrast-enhanced CT and conventional-dose gadopentetate dimeglumine MRI studies in the same patients. Comput. Med. Imaging Graph. 18, 391–399.
Kuiper, J.L., Hendriks, L.E., van der Wekken, A.J., de Langen, A.J., Bahce, I., Thunnissen, E., et al., 2015. Treatment and survival of patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: a retrospective cohort analysis. Lung Cancer 89, 255–261.
Langer, C.J., 2013. Epidermal growth factor receptor inhibition in mutation-positive non-small-cell lung cancer: is afatinib better or simply newer? J. Clin. Oncol. 31, 3303–3306.
Langer, C.J., Mehta, M.P., 2005. Current management of brain metastases, with a focus on systemic options. J. Clin. Oncol. 23, 6207–6219.
Lassman, A.B., DeAngelis, L.M., 2003. Brain metastases. Neurol. Clin. 21, 1–23 vii.
Lassman, A.B., Rossi, M.R., Raizer, J.J., Abrey, L.E., Lieberman, F.S., Grefe, C.N., et al., 2005. Molecular study of malignant gliomas treated with epidermal growth factor receptor inhibitors: tissue analysis from North American Brain Tumor Consortium Trials 01-03 and 00-01. Clin. Cancer Res. 11, 7841–7850.
Lee, V.H., Tin, V.P., Choy, T.S., Lam, K.O., Choi, C.W., Chung, L.P., et al., 2013. Association of exon 19 and 21 EGFR mutation patterns with treatment outcome after first-line tyrosine kinase inhibitor in metastatic non-small-cell lung cancer. J. Thorac. Oncol. 8, 1148–1155.
Lee, M.H., Kong, D.S., Seol, H.J., Nam, D.H., Lee, J.I., 2017. The influence of biomarker mutations and systemic treatment on cerebral metastases from NSCLC treated with radiosurgery. J. Korean Neurosurg. Soc. 60, 21–29.
Levy, A., Faivre-Finn, C., Hasan, B., De Maio, E., Berghoff, A.S., Girard, N., et al., 2018. Diversity of brain metastases screening and management in non-small cell lung cancer in Europe: results of the European Organisation for Research and Treatment of Cancer lung Cancer group survey. Eur. J. Cancer 93, 37–46.
Liang, W., Xia, X., Guo, M., He, J., 2018. MA08.03 - EGFR-TKI plus brain radiotherapy versus EGFR-TKI alone in the management of EGFR mutated NSCLC patients with brain metastases: a meta-analysis. J. Thorac. Oncol. 13 abstr MA08.3.
Liao, B.C., Lee, J.H., Lin, C.C., Chen, Y.F., Chang, C.H., Ho, C.C., et al., 2015. Epidermal growth factor receptor tyrosine kinase inhibitors for non-small-Cell lung Cancer patients with leptomeningeal carcinomatosis. J. Thorac. Oncol. 10, 1754–1761.
Lin, N.U., Lee, E.Q., Aoyama, H., Barani, I.J., Barboriak, D.P., Baumert, B.G., et al., 2015. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 16, e270–8.
Liu, S., Qiu, B., Chen, L., Wang, F., Liang, Y., Cai, P., et al., 2015. Radiotherapy for asymptomatic brain metastasis in epidermal growth factor receptor mutant non-small cell lung cancer without prior tyrosine kinase inhibitors treatment: a retrospective clinical study. Radiat. Oncol. 10, 118.
Luo, S., Chen, L., Chen, X., Xie, X., 2015. Evaluation on efficacy and safety of tyrosine kinase inhibitors plus radiotherapy in NSCLC patients with brain metastases. Oncotarget. 6, 16725–16734.
Magnuson, W.J., Lester-Coll, N.H., Wu, A.J., Yang, T.J., Lockney, N.A., Gerber, N.K., et al., 2017. Management of brain metastases in tyrosine kinase inhibitor-naive epidermal growth factor receptor-mutant non-small-Cell lung Cancer: a retrospective multi-institutional analysis. J. Clin. Oncol. 35, 1070–1077.
