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TARGETED THERAPY IN BRAIN METASTASIS

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Abstract

Purpose of review: To review the state of the art and new developments in the field of targeted agents for brain metastases.

Recent findings: The huge amount of information on new molecular compounds and the advances in understanding the molecular pathways that mediate brain colonization have led to an increase of interest in preclinical and clinical investigations in the field of brain metastases. Targeted therapies can be employed either on established brain metastases or in a prevention setting. Targeting angiogenesis is an attractive approach. Up to date, large clinical trial datasets have shown that antiangiogenic agents do not increase the risk of bleeding into the brain. Bevacizumab (an anti-VEGF agent) is undergoing investigation in clinical trials on brain metastases from non-small cell lung cancer (NSCLC), breast cancer and melanoma. Sunitinib, a multitarget small molecule tyrosine kinase inhibitor (TKI), is a promising agent in brain metastases from renal cell cancer. The EGFR inhibitors gefitinib and erlotinib have a definite activity in brain metastases from NSCLC with activating EGFR mutations. Regarding HER2-positive breast cancer patients with established brain metastases, lapatinib (small molecule TKI) seems particularly active in association with capecitabine. Lapatinib alone is attractive in the prevention setting. Brain metastases from melanoma with BRAF V600E mutations respond to a specific inhibitor, such as vemurafenib. The immunomodulator ipilimumab is also active on brain metastases from melanoma.

Summary: The use of targeted agents in brain metastases from solid tumors is promising. The setting of prevention will be probably expanded in the next years. Well designed clinical trials with proper endpoints are needed.

INTRODUCTION

Brain metastases occur in up to 40% of cancer patients and represent a major cause of mortality and morbidity [1*]. The majority of brain metastases originate from primary cancers in the lung (40–50%), breast (15–25%) and melanoma (5–20%). The incidence of brain metastases has raised as a result of a better detection of oligometastases by MRI, increase of survival of cancer patients because of progress in the treatment of the systemic disease and aging population.

The standard management of patients with brain metastases has been optimized over time, owing to technical improvements in surgery and radiation therapy, and a better definition of prognostic factors that has led to a

more accurate patient selection [2*,3*]. The role of chemotherapy with cytotoxic drugs is limited to palliation, and the efficacy depends on the chemosensitivity of the primary tumor [4].

Targeted therapies have been initially employed in primary cancers, based on the identification of molecular targets critical for tumor growth. More recently, the increased amount of information on new molecular compounds and the advances in understanding the molecular pathways that mediate brain colonization have led to a new interest in both preclinical and clinical investigations in the field of brain metastases [5*–7*].

TARGETED THERAPIES ON ESTABLISHED BRAIN METASTASES

Most clinical trials enrolled patients with established brain metastases who have progressed after whole-brain radiation therapy (WBRT). Less frequently targeted agents, either alone or in combination with WBRT, have been investigated in newly diagnosed brain metastases.

KEY POINTS

- Targeting angiogenesis is an evolving approach, with compounds such as bevacizumab, sunitinib, sorafenib and cilengitide being actively investigated.
- Response of NSCLC brain metastases to EGFR inhibitors is highly dependent on the presence of activating EGFR mutations.
- Among HER2-positive breast cancer patients, lapatinib in combination with capecitabine is active in the treatment of established brain metastases.
- An impressive rate of responses has been reported with the immunomodulator ipilimumab in brain metastases from melanoma, and specific BRAF inhibitors are being investigated.
- New prevention strategies and designing appropriate clinicotranslational studies are a challenge for the future.

