Central nervous system (CNS) dissemination is a severe complication in cancer and a leading cause of cancer-related mortality. Brain metastases (BM) are the most common types of malignant intracranial tumors and are reported in approximately 25% of patients with metastatic cancers. The recent increase in incidence of BMs is due to several factors including better diagnostic assessments and the development of improved systemic therapies that have lower activity on the CNS. However, newer systemic therapies are being developed that can cross the blood–brain barrier giving us additional tools to treat BMs. The guidelines presented here focus on the efficacy of new targeted systemic therapies and immunotherapies on CNS BMs from breast, melanoma, and lung cancers.

Keywords  Brain metastasis · Blood–brain barrier · Targeted therapies · Immunotherapy · Guidelines
Introduction

Central nervous system (CNS) dissemination is a severe complication in cancer. Brain metastases (BMs) are reported in approximately 25% of patients with metastatic cancer [1] and its incidence has been increasing mainly due to the impact of systemic therapies on survival and the improvement and availability of radiological techniques and screening. Lung cancer is the most frequent primary tumor for BMs, followed by breast cancer and melanoma. Globally, there is a 40–60% risk of presenting BM in melanoma, 20–45% in lung cancer, and 5–30% in breast cancer [1]. Selection of the systemic therapy should be determined not only by the histological tumor type but also by the specific molecular subtype since both of these factors influence risk. Clinical practice guidelines for diagnosis, treatment (including surgery and radiotherapy), and follow-up of patients with BM have been published recently [2, 3]. The present guidelines from the Spanish Society of Medical Oncology (SEOM) have been developed with the consensus of 10 medical oncologists from SEOM and the Spanish Group of Neuro Oncology (GEINO). These guidelines will focus on systemic management of BM from breast, melanoma, and lung cancer, as well as recommendations for treatment of elderly patients.

Methodology

Studies published in peer-reviewed journals were reviewed for the SEOM-GEINO Guidelines. The US Agency for Healthcare Research and Quality Service Grading System (USPSTF) was used to assign levels of evidence and grades of recommendation [4].

Management of symptoms in BM

Brain edema is a common condition found in the magnetic resonance Imaging (MRI) and computed tomography (CT) scans of patients with BMs but the need for anti-edema treatment is primarily based on a patient’s symptoms and not only on radiological findings. Dexamethasone is the most frequently used steroid for this purpose with standard doses between 4 and 16 mg/day [5].

Seizures are a major issue in brain tumor patients but, unfortunately, there are no randomized trials assessing the efficacy of antiepileptic drugs (AEDs) in this population. However, levetiracetam may be the most appropriate drug since it has significant efficacy in seizure control and has no significant drug interactions [6]. Newer drugs, such as lacosamide and brivaracetam, can be also recommended since both have no reported drug interactions and their adverse effects are manageable [7, 8]. There is insufficient evidence to recommend prophylaxis with AEDs [9]. Venous thromboembolism is significantly increased in BM patients but anti-coagulants can increase the risk of intracranial hemorrhage. Therefore, the prescription of prophylactic anticoagulation in these patients requires a careful risk–benefit assessment.

Management of breast cancer BM

Management of HER2-positive breast cancer BMs

BM is the leading cause of death in patients with HER2-positive breast cancer, despite approved anti-HER2 treatment options [10]. Promising new molecules have demonstrated activity in heavily pretreated HER2-positive metastatic breast cancer patients. In the phase III HER2CLIMB trial [11], tucatinib, an oral tyrosine kinase inhibitor (TKI) with high selectivity for HER2, was combined with trastuzumab and capecitabine in 612 patients with previously treated HER2-positive metastatic breast cancer. Among the 219 patients with BM, progression-free survival (PFS) at 1 year was 24.9% in the tucatinib combination group and 0% in the placebo combination group (HR 0.48; 95% CI 0.34–0.69; \( p < 0.001 \)), and the median PFS for CNS-target lesions was 9.9 months (HR 0.32; 95% CI 0.22–0.48, \( p < 0.0001 \)) compared to 4.2 months in the control arm. The overall response rate (ORR) was 47% vs 20% and prolonged overall survival (OS) was 18.1 vs 12 months (HR 0.58; CI 95% = 0.40–0.85; \( p = 0.005 \)) in the tucatinib vs control arms, respectively (see Fig. 1).