Mehta, M.P., Paleologos, N.A., Mikkelsen, T., Robinson, P.D., Ammirati, M., Andrews, D.W., et al., 2010. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J. Neurooncol. 96, 71–83.
Mintz, A.H., Kestle, J., Rathbone, M.P., Gaspar, L., Hugenholtz, H., Fisher, B., et al., 1996. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer. 78, 1470–1476.
Mok, T.S., Wu, Y.L., Ahn, M.J., Garassino, M.C., Kim, H.R., Ramalingam, S.S., et al., 2017. Osimertinib or platinum-pemetrexed in EGFR T790M-Positive lung Cancer. N. Engl. J. Med. 376, 629–640.
Morin-Ben Abdallah, S., Wong, A., 2018. Brain metastases in non-small-cell lung cancer: are tyrosine kinase inhibitors and checkpoint inhibitors now viable options? Curr. Oncol. 25 S103-S14.
Morris, P.G., Reiner, A.S., Szenberg, O.R., Clarke, J.L., Panageas, K.S., Perez, H.R., et al., 2012. Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy. J. Thorac. Oncol. 7, 382–385.
Mujoomdar, A., Austin, J.H., Malhotra, R., Powell, C.A., Pearson, G.D., Shiau, M.C., et al., 2007. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. Radiology. 242, 882–888.
Mulvenna, P., Nankivell, M., Barton, R., Faivre-Finn, C., Wilson, P., McColl, E., et al., 2016. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet 388, 2004–2014.
Na, I.I., Lee, T.H., Choe, D.H., Cheon, G.J., Kim, C.H., Koh, J.S., et al., 2008. A diagnostic model to detect silent brain metastases in patients with non-small cell lung cancer. Eur. J. Cancer 44, 2411–2417.
Na, Y.C., Jung, H.H., Kim, H.R., Cho, B.C., Chang, J.W., Park, Y.G., et al., 2017. Predictive factors of early distant brain failure after gamma knife radiosurgery alone in patients with brain metastases of non-small-cell lung cancer. J. Neurooncol. 132, 333–340.
Nanjo, S., Hata, A., Okuda, C., Kaji, R., Okada, H., Tamura, D., et al., 2018. Standard-dose osimertinib for refractory leptomeningeal metastases in T790M-positive EGFR-mutant non-small cell lung cancer. Br. J. Cancer 118, 32–37.
National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 2.2018). http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 18 of December 2017.
NCCN Clinical Practice Guidelines Oncology Non-small cell lung cancer. Version 2.2017 – October 26, 2016.

NCCN Guidelines. Central nervous system cancers. Version 1.2017.
Nguyen, T., Deangelis, L.M., 2004. Treatment of brain metastases. J. Support. Oncol. 2, 405–410 discussion 11-6.
Nishikawa, T., Ueba, T., Kawashima, M., Kajiwara, M., Iwata, R., Kato, M., et al., 2010. Early detection of metachronous brain metastases by biannual brain MRI follow-up may provide patients with non-small cell lung cancer with more opportunities to have radiosurgery. Clin. Neurol. Neurosurg. 112, 770–774.
Novello, S., Barlesi, F., Califano, R., Cufer, T., Ekman, S., Levra, M.G., et al., 2016. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 27 v1-v27.
O'Neill, B.P., Iturria, N.J., Link, M.J., Pollock, B.E., Ballman, K.V., O'Fallon, J.R., 2003. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. Int. J. Radiat. Oncol. Biol. Phys. 55, 1169–1176.
Pan, Z., Yang, G., He, H., Zhao, G., Yuan, T., Li, Y., et al., 2016. Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: a prospective and single-arm study. Int. J. Cancer 139, 1864–1872.