Graphic Box 1

Targeting angiogenesis

In the past, patients with brain metastases have been largely excluded from clinical trials with antiangiogenic agents based on concerns regarding the risk of central nervous system (CNS) hemorrhage. However, recent reviews of large clinical trial datasets, retrospective and prospective studies have shown that patients with and without CNS metastases are at a similar risk of bleeding into the brain (0.8–3.3%), independent of antiangiogenic therapy [8–11]. Several phase I and II studies on bevacizumab alone or combined with other antineoplastic agents are ongoing in brain metastases from non-small cell lung cancer (NSCLC), breast cancer and melanoma. Trials employing anti-VEGF (vascular endothelial growth factor) agents (bevacizumab and cediranib) in brain metastases must monitor their potential proinvasive effects, as already demonstrated in glioblastoma. Sunitinib is an oral, small molecule, tyrosine kinase inhibitor (TKI) that targets the VEGF receptors 1 to 3 and the platelet-derived growth factor (PDGF) receptors α and β , and is able to cross the blood–brain barrier (BBB) rapidly [12]. The drug is registered for the treatment of advanced

renal cell cancer (RCC) and has yielded an overall response rate of 12% among 213 patients with brain metastases compared with 17% in the overall population of 3464 patients [13]. More recently, it has been reported that two out of six patients with RCC and newly diagnosed brain metastases (small, asymptomatic and without hemorrhage on MRI) achieved a near complete response (CR) to therapy with sunitinib with a duration of 23+ and 47+ months [14*]. A phase II study in patients with NSCLC and irradiated brain metastases [15] has shown a marginal antitumor activity [partial response (PR) 1.6%, median progression-free survival 9.4 weeks and overall survival (OS) 25.1 weeks]. Sunitinib is undergoing investigation in patients with brain metastases from breast cancer and melanoma. Other antiangiogenic agents, that are investigated in phase I and II trials on brain metastases, include sorafenib (miscellanea and kidney cancer) and cilengitide in lung cancer.

Targeting specific tumor types

Over time, clinical trials have increasingly investigated new agents that target specific molecular pathways in specific tumor types.

Non-small cell lung cancer

Between 10 and 25% of NSCLC patients (mainly adenocarcinomas) carry activating EGFR (epidermal growth factor receptor) mutations, with the highest prevalence (up to 55%) in never-smoking women from East Asia. Brain metastases from NSCLC have been shown to respond to oral EGFR TKIs gefitinib and erlotinib. Response rates (complete and partial) after gefitinib range from 10 to 38% with a median duration of response of 9–13.5 months, and the latency between the start of treatment and appearance of response is short (~1 month) [16–20]. Similar findings have been documented with erlotinib [21–24,25*,26]. As for extracranial disease, response to EGFR inhibitors is highly dependent on the presence of activating EGFR mutations [25*,27]. Chemo-naïve patients seem particularly responsive: among 23 Asian never smokers with brain metastases from NSCLC receiving first-line gefitinib or erlotinib, a 70% CNS response rate was observed [28], and all seven patients with brain metastases and chemo-naïve, advanced-stage, NSCLC achieved an objective CNS response [29]. Moreover, patients with brain metastases from EGFR-mutant NSCLC have improved overall survival compared with EGFR wild-type tumors when receiving an EGFR inhibitor [30]. EGFR inhibitors can be safely administered concurrently with WBRT [31,32]. A recent phase II randomized study in brain metastases from NSCLC, comparing WBRT plus gefitinib vs. WBRT plus temozolomide (TMZ), has failed to show any advantage (OS 6.3 months in the gefitinib arm and 4.9 months in the TMZ arm), despite the fact that the majority of patients were previously untreated and with a relatively good performance status [33*]. In the UK, a phase II trial comparing WBRT plus placebo versus WBRT plus erlotinib has been completed, and results are awaited for late 2012. Erlotinib seems to produce higher CSF levels than gefitinib [34*], and therefore could be preferable. In about 4% of patients with NSCLC, an ALK (anaplastic lymphoma kinase) rearrangement occurs: crizotinib is an oral selective inhibitor of activated ALK, leading to objective response or stabilization in most patients harboring this molecular alteration [35]. There are no data on the activity of crizotinib in patients with brain metastases so far: however, a poor penetration of the agent into the brain could limit the potential efficacy [36].