In the NALA Trial [12], neratinib, another HER2-selective TKI, was compared against lapatinib, with both drugs in combination with capecitabine. Mean PFS at 24 months in 101 BM patients was 7.8 months with neratinib vs 5.5 months with lapatinib (HR 0.66), and mean OS through 48 months was 16.4 vs 15.4 months, respectively (HR 0.90). In patients with target CNS lesions at baseline (\( n = 32 \)), confirmed intracranial objective response rates were 26.3% and 15.4%, respectively.

For the Destiny-Breast 01 [13] phase II study, trastuzumab deruxtecan, an antibody–drug conjugate, had demonstrated activity in patients pretreated with trastuzumab emtansine. Although only 13% of the included patients had BMs, this subgroup had a CNS response rate of 55%. In addition, only 8% of all patients showed brain progression.
Management of BM for triple-negative breast cancer (TNBC)

The incidence of BM is as high as 46% among patients with advanced TNBC, with 14% presenting BM in the initial diagnosis of breast cancer [14]. BM occurs earlier and is more frequently accompanied by extracranial systemic lesions. In addition, it has a poor clinical prognosis, and is defined as refractory breast cancer due to its resistance to treatment. Patients with TNBC and BM also have a much shorter survival time, with a median OS of approximately 6 months and the worst breast cancer-specific survival and OS [15]. Furthermore, gene expression patterns in primary TNBC do not predict the occurrence of BM in this population [16].

To date, there is no standard treatment for BM-TNBC [17]. Only preliminary and non-randomized studies have been conducted on these patients using chemotherapy which have yielded varying results. Radiation therapy to the brain compromises the blood–brain barrier (BBB) and reduces expression of the efflux transporter P-glycoprotein (P-gp) [18]. P-gp effluxes a broad spectrum of natural compounds including chemotherapeutic drugs, such as anthracyclines, taxanes, and epipodophyllotoxin. However, carboplatin [19], 5-fluorouracil, and capecitabine [20] are capable of crossing the BBB and can be used to treat BM-TNBC without radiation therapy.

General recommendations for breast cancer BM

Figure 1.

Management of melanoma BM

Targeted therapies

Among patients with BRAF-mutant melanoma and brain metastases (MBM), treatment with the BRAF inhibitors dabrafenib or vemurafenib leads to response rates of 20% and 38%, respectively, in patients with radiotherapy-naïve disease [21, 22]. Furthermore, the combination of dabrafenib with trametinib was evaluated in the COMBI-MB study [23]. Among the 125 patients enrolled, 76 BRAF<sup>V600</sup> patients were asymptomatic MBM and with no previous local brain therapy, (cohort A); 16 BRAF<sup>V600</sup> patients were asymptomatic MBM and with previous local brain therapy (cohort B); and 16 BRAF<sup>V600D/K/R</sup> patients were asymptomatic MBM with or without previous local therapy (cohort C) and 17 BRAF<sup>V600D/K/R</sup> symptomatic melanoma brain metastases with or without previous local brain therapy, and an ECOG performance status of 0, 1, or 2 (cohort D). An intracranial response was achieved in 58%, 56%, 44%, and 59% of patients in cohorts A, B, C, and D, respectively. In cohort A, the median PFS was 5.6 months, the median OS was 10.8 months, and adverse events greater than grade 3 or 4 were reported in 48% of patients. Median PFS was almost half (5.6 vs 10.1 months) as compared to that observed with the same treatment in patients with extracranial disease [24],
which suggests an earlier treatment failure in the brain. Triplet therapy including anti-PD-1/L1 is being explored in BRAF-mutant MBM to increase intracranial efficacy (NCT 03625141) (Fig. 2).