Park, S.J., Kim, H.T., Lee, D.H., Kim, K.P., Kim, S.W., Suh, C., et al., 2012. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer 77 (Sep. (3)), 556–560 PubMed PMID: 22677429. Epub 2012/06/09. eng.
Park, K., Tan, E.H., O'Byrne, K., Zhang, L., Boyer, M., Mok, T., et al., 2016. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 17 (May (5)), 577–589 PubMed PMID: 27083334. Epub 2016/04/17. eng.
Patchell, R.A., Tibbs, P.A., Regine, W.F., Dempsey, R.J., Mohiuddin, M., Kryscio, R.J., et al., 1998. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280, 1485–1489.
Pazdur, R., 2008. Endpoints for assessing drug activity in clinical trials. Oncologist. 13 (Suppl 2), 19–21.
Pechoux, C.L., Dhermain, F., Besse, B., 2016. Whole brain radiotherapy in patients with NSCLC and brain metastases. Lancet 388, 1960–1962.
Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E.F., Faivre-Finn, C., et al., 2018. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 29 iv192-iv237.
Pollock, B.E., Brown, P.D., Foote, R.L., Stafford, S.L., Schomberg, P.J., 2003. Properly selected patients with multiple brain metastases may benefit from aggressive treatment of their intracranial disease. J. Neurooncol. 61, 73–80.
Porta, R., Sanchez-Torres, J.M., Paz-Ares, L., Massuti, B., Reguart, N., Mayo, C., et al., 2011. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur. Respir. J. 37, 624–631.
Proto, C., Imbimbo, M., Gallucci, R., Brissa, A., Signorelli, D., Vitali, M., et al., 2016. Epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of central nervous system metastases from non-small cell lung cancer: the present and the future. Transl. Lung Cancer Res. 5, 563–578.
Rades, D., Kueter, J.D., Veninga, T., Gliemroth, J., Schild, S.E., 2009. Whole brain radiotherapy plus stereotactic radiosurgery (WBRT + SRS) versus surgery plus whole brain radiotherapy (OP + WBRT) for 1-3 brain metastases: results of a matched pair analysis. Eur. J. Cancer 45, 400–404.
Rangachari, D., Yamaguchi, N., VanderLaan, P.A., Folch, E., Mahadevan, A., Floyd, S.R., et al., 2015. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 88, 108–111.
Reungwetwattana, T., Nakagawa, K., Cho, B.C., Cobo, M., Cho, E.K., Bertolini, A., et al., 2018. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-Mutated advanced non-small-Cell lung Cancer. J. Clin. Oncol JCO2018783118.
Sadoyama, S., Sekine, A., Satoh, H., Iwasawa, T., Kato, T., Ikeda, S., et al., 2018. Isolated brain metastases as the first relapse after the curative surgical resection in non-small-Cell lung Cancer patients with an EGFR mutation. Clin. Lung Cancer 19, 29–36.
Sahgal, A., Aoyama, H., Kocher, M., Neupane, B., Collette, S., Tago, M., et al., 2015. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. Int. J. Radiat. Oncol. Biol. Phys. 91, 710–717.
Sanchez de Cos, J., Sojo Gonzalez, M.A., Montero, M.V., Perez Calvo, M.C., Vicente, M.J., Valle, M.H., 2009. Non-small cell lung cancer and silent brain metastasis. Survival and prognostic factors. Lung Cancer 63, 140–145.
Schoggl, A., Kitz, K., Reddy, M., Wolfsberger, S., Schneider, B., Dieckmann, K., et al., 2000. Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. Acta Neurochir (Wien) 142, 621–626.
Schuette, W., 2004. Treatment of brain metastases from lung cancer: chemotherapy. Lung Cancer 45 (Suppl. 2), S253–7.