Breast cancer

The risk of developing brain metastases among patients with breast cancer is higher for tumors that are HER2 positive or triple negative (i.e. lacking expression of HER2, estrogen and progesterone receptors), or of the basal-like subtype. HER2-positive patients (up to 25% of the overall population) have the greatest risk

(especially if estrogen/progesterone receptor negative) [37]. The frequency of brain metastases among HER2-positive patients treated with trastuzumab (a monoclonal antibody targeting HER2) in the metastatic setting is between 25 and 40% [38–42,43*]; similarly, when analyzing large phase III trials in the adjuvant setting, CNS metastases are significantly increased in the trastuzumab-containing treatment arms compared with the nontrastuzumab-containing arms [44**]. Moreover, the brain seems to be more frequently the first site of relapse in patients treated with trastuzumab, whether in the metastatic or adjuvant setting [45*]. A combination of factors likely explains the increased incidence of CNS disease in these patients, including a high propensity of HER2 cells for brain colonization [46,47], and improved control of systemic disease with trastuzumab, which has poor BBB penetration [48], and therefore is not able to target micrometastases that are protected by an intact BBB. It is interesting to note that the HER2 status seems to be consistent between matched primary tumors and brain metastases in the majority of patients [49]. This latter point, along with the well known disruption of the BBB in lesions greater than 1 cm of diameter, could argue in favor of some role of trastuzumab in the treatment of established brain metastases. In this regard, some recent studies have reported that trastuzumab improves the prognosis of HER2-positive patients with brain metastases [43*,50,51,52*].

Lapatinib is an orally dual TKI targeting EGFR and HER2 pathway, and is primarily used for the treatment of trastuzumab-resistant advanced breast cancer. Phase II trials have evaluated lapatinib as a single agent in patients with progressive HER2-positive breast cancer and brain metastases despite standard radiotherapy [53,54], and showed only modest efficacy with objective responses in 2 and 6% of patients, respectively. Minor responses were reported in a further 18 and 21% of patients. Interestingly, responding patients had an improved time-to-progression compared to no responding patients. The combination of lapatinib and capecitabine, an active drug against metastatic breast cancer, has yielded better results, with CNS responses ranging from 18 to 38% in the refractory setting (after previous WBRT) [54–56,57*,58*]. Only one study addressed the role of lapatinib plus capecitabine prior to WBRT and showed an impressive CNS response rate of 67%, with a median time to progression of 5.5 months and a median time to WBRT of 8.3 months [59*]. These results could open the door for studies comparing WBRT versus lapatinib plus capecitabine as initial therapy for HER2-positive patients. The combination of lapatinib with topotecan is not active and associated with excess toxicity [58*]. Another approach could be the association of lapatinib alone or combined with capecitabine with WBRT; preliminary results in terms of response are encouraging, but there are still issues of tolerance [60]. The RTOG is in the process of initiating a randomized phase II trial comparing WBRT alone with WBRT plus lapatinib.

PARP inhibitors include compounds, such as iniparib, olaparib and veliparib, that target the PARP pathway involved in the DNA single-strand break repair after radiotherapy and chemotherapy. These drugs have shown activity in triple-negative and BRCA-deficient breast cancer [61*]. In particular, iniparib, which is an intravenously administered drug, has been shown to favorably impact PFS and OS in a phase II trial on triple-negative and BRCA-deficient breast cancer patients [62], and is currently investigated (phase II trial), in combination with irinotecan, on triple-negative breast cancer brain metastases.

Melanoma

Up to 60% of melanomas carry an activating mutation in the gene encoding BRAF, a serine-threonine protein kinase. More than 85% of BRAF mutations are of the V600E type, which leads to constitutive kinase activity of BRAF and downstream activation of mitogen-activated protein kinase (MAPK) pathway, thereby enhancing the proliferative and metastatic capacity of the tumor. BRAF V600E mutations can now be easily detected immunohistochemically by the mutation-specific monoclonal antibody VE1 [63*] and seem consistent between primary melanomas and distant metastases [64*]. Vemurafenib, a specific inhibitor of

BRAF V600E mutated protein, has yielded response rates of up to 70% with improved PFS and OS in BRAF V600E mutated metastatic melanoma patients [65**]. Phase II trials investigating vemurafenib in patients with melanoma and brain metastases are ongoing, and an activity has been preliminarily reported [66*]. Recently, a case of successful use of vemurafenib in a child with metastatic melanoma to the brain has been described [67*]. In a phase I/II study, using another BRAF inhibitor (dabrafenib) in metastatic melanoma, all seven patients with previously untreated brain metastases showed CNS tumor shrinkage, including three CRs, and parallel extracranial responses were observed in most patients [68].