**Immunotherapies**

Systemic treatment with immunotherapy has improved the efficacy of MBM treatment. Monotherapy treatment with either anti-CTLA-4 or anti-PD-1 in BM patients reproduces the systemic efficacy observed in these patients. Intracranial response rates have been reported as 16% for anti-CTLA-4 and 20–26% for anti-PD-1 [25]. The activity of ipilimumab in combination with nivolumab was evaluated in two phase II studies, showing a high rate of durable intracranial responses (51–54%) in patients with asymptomatic MBM [26–28]. However, this scheme has shown limited efficacy in patients with symptomatic metastases or receiving steroid therapy [28]. Addition of localized treatment, such as surgery or radiotherapy, could increase brain control and survival [29]. Prospective randomized clinical trials are needed to better delineate the optimal associations of immunotherapy and radiotherapy [30]. At least one retrospective study has suggested that it is safe to interrupt treatment when a complete response is achieved.

**General recommendations for melanoma BM**

Figure 2.

---

**Management of lung cancer BM**

**EGFR-mutated non-small cell lung cancer (NSCLC)**

NSCLC patients with EGFR mutations have a higher risk of developing BMs, ranging between 24% at diagnosis to more than 45% at 3 years post-diagnosis [31]. Multiple studies have demonstrated better activity in the CNS with 1st- and 2nd-generation TKIs compared to cytotoxic chemotherapy [32], although in general, the efficacy of 1st- and 2nd-generation TKIs is limited at the brain level mainly due to a modest penetration of the BBB. A retrospective study of 306 NSCLC patients compared the efficacy of 1st- and 2nd-generation EGFR TKIs showed no significant differences in the cumulative incidences of subsequent BM at 6, 12, and 24 months when comparing gefitinib vs erlotinib and afatinib ($p = 0.80$) [33]. Osimertinib, a 3rd-generation EGFR TKI, has a higher BBB penetration than 1st- and 2nd-generation EGFR TKIs. In previously treated EGFR$^{T790M}$-positive advanced NSCLC, osimertinib was compared to pemetrexed/platinum combination in the randomized phase III AURA3 trial: CNS ORR was found to be higher in those patients receiving osimertinib vs pemetrexed/platinum (70% vs 31%, respectively) [34]. Similarly, a pooled analysis from two phase II studies that included patients with EGFR$^{T790M}$-positive advanced NSCLC that progressed following treatment with an EGFR TKI showed a CNS relative risk of 54% and disease control rate of 92% [35]. In previously untreated EGFR-mutant advanced NSCLC, osimertinib was compared to gefitinib or erlotinib in the randomized phase III Flaura trial: 22% of patients that received osimertinib presented BM compared with 24% treated with erlotinib or gefitinib. The median CNS PFS was
not reached with osimertinib and limited to 13.9 months with 1st-generation TKI (HR 0.48). CNS ORR was 91% and 68% in patients with ≥ 1 measurable CNS lesions and 66% and 43% in patients with measurable and/or non-measurable CNS lesions, respectively. The risk of CNS progression at 12 months was 8% with osimertinib and 24% with either gefitinib or erlotinib [36]. Based on the systemic and brain activity profiles, osimertinib can be considered the preferred 1st-line option for patients harboring EGFR mutations and BM (Fig. 3).