Schuler, M., Wu, Y.L., Hirsh, V., O'Byrne, K., Yamamoto, N., Mok, T., et al., 2016. First-line afatinib versus chemotherapy in patients with non-small cell lung Cancer and common epidermal growth factor receptor gene mutations and brain metastases. J. Thorac. Oncol. 11, 380–390.
Seiji, Y., Shigeki, N., Sachiko, A., Shinji, T., Tadaaki, Y., Yasunori, O., et al., 2017. OA08.03 MET copy number gain associates with gefitinib resistance in leptomeningeal carcinomatosis of EGFR mutant lung Cancer - journal of thoracic oncology. J. Thorac. Oncol. 12.
Sekine, A., Satoh, H., Iwasawa, T., Tamura, K., Hayashihara, K., Saito, T., et al., 2014. Prognostic factors for brain metastases from non-small cell lung cancer with EGFR mutation: influence of stable extracranial disease and erlotinib therapy. Med. Oncol. 31, 228.
Shen, C.J., Rigamonti, D., Redmond, K.J., Kummerlowe, M.N., Lim, M., Kleinberg, L.R., 2016. The strategy of repeat stereotactic radiosurgery without whole brain radiation treatment for new brain metastases: outcomes and implications for follow-up monitoring. Pract. Radiat. Oncol. 6, 409–416.
Shin, D.Y., Na, I.I., Kim, C.H., Park, S., Baek, H., Yang, S.H., 2014. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. J. Thorac. Oncol. 9, 195–199.
Sneed, P.K., Mendez, J., Vemer-van den Hoek, J.G., Seymour, Z.A., Ma, L., Molinaro, A.M., et al., 2015. Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. J. Neurosurg. 123, 373–386.
Soffietti, R., Abacioglu, U., Baumert, B., Combs, S.E., Kinhult, S., Kros, J.M., et al., 2017. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro Oncol. 19, 162–174.
Soon, Y.Y., Leong, C.N., Koh, W.Y., Tham, I.W., 2015. EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: a systematic review and meta-analysis. Radiother. Oncol. 114, 167–172.
Soria, J.C., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B., Lee, K.H., et al., 2018. Osimertinib in untreated EGFR-Mutated advanced non-small-Cell lung Cancer. N. Engl. J. Med. 378, 113–125.
Sperduto, P.W., Berkey, B., Gaspar, L.E., Mehta, M., Curran, W., 2008. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int. J. Radiat. Oncol. Biol. Phys. 70, 510–514.
Sperduto, P.W., Chao, S.T., Sneed, P.K., Luo, X., Suh, J., Roberge, D., et al., 2010. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int. J. Radiat. Oncol. Biol. Phys. 77, 655–661.
Sperduto, P.W., Wang, M., Robins, H.I., Schell, M.C., Werner-Wasik, M., Komaki, R., et al., 2013. 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.
Sperduto, P.W., Shanley, R., Luo, X., Andrews, D., Werner-Wasik, M., Valicenti, R., et al., 2014. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). Int. J. Radiat. Oncol. Biol. Phys. 90, 526–531.
Sperduto, P.W., Yang, T.J., Beal, K., Pan, H., Brown, P.D., Bangdiwala, A., et al., 2017. Estimating survival in patients with lung Cancer and brain metastases: an update of the graded prognostic assessment for lung Cancer Using molecular markers (Lung-molGPA). JAMA Oncol. 3, 827–831.
Subira, D., Serrano, C., Castanon, S., Gonzalo, R., Illan, J., Pardo, J., et al., 2012. Role of flow cytometry immunophenotyping in the diagnosis of leptomeningeal carcinomatosis. Neuro Oncol. 14, 43–52.
Subira, D., Simo, M., Illan, J., Serrano, C., Castanon, S., Gonzalo, R., et al., 2015. Diagnostic and prognostic significance of flow cytometry immunophenotyping in patients with leptomeningeal carcinomatosis. Clin. Exp. Metastasis 32, 383–391.