Another novel approach to treat advanced melanoma is the blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4), a molecule that downregulates the pathways of T-cell activation [69]. Ipilimumab is a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 and potentiates antitumor immune responses [70]. In two phase III trials, ipilimumab has shown a statistically significant improvement in OS as monotherapy in previously treated patients [71**] and in combination with dacarbazine in treatment-naïve patients [72**].

An antitumor activity of ipilimumab in patients with brain metastases was originally suggested by Downey et al. [73], who treated 139 patients with stage IV melanoma: one of the 10 patients with brain metastases had a CR and two a PR. Two case studies have provided further support [74,75]. A recent retrospective analysis of a phase 2 trial [76*] has shown that 12 patients with previously treated stable brain metastases given ipilimumab had an overall survival of 14 months; moreover, two patients with partial response and one with stable disease survived for more than 4 years. In early 2012, an open-label, phase 2, multicenter U.S. trial [77**] has confirmed that ipilimumab has activity in patients with melanoma brain metastases, particularly when they have stable and asymptomatic metastases that do not need steroids: disease control (CR + PR + SD) after 12 weeks of treatment was 16% in the cohort of asymptomatic patients without steroids compared to 5% in the cohort of symptomatic patients receiving steroids. Importantly, the investigators did not report any neurological deterioration as an effect of an inflammatory response to treatment in the CNS, even in patients who received prior radiation therapy. The possibility remains that steroid treatment at the initiation of ipilimumab could abrogate or downmodulate the immune response. Ipilimumab has similar activity in CNS and non-CNS lesions: an explanation is that T cells could pass through an intact BBB [78] and promote an antitumor T-cell response and necrosis in brain lesions similar to that observed in extracranial lesions [79]. Further studies could assess the combinations of ipilimumab with radiotherapy, conventional cytotoxic drugs, such as TMZ or fotemustine [80], BRAF inhibitors and other emerging immunotherapies [81*,82*].

Factors limiting the efficacy of targeted agents

Overall, responses of established brain metastases to targeted agents have not been achieved in the majority of patients, and the reasons are multifactorial [83**]. Targeted agents may have still a limited capacity to cross the BBB, as in the case of cytotoxic drugs [84]. A recent study performed on experimental brain metastases from breast cancer [85*] has shown that brain metastases concentration of lapatinib was seven-fold to nine-fold greater than surrounding brain tissue, but average lapatinib concentration in brain metastases was 10–20% of that in peripheral metastases, and only in a subset of brain lesions (17%) did lapatinib concentration approach that of systemic metastases. Drug efflux pumps markedly contribute to the lack of brain permeability of compounds such as gefinitib, erlotinib, lapatinib, sunitinib and sorafenib [86*,87]. Many molecular therapeutics are cytostatic and not cytotoxic, and thus not enough tumor cells in a lesion are killed to achieve a clinical response. Moreover, the increased interstitial fluid pressure from edema limits drug distribution.

PREVENTION STRATEGIES

Almost all of the preclinical molecular compounds that have been reported to date were tested in a prevention setting and, overall, the studies have shown that prevention of the outgrowth of brain metastases is feasible. In a prevention scenario, a partially permeable targeted drug could potentially reach and control the outgrowth of micrometastases [88*]. Experimental models have shown that bevacizumab may prevent early angiogenesis and induce prolonged dormancy of micrometastases [89,90*] and the VEGF antagonist cediranib may inhibit brain metastasis formation [91]. Lapatinib, vorinostat and pazopanib are able to prevent the formation of metastases by brain-tropic breast cancer cells [92*,93,94*]. The selective PLK1 inhibitor GSK 4611364A, in a xenograft model of breast cancer brain metastases, inhibits the development of large brain metastases and prolongs the survival in comparison to untreated animals [95].