ALK-rearranged NSCLC

ALK-positive NSCLC is characterized by a high incidence of BM (24–48%) [31]. In the 1st-line setting, 1st-generation ALK inhibitor (ALKi) crizotinib demonstrated higher intracranial disease control rate over chemotherapy. However, progression in the brain remained a significant clinical problem with crizotinib treatment [37, 38]. A 2nd-generation ALKi, ceritinib, significantly improved intracranial response rate (icRR) over chemotherapy (72.7% vs 27.3%, respectively). Nevertheless, due to the toxicity profile its use has not been commonly extended [39]. Alectinib and brigatinib are 2nd-generation ALKis that have shown a significant improvement in icRR (81–78%, and 50–29%, respectively) and longer time to CNS progression over crizotinib (HR 0.16; 95% CI 0.10–0.28 vs HR 0.30; 95% CI 0.15–0.60; respectively) [40–42]. Similarly, upfront treatment with a 3rd-generation ALKi with broad range activity against ALK-resistant mutations achieved a significantly higher icRR and longer time to CNS progression compared to crizotinib (HR 0.07; 95% CI 0.03–0.17; 82% vs 23%, respectively) [43]. In patients progressing to frontline crizotinib, next-generation ALKi demonstrated promising CNS activity (icRRs ranging from 67 to 35%) [44–47]. In patients previously treated with at least one prior 2nd-generation ALKI and only one prior 2nd-generation ALKi, lorlatinib demonstrated an icRR of 56.1% and 66.7% and prolonged median intracranial duration of response of 12.4 months (95% CI 6.0–37.1) and 20.7 months (95% CI 4.1–37.1), respectively [48]. Data with other ALKis in the post-2nd-generation ALKi setting are still limited.

ROS1-rearranged NSCLC

Up to 36% of patients with ROS1-positive NSCLCs have a BM at the diagnosis of metastatic disease [49]. In this NSCLC population, crizotinib was approved as the standard 1st-line treatment, however, suboptimal CNS penetration has been observed [50]. Next-generation ROS1 inhibitors (ROS1i) such as lorlatinib have demonstrated remarkable intracranial activity in both ROS1i-naive and crizotinib-pre-treated patients (64% and 50%, respectively) [51]. Entrectinib, a multikinase inhibitor with activity against ROS1, demonstrated CNS activity in ROSi-naive patients with an icRR of 55% (79.2% in patients with measurable disease)
Clinical and Translational Oncology

13

CNS efficacy data with other next-generation ROS1i are still limited.

General recommendations for NSCLC BM

Figure 3.

- We recommend a baseline brain MRI for patients with oncogene-addicted NSCLC [IV, A]
- In patients with asymptomatic and multiple BMs and NSCLC with driver alterations for whom TKIs with high efficacy and brain penetration are available, we consider it reasonable to use these targeted therapies as a 1st-line treatment and to delay the use of whole brain radiation therapy [II, A]
- Mildly symptomatic patients may still be considered for treatment with a TKI given the high icRR and the expected rapidity of response if close monitoring is ensured and endorsed by multidisciplinary discussion [IV, A]
- Patients with large volume, life-threatening, or highly symptomatic BM involvement should receive locoregional treatments (either salvage stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT)) based on the number and dimensions of the lesions, in addition to the appropriate systemic therapies [III, B]
- EGFR
  - Patients with BMs should be included in clinical trials whenever possible
  - At 1st-line setting, in EGFR TKI-naïve patients with asymptomatic or symptomatic multiple BMs, it is advisable to start treatment with osimertinib [III, A]
  - In EGFR T790M-positive patients progressing to 1st- or 2nd-generation EGFRi, the 3rd-generation TKI osimertinib is recommended [III, A]
- ALK
  - BM patients should be included in clinical trials whenever possible
  - Crizotinib is not the preferred 1st-line agent for BM patients due to its low ability to penetrate the BBB [IV, A]
  - At 1st-line setting, the 2nd-generation ALKi alectinib [III, A], brigatinib [III, A], and ceritinib [IV, A] could be considered standard treatment; however, due to safety profiles, alectinib and brigatinib are the preferred options
  - In patients progressing to crizotinib in the CNS, a second-generation ALKi is recommended [III, A]
- ROS1
  - BM patients should be included in clinical trials whenever possible
  - Crizotinib is the only approved 1st-line agent for patients with ROS1-positive disease [IV, A]