Suh, J.H., Stea, B., Nabid, A., Kresl, J.J., Fortin, A., Mercier, J.P., et al., 2006. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. J. Clin. Oncol. 24, 106–114.
Sung, S., Lee, S.W., Kwak, Y.K., Kang, J.H., Hong, S.H., Kim, Y.S., 2018. Intracranial control and survival outcome of tyrosine kinase inhibitor (TKI) alone versus TKI plus radiotherapy for brain metastasis of epidermal growth factor receptor-mutant non-small cell lung cancer. J. Neurooncol. 139, 205–213.
Takamori, S., Toyokawa, G., Shimokawa, M., Kinoshita, F., Kozuma, Y., Matsubara, T., et al., 2018. Radiological features of brain metastases from non-small cell lung Cancer Harboring EGFR mutation. Anticancer Res. 38, 3731–3734.
Tamiya, A., Tamiya, M., Nishihara, T., Shiroyama, T., Nakao, K., Tsuji, T., et al., 2017. Cerebrospinal fluid penetration rate and efficacy of afatinib in patients with EGFR mutation-positive non-small cell lung Cancer with leptomeningeal carcinomatosis: a multicenter prospective study. Anticancer Res. 37, 4177–4182.
Tan, D.S., Yom, S.S., Tsao, M.S., Pass, H.I., Kelly, K., Peled, N., et al., 2016. The international association for the study of lung Cancer consensus statement on optimizing management of EGFR mutation-positive non-small cell lung Cancer: status in 2016. J. Thorac. Oncol. 11, 946–963.
Tan, J., Li, M., Zhong, W., Hu, C., Gu, Q., Xie, Y., 2017. Tyrosine kinase inhibitors show different anti-brain metastases efficacy in NSCLC: a direct comparative analysis of icotinib, gefitinib, and erlotinib in a nude mouse model. Oncotarget 8, 98771–98781.
Thomas-Schoemann, A., Blanchet, B., Bardin, C., Noe, G., Boudou-Rouquette, P., Vidal, M., et al., 2014. Drug interactions with solid tumour-targeted therapies. Crit. Rev. Oncol. Hematol. 89, 179–196.
Togashi, Y., Masago, K., Masuda, S., Mizuno, T., Fukudo, M., Ikemi, Y., et al., 2012. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. Cancer Chemother. Pharmacol. 70, 399–405.
Tomasini, P., Serdjebi, C., Khobta, N., Metellus, P., Ouafik, L., Nanni, I., et al., 2016. EGFR and KRAS mutations predict the incidence and outcome of brain metastases in non-small cell lung Cancer. Int. J. Mol. Sci. 17.
Trifiletti, D.M., Larner, J.M., Sheehan, J.P., 2016. When should patients with brain metastases receive whole brain irradiation? J. Radiosurg. SBRT 4, 1–3.
Tsao, M.S., Sakurada, A., Cutz, J.C., Zhu, C.Q., Kamel-Reid, S., Squire, J., et al., 2005. Erlotinib in lung cancer - molecular and clinical predictors of outcome. N. Engl. J. Med. 353, 133–144.
Tsao, M., Xu, W., Sahgal, A., 2012. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer 118, 2486–2493.
Tsimberidou, A.M., Letourneau, K., Wen, S., Wheler, J., Hong, D., Naing, A., et al., 2011. Phase I clinical trial outcomes in 93 patients with brain metastases: the MD anderson Cancer center experience. Clin. Cancer Res. 17, 4110–4118.

Usery, J.B., Michael, L.M., Sills, A.K., Finch, C.K., 2010. A prospective evaluation and literature review of levetiracetam use in patients with brain tumors and seizures. J. Neurooncol. 99, 251–260.
Vecht, C.J., Haaxma-Reiche, H., Noordijk, E.M., Padberg, G.W., Voormolen, J.H., Hoekstra, F.H., et al., 1993. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann. Neurol. 33, 583–590.