Limited clinical data also support the hypothesis that prevention of brain metastases is more achievable than significant shrinkage of established lesions. A long-term follow-up from the metastatic breast cancer trial of lapatinib plus capecitabine versus capecitabine alone reported a significant reduction in the incidence of metastases in the brain as first site of relapse after combined treatment [96]. A retrospective review of a subcohort of patients with advanced EGFR-mutated NSCLC treated with gefinitib or erlotinib reported 1-year and 2-year CNS relapse rates of 6 and 13%, respectively, these rates being much lower than historical data [97]. A retrospective analysis of the clinical trial data from sorafenib in patients with RCC and brain metastases demonstrated a 75% prevention of brain metastases development, compared with 4% response rate on established metastases [98]. A recent review of patients enrolled in a phase III trial on RCC (TARGET trial) revealed a significant lower incidence of brain metastases in patients who received sorafenib (3%) than in those who received placebo (12%) [99]. The protective effect of TKIs (sorafenib, sunitinib and pazopanib) from metastatic RCC involvement of the brain has been recently outlined [100*].

Ultimately, for both primary and secondary prevention studies, in addition to the promising new agents in preclinical models, the major challenge is the identification of patients at highest risk of developing brain metastases because of tumor and host factors. Up to date, only HER2-positive breast cancer patients have entered prevention trials to better define the role of lapatinib.

CHALLENGES IN DEVELOPING TRIALS ON TARGETED AGENTS IN BRAIN METASTASES

The design of clinical trials on targeted agents in brain metastases poses several problems [101*]. The choice of endpoints is influenced by factors such as the patient population (in particular regarding the different natural history of systemic disease and brain metastasis among different solid tumors), the type of trial (phase 0, phase I, phase II and phase III) and the setting (treatment of established brain metastases or prevention). The ideal measure of drug activity in the brain is the assay of target modulation within the tumor in the resected tissue of patients treated preoperatively. Moreover, advanced neuroimaging techniques may provide valuable surrogate pharmacodynamic information [102]. Objective response has been commonly used as primary endpoint for phase II trials in patients with brain metastases, being a possible surrogate for other markers of clinical benefit, such as neurological status, neurocognitive decline or neurological deterioration free-survival. Unfortunately, none of the standard response criteria (Recist, WHO, MacDonald and RANO) were designed specifically for brain metastases. There is a need to standardize the MRI criteria for lesion measurement (tumor area vs. volume) and definition of the entity of shrinkage required to qualify for response, and to include steroids and neurological symptoms in the response criteria. Special drugs (antiangiogenic agents and immunomodulators) will require specific adaptations. A clear distinction between intracranial, extracranial and overall progression-free survival is important. When the concurrent systemic

disease is controlled by a standard systemic regimen, the safety (not only the efficacy) of the association of an investigational agent for brain metastasis must be carefully evaluated.

As the number of experimental agents increases and available resources contract, new trial designs could be required: for instance, adaptive randomization can make clinical trials more efficient in reaching endpoints with fewer patients than required with conventional randomization [103].

All these issues are now being discussed within the international RANO (response assessment in neurooncology) working group, which already developed response criteria for primary brain tumors [104].

CONCLUSION

At present, definite data on the clinical activity of targeted agents in brain metastases are lacking, as virtually no well designed clinical trials have been performed. There is a need to understand novel targets and secondary resistance mechanisms. The combination of agents that target signal transduction pathways with those that modulate the immunological response to tumor is promising. Ultimately, the concept of prevention (primary or secondary) is the most appealing.

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Conflicts of interest

All the authors have no conflicts of interests.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

REFERENCES

1*. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep* 2012; 14:48–54.
An updated review on the epidemiology of brain metastases.