Management of BM in elderly patients

Elderly cancer patients require specific management (Fig. 3). Aging modifies functional reserve, and, together with comorbidity and geriatric syndromes, situates this population in a vulnerable position for the toxicity of treatments. Therapeutic decisions in elderly cancer patients should be based on geriatric assessment and at a level I of evidence [53–56]. Individualized treatment decisions for elderly cancer patients affected by BMs are a priority. An aggressive approach could be deleterious. To avoid toxicity, we must identify functional reserve, frailty, and ability to respond. Furthermore, stress must be managed properly in a population with a limited life expectancy because of aging itself. Elderly patients are often treated differently than younger individuals due to concerns regarding tolerance and survival [56]. Studies have focused on patients with 1–3 metastases. Patients with 1–2 BMs have a better prognosis than those with multiple lesions and appear to benefit from more aggressive approaches than WBRT alone. However, the cutoff age for the definition of elderly patients is 65 years, an age that nowadays is not considered the definition of an aged person [57]. Prognostic factors and treatment criteria in this patient group (≥ 65 years and 1 lesion) are performance status, histology of primary tumor, and time between diagnosis and BM detection [57, 58]. There is a lack of evidence for specific management of elderly cancer patients with multiple BMs [59].

General principles for surveillance and monitoring of BM

Based on contemporary data, median survival of BM patients exceeds 6 months for all major cancer types and ranges from 8 to 16 months depending on the primary tumor [60]. Up to 50% of surviving patients with BMs will develop new lesions or progression of previously treated lesions within 6–12 months of initial therapy. Recurrent disease
may be amenable to treatment with SRS, surgery, or WBRT, depending on the overall condition of the patient and the extent and location of the disease. In limited BM and in multiple BMs, we recommend a brain MRI every 2 months for those treated with SRS alone and every 3 months for the rest for the first 2 years and then every 4–6 months indefinitely. Imaging to evaluate emergent signs and symptoms is appropriate at any time [3] [IIA].

Acknowledgements Editorial assistance, in the form of language editing and correction, was provided by XpertScientific Editing and Consulting Services.

Declarations

Conflict of interest MMG reports Advisory Board from Seagen; Advisory Board and Other from Roche and Celgene; Speaker, Grant and Other from Pfizer. SST reports Speaker from Roche and Novartis; Advisory Board from MSD, Dalchi-Sankyo and Genomic Health; Advisory Board and Speaker from Astrazeneca. RGC reports Advisory Board from BMS, MSD, Roche, Takeda and Pfizer; Advisory Board from Janssen and Sanofi. AAF reports Advisory Board and Speaker from BMS, MSD, Roche, Takeda and Pfizer; Advisory Board from Astrazeneca. RGC reports Advisory Board from MSD, Daïchi-Sankyo and Genomic Health; Other from Pfizer. SST reports Speaker from Roche and Novartis; Advisory Board and Other from Roche and Celgene; Speaker, Grant and Other from MMG reports Advisory Board from Seagen; Advisory Board and Other from Roche and Celgene; Speaker, Grant and Other from Pfizer. SST reports Speaker from Roche and Novartis; Advisory Board and Other from Roche and Celgene; Speaker, Grant and Other from MMG reports Advisory Board from Seagen; Advisory Board and Other from Roche and Celgene; Speaker, Grant and Other from Pfizer.

Ethical approval The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All authors contributed equally to the development of this guideline.