Wang, C., Lu, X., Lyu, Z., Bi, N., Wang, L., 2018. Comparison of up-front radiotherapy and TKI with TKI alone for NSCLC with brain metastases and EGFR mutation: a meta-analysis. Lung Cancer 122, 94–99.
Wasserstrom, W.R., Glass, J.P., Posner, J.B., 1982. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. Cancer 49, 759–772.
Weickhardt, A.J., Scheier, B., Burke, J.M., Gan, G., Lu, X., Bunn Jr., P.A., et al., 2012. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J. Thorac. Oncol. 7, 1807–1814.
Wong, J., Hird, A., Kirou-Mauro, A., Napolskikh, J., Chow, E., 2008. Quality of life in brain metastases radiation trials: a literature review. Curr. Oncol. 15, 25–45.
Wu, Y., Li, P., Zhang, H., Shi, Y., Wu, H., Zhang, J., et al., 2013. Diagnostic value of fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography for the detection of metastases in non-small-cell lung cancer patients. Int. J. Cancer 132, E37–47.
Wu, Y.L., Ahn, M.J., Garassino, M.C., Han, J.Y., Katakami, N., Kim, H.R., et al., 2018. CNS efficacy of Osimertinib in patients with T790M-Positive advanced non-small-Cell lung Cancer: data from a randomized phase III trial (AURA3). J. Clin. Oncol. 36, 2702–2709.
Xie, L., Nagpal, S., Wakelee, H.A., Li, G., Soltys, S.G., Neal, J.W., 2018. Osimertinib for EGFR-Mutant lung Cancer with brain metastases: results from a single-center retrospective study. Oncologist.
Yamamoto, M., Serizawa, T., Shuto, T., Akabane, A., Higuchi, Y., Kawagishi, J., et al., 2014. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 15, 387–395.
Yang, J.J., Zhou, C., Huang, Y., Feng, J., Lu, S., Song, Y., et al., 2017. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. Lancet Respir. Med. 5, 707–716.
Yang, J.C.H., Wu, Y.L., Hirsh, V., O'Byrne, K., Yamamoto, N., Popat, S., et al., 2018a. 143PD competing central nervous system or systemic progression analysis for patients with EGFR mutation-positive NSCLC receiving afatinib in LUX-Lung 3, 6, and 7. J. Thorac. Oncol. 13 S84-S5; abstr 143PD.
Yang, Z., Zhang, Y., Li, R., Yisikandaer, A., Ren, B., Sun, J., et al., 2018b. MA08.01 - phase 3 trial of whole brain radiotherapy with concurrent erlotinib versus WBRT alone for NSCLC with brain metastases (ENTER). J. Thorac. Oncol. 13 abstr MA08.1.
Zhang, Q., Zhang, X., Yan, H., Jiang, B., Xu, C., Yang, J., et al., 2016. Effects of epidermal growth factor receptor-tyrosine kinase inhibitors alone on EGFR-mutant non-small cell lung cancer with brain metastasis. Thorac. Cancer 7 (Nov. (6)), 648–654 PubMed PMID: 27755835. PMCID: PMC5093172. Epub 2016/11/04. eng.
Zhao, J., Chen, M., Zhong, W., Zhang, L., Li, L., Xiao, Y., et al., 2013. Cerebrospinal fluid concentrations of gefitinib in patients with lung adenocarcinoma. Clin. Lung Cancer 14, 188–193.
Zheng, H., Liu, Q.X., Hou, B., Zhou, D., Li, J.M., Lu, X., et al., 2017. Clinical outcomes of WBRT plus EGFR-TKIs versus WBRT or TKIs alone for the treatment of cerebral metastatic NSCLC patients: a meta-analysis. Oncotarget 8, 57356–57364.
Zhu, Q., Sun, Y., Cui, Y., Ye, K., Yang, C., Yang, D., et al., 2017. Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC). Oncotarget 8, 13304–13311.