2*. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multiinstitutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys* 2010; 77:655–661.
An important study demonstrating that clinical prognostic factors may vary according to primary tumor type.

- 3*. Barnholtz-Sloan JS, Yu C, Sloan AE, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol* 2012; 14:910–918.
A study that describes a nomogram providing individualized estimates of survival among patients with brain metastases.
4. Soffietti R, Rudà R, Trevisan E. Brain metastases: current management and new developments. *Curr Opin Oncol* 2008; 20:676–684.
- 5*. Eichler AF, Chung E, Kodack DP, et al. The biology of brain metastases-translation to new therapies. *Nat Rev Clin Oncol* 2011; 8:344–356.
A detailed review of the biology and preclinical models of brain metastases.
- 6*. Fidler IJ. The role of the organ microenvironment in brain metastasis. *Semin Cancer Biol* 2011; 21:107–112.
A thorough review of the interactions between unique tumor cells and the specific organ microenvironment that lead to brain metastases formation.
- 7*. Preusser M, Capper D, Ilhan-Mutlu A, et al. Brain metastases: pathobiology and emerging targeted therapies. *Acta Neuropathol* 2012; 123:205–222.
A detailed review of the biological bases of targeted therapies in brain metastases.
8. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol* 2009; 10:757–763.
9. Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with nonsmall-cell lung cancer and brain metastases. *J Clin Oncol* 2009; 27:5255–5261.
10. Besse B, Lasserre SF, Compton P, et al. Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res* 2010; 16:269–278.
11. De Braganca KC, Janjigian YY, Azzoli CG, et al. Efficacy and safety of bevacizumab in active brain metastases from nonsmall cell lung cancer. *J Neurooncol* 2010; 100:443–447.
12. Patyna S, Peng J. Distribution of sunitinib and its active metabolite in brain and spinal cord tissue following oral or intravenous administration in rodents and monkeys. *Eur J Cancer* 2006; 4:21 (abstract).
13. Gore ME, Hariharan S, Porta C, et al. Sunitinib in metastatic renal cell carcinoma patients with brain metastases. *Cancer* 2011; 117:501–509.
- 14*. Lim ZD, Mahajan A, Weinberg J, et al. Outcome of patients with renal cell carcinoma metastatic to the brain treated with sunitinib without local therapy. *Am J Clin Oncol* 2012
An interesting report of the efficacy of upfront sunitinib in brain metastases from RCC.
15. Novello S, Camps C, Grossi F, et al. Phase II study of sunitinib in patients with nonsmall cell lung cancer and irradiated brain metastases. *J Thorac Oncol* 2011; 6:1260–1266.
16. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from nonsmall-cell lung cancer: a prospective trial. *Ann Oncol* 2004; 15:1042–1047.
17. Hotta K, Kiura K, Ueoka H, et al. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced nonsmall-cell lung cancer. *Lung Cancer* 2004; 46:255–261.
18. Namba Y, Kijima T, Yokota S, et al. Gefitinib in patients with brain metastases from nonsmall-cell lung cancer: review of 15 clinical cases. *Clin Lung Cancer* 2004; 6:123–128.
19. Chiu CH, Tsai CM, Chen YM, et al. Gefitinib is active in patients with brain metastases from nonsmall cell lung cancer and response is related to skin toxicity. *Lung Cancer* 2005; 47:129–138.