Informed consent For this type of study formal consent is not required.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Ostrom QT, Wright CH, Barnholtz-Sloan JS. Brain metastases: epidemiology. Handb Clin Neurol. 2018;149:27–42. https://doi.org/10.1016/B978-0-12-811161-1.00002-5.
2. Le Rhun E, Guckenberger M, Smits M, et al. EANO–ESMO clinical practice guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021. https://doi.org/10.1016/j.annonc.2021.07.016.
3. Nabors LB, Portnow J, Aihuvalia M, et al. Central nervous system cancers, version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020;18(11):1537–70. https://doi.org/10.6004/jnccn.2020.0052.
4. Grade Definitions. US Preventive Services Task Force. 2016. https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions.
5. Hempen C, Weiss E, Hess CF. Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? Support care cancer Off J Multinatl Assoc Support Care Cancer. 2002;10(4):322–8. https://doi.org/10.1007/s00520-001-0333-0.
6. Radu R, Mo F, Pellerino A. Epilepsy in brain metastasis: an emerging entity. Curr Treat Options Neurol. 2020;22(2):6. https://doi.org/10.1007/s11940-020-0613-y.
7. Sepúlveda-Sánchez JM, Conde-Moreno A, Barón M, Pardo J, Reynés G, Belenguer A. Efficacy and tolerability of lacosamide for secondary epileptic seizures in patients with brain tumor: a multicenter, observational retrospective study. Oncol Lett. 2017;13(6):4093–100. https://doi.org/10.3892/ol.2017.5988.
8. Maschio M, Maialetti A, Mocellini C, et al. Effect of brivaracetam on efficacy and tolerability in patients with brain tumour-related epilepsy: a retrospective multicenter study. Front Neurol. 2020;11:813. https://doi.org/10.3389/fneur.2020.00813.
9. Walbert T, Harrison RA, Schiff D, et al. SNO and EANO practice guideline update: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro Oncol. 2021;23(11):1835–44. https://doi.org/10.1093/neucom/noab132.
10. Mills MN, Figura NB, Arrington JA, et al. Management of brain metastases in breast cancer: a review of current practices and emerging treatments. Breast Cancer Res Treat. 2020;180(2):279–300. https://doi.org/10.1007/s10549-020-05552-2.
11. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382(7):597–609. https://doi.org/10.1056/NEJMoa1914609.
12. Hurvitz SA, Saura C, Oliveire M, et al. Efficacy of neratinib plus capecitabine in the subgroup of patients with central nervous system involvement from the NALA trial. Oncologist. 2021;26(8):e1327–38. https://doi.org/10.1002/ono.13830.
13. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610–21. https://doi.org/10.1056/NEJMoa1914510.
14. Li X, Yang J, Peng L, et al. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. Breast Cancer Res Treat. 2017;161(2):279–87. https://doi.org/10.1007/s10549-016-4059-6.
15. Vener VA, Aahuvalia MS. Targeted therapy in brain metastases: ready for primetime? Am Soc Clin Oncol Educ book Am Soc Clin Oncol Annu Meet. 2016;35:e123–30. https://doi.org/10.1200/EDBK_100006.
16. Duchnowska R, Jarzáb M, Żebracka-Gala J, et al. Brain metastasis prediction by transcriptomic profiling in triple-negative breast cancer. Clin Breast Cancer. 2017;17(2):e65–75. https://doi.org/10.1016/j.clbc.2016.08.008.
17. Ly Y, Ma X, Du Y, Feng J. Understanding patterns of brain metastasis in triple-negative breast cancer and exploring potential therapeutic targets. Onco Targets Ther. 2021;14:589–607. https://doi.org/10.2147/OTT.S293685.
18. Bart J, Nagengast WB, Coppers RP, et al. Irradiation of rat brain reduces P-glycoprotein expression and function, Br J Cancer. 2007;97(3):322–6. https://doi.org/10.1038/sj.bjc.6603864.
19. Lin NU. Breast cancer brain metastases: new directions in systemic therapy. Ecancermedicalscience. 2013;7:307. https://doi.org/10.3332/ecancer.2013.307.
20. Ekenel M, Hormigo AM, Peak S, Deangelis LM, Abrey LE. Capecitabine therapy of central nervous system metastases from
breast cancer. J Neurooncol. 2007;85(2):223–7. https://doi.org/10.1007/s11060-007-9409-0.

21. Long GV, Keff RF, Phd R, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(13):1087–95. https://doi.org/10.1016/S1470-2045(12)70431-X.

22. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2 multicentre study. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(3):634–41. https://doi.org/10.1093/annonc/mdw641.

23. Davies MA, Saig P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18(7):863–73. https://doi.org/10.1016/S1470-2045(17)30429-1.

24. Long GV, Stroyakovskiy D, Dogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet (London, England). 2015;386(9992):444–51. https://doi.org/10.1016/S0140-6736(15)60898-4.

25. Ahmed KA, Abuodeh YA, Echevarria MI, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. Ann Oncol. 2016;27(12):2288–94. https://doi.org/10.1093/annonc/mdw417.

26. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018;19(5):672–81. https://doi.org/10.1016/S1470-2045(18)30139-6.

27. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and Ipilimumab in melanoma metastatic to the Brain. N Engl J Med. 2018;379(8):722–30. https://doi.org/10.1056/NEJMoa1805453.

28. Tawbi HA, Forsyth PA, Hodi FS, et al. Safety and efficacy of the combination of nivolumab plus ipilimumab in patients with melanoma and asymptomatic or symptomatic brain metastases (CheckMate 204). Neuro Oncol. 2021. https://doi.org/10.1093/neuono/mob094.

29. Amral T, Kieseker F, Schaefer S, et al. Combined immunotherapy with nivolumab and ipilimumab with and without local therapy in patients with melanoma brain metastasis: a DeCOG* study in 380 patients. J Immunother Cancer. 2020. https://doi.org/10.1007/jitc-2019-000333.

30. Dimitriou F, Zaremba A, Allayous C, et al. Sustainable responses in metastatic melanoma patients with and without brain metastases after elective discontinuation of anti-PD1-based immunotherapy due to complete response. Eur J Cancer. 2021;149:37–48. https://doi.org/10.1016/j.ejca.2021.02.037.

31. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer. 2015. https://doi.org/10.1016/j.lungcan.2015.01.020.

32. Heon S, Yeap BY, Lindeman NI, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. Clin cancer Res an Off J Am Assoc Cancer Res. 2012;18(16):4406–14. https://doi.org/10.1158/1078-0432.CCR-12-0357.

33. Su P-L, Wu Y-L, Chang W-Y, et al. Preventing and treating brain metastases with three first-line EGFR-tyrosine kinase inhibitors in patients with EGFR mutation-positive advanced non-small cell lung cancer. Ther Adv Med Oncol. 2018;10:1758835918797589. https://doi.org/10.1177/1758835918797589.

34. Wu Y-L, Ahn M-J, Garassino MC, et al. 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 Off J Am Soc Clin Oncol. 2018;36(26):2702–9. https://doi.org/10.1200/JCO.2018.77.9363.

35. Goss G, Tsai C-M, Shepherd FA, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. Ann Oncol Off J Eur Soc Med Oncol. 2018;29(3):687–93. https://doi.org/10.1093/annonc/mdx820.

36. Reungwetwattana T, Nakagawa K, Cho BC, et al. 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 Off J Am Soc Clin Oncol. 2018. https://doi.org/10.1200/JCO.2018.73.3118.

37. Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014. https://doi.org/10.1056/NEJMoa1408440.

38. Solomon BJ, Cappuzzo F, Felip E, et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non–small-cell lung cancer: results from PROFILE 1014. J Clin Oncol. 2016. https://doi.org/10.1200/JCO.2015.63.5888.

39. Sorria J-C, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non–small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017. https://doi.org/10.1016/S0140-6736(17)30123-X.

40. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non–small–cell lung cancer. N Engl J Med. 2017. https://doi.org/10.1056/NEJMoa1704795.

41. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Ann Oncol. 2018. https://doi.org/10.1093/annonc/mdy405.

42. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in ALK-positive non–small–cell lung cancer. N Engl J Med. 2018;379(21):2027–39. https://doi.org/10.1056/NEJMoa1810171.

43. Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2027187.

44. Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non–small–cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017. https://doi.org/10.1016/S1470-2045(17)30339-X.

45. Novello S, Mazières J, Oh I-J, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non–small–cell lung cancer: results from the phase III ALUR study. Ann Oncol. 2018. https://doi.org/10.1093/annonc/mdy121.

46. Kim D-W, Tiseo M, Ahn M-J, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non–small–cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol. 2017. https://doi.org/10.1200/JCO.2016.71.5904.

47. Huber RM, Hansen KH, Paz-Ares Rodríguez L, et al. Brigatinib in crizotinib-refractory ALK+ NSCLC: 2-year follow-up on systemic and intracranial outcomes in the phase 2 ALTA trial. J Thorac Oncol. 2020. https://doi.org/10.1016/j.jtho.2019.11.004.

48. Felip E, Shaw AT, Bearz A, et al. Intracranial and extracranial efficacy of lorlatinib in patients with ALK-positive non–small–cell lung cancer previously treated with second-generation ALK TKIs. Ann Oncol. 2021. https://doi.org/10.1016/j.annonc.2021.02.012.
49. Gainor JF, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. JCO Precis Oncol. 2017. https://doi.org/10.1200/PO.17.00063.

50. Shaw AT, Riely GJ, Bang Y-J, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. Ann Oncol. 2019. https://doi.org/10.1093/annonc/mdz131.

51. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial. Lancet Oncol. 2019. https://doi.org/10.1016/S1470-2045(19)30655-2.

52. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials. Lancet Oncol. 2020. https://doi.org/10.1016/S1470-2045(19)30690-4.

53. Mohile SG, Mohamed MR, Culakova E, et al. A geriatric assessment (GA) intervention to reduce treatment toxicity in older patients with advanced cancer: A University of Rochester Cancer Center NCI community oncology research program cluster randomized clinical trial (CRCT). J Clin Oncol. 2020;38(15_suppl):12009. https://doi.org/10.1200/JCO.2020.38.15_suppl.12009.

54. Li D, Sun C-L, Kim H, et al. Geriatric assessment-driven intervention (GAIN) on chemotherapy toxicity in older adults with cancer: a randomized controlled trial. J Clin Oncol. 2020;38(15_suppl):12010. https://doi.org/10.1200/JCO.2020.38.15_suppl.12010.

55. Soo W-K, King M, Pope A, Parente P, Darzins P, Davis ID. Integrated geriatric assessment and treatment (INTEGRATE) in older people with cancer planned for systemic anticancer therapy. J Clin Oncol. 2020;38(15_suppl):12011. https://doi.org/10.1200/JCO.2020.38.15_suppl.12011.

56. Rades D, Pluemer A, Veninga T, Schild SE. Comparison of different treatment approaches for one to two brain metastases in elderly patients. Strahlenther Onkol. 2008;184(11):565–71. https://doi.org/10.1007/s00066-008-1908-1.

57. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of “elderly.” Geriatr Gerontol Int. 2006;6(3):149–58. https://doi.org/10.1111/j.1447-0594.2006.00341.x.

58. Rades D, Nguyen T, Schild SE. Elderly patients with single brain metastasis—overall survival after surgery plus whole-brain irradiation and a radiation boost. In Vivo. 2020;34(3):1421–5. https://doi.org/10.21873/invivo.11923.

59. Rades D, Nguyen T, Janssen S, Schild SE. An instrument to guide physicians when estimating the survival of elderly patients with brain metastasis from gynecological cancer. Anticancer Res. 2020;40(4):2257–60. https://doi.org/10.21873/anticancer.14188.

60. Sperduto PW, Mesko S, Li J, et al. Survival in patients with brain metastases: summary report on the updated diagnosis-specific graded prognostic assessment and definition of the eligibility quotient. J Clin Oncol Off J Am Soc Clin Oncol. 2020;38(32):3773–84. https://doi.org/10.1200/JCO.20.01255.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.