20. Wu C, Li YL, Wang ZM, et al. Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain. *Lung Cancer* 2007; 57:359–364.
21. Lai CS, Boshoff C, Falzon M, et al. Complete response to erlotinib treatment in brain metastases from recurrent NSCLC. *Thorax* 2006; 61:91 (abstract).
22. Fekrazad MH, Ravindranathan M, Jones DV Jr. Response of intracranial metastases to erlotinib therapy. *J Clin Oncol* 2007; 25:5024–5026.
23. Popat S, Hughes S, Papadopoulos P, et al. Recurrent responses to nonsmall cell lung cancer brain metastases with erlotinib. *Lung Cancer* 2007; 56:135–137.
24. Altavilla G, Arrigo C, Santarpia MC, et al. Erlotinib therapy in a patient with nonsmall-cell lung cancer and brain metastases. *J Neurooncol* 2008; 90:31–33.
- 25*. Porta R, Sanchez-Torres JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J* 2011; 37:624–631.
A study confirming the importance of EGFR mutations for the efficacy of erlotinib in brain metastases from NSCLC.
26. Bai H, Han B. The effectiveness of erlotinib against brain metastases in nonsmall-cell lung cancer patients. *Am J Clin Oncol* 2012.
27. Shimato S, Mitsudomi T, Kosaka T, et al. EGFR mutations in patients with brain metastases from lung cancer: association with the efficacy of gefitinib. *Neuro Oncol* 2006; 8:137–144.
28. Kim JE, Lee DH, Choi Y, et al. 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* 2009; 65:351–354.
29. Paz-Ares L, Sanchez JM, Garcia-Velasco A, et al. A prospective phase II trial of erlotinib in advanced nonsmall-cell lung cancer (NSCLC) patients with mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR). *J Clin Oncol* 2006; 24:369s (abstract).
30. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. *Neuro Oncol* 2010; 12:1193–1199.
31. Lind JS, Lagerwaard FJ, Smit EF, et al. Phase I study of concurrent whole brain radiotherapy and erlotinib for multiple brain metastases from nonsmall-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009; 74:1391–1396.
32. Ma S, Xu Y, Deng Q, Yu X. Treatment of brain metastasis from nonsmall cell lung cancer with whole brain radiotherapy and Gefitinib in a Chinese population. *Lung Cancer* 2009; 65:198–203.
- 33*. Pesce GA, Klingbiel D, Ribi K, et al. Outcome, quality of life and cognitive function of patients with brain metastases from nonsmall cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). *Eur J Cancer* 2012; 48:377–3784.
Final results of a randomized phase II trial that failed to demonstrate an activity of gefitinib given to an unselected population of patients with brain metastases from NSCLC (no analysis of EGFR mutations was carried out).
- 34*. Masuda T, Hattori N, Hamada A, et al. Erlotinib efficacy and cerebrospinal fluid concentration in patients with lung adenocarcinoma developing leptomeningeal metastases during gefitinib therapy. *Cancer Chemother Pharmacol* 2011; 67:1465–1469.

An interesting study reporting higher CSF levels of erlotinib compared to gefinitib with good correlation with response to brain metastases.

35. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in nonsmall-cell lung cancer. *N Engl J Med* 2010; 363:1693–1703.

36. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 2011; 29:e443–e445.

37. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol* 2010; 28:3271–3277.

38. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 2003; 97:2972–2977.

39. Stemmler HJ, Kahlert S, Siekiera W, et al. Characteristics of patients with brain metastases receiving trastuzumab for HER2 overexpressing metastatic breast cancer. *Breast* 2006; 15:219–225.

40. Yau T, Swanton C, Chua S, et al. Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab. *Acta Oncol* 2006; 45:196–201.

41. Lin NU, Winer EP. Brain metastases: the HER2 paradigm. *Clin Cancer Res* 2007; 13:1648–1655.

42. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. *J Clin Oncol* 2009; 27:5278–5286.

43*. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. *Clin Cancer Res* 2011; 17:4834–4843.

An extensive analysis of natural history and management of patients with brain metastases from HER2-positive breast cancer.

44**. Yin W, Jiang Y, Shen Z, et al. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. *PLoS One* 2011; 6:e21030.

A meta-analysis of clinical trials employing trastuzumab in the adjuvant setting in HER2-positive breast cancer patients.

45*. Musolino A, Ciccolallo L, Panebianco M, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. *Cancer* 2011; 117:1837–1846.

A detailed retrospective study demonstrating that the brain is at risk of first recurrence in patients with HER2-positive breast cancer receiving trastuzumab either adjuvantly or in the metastatic setting.

46. Pestalozzi BC, Zahrieh D, Price KN, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). *Ann Oncol* 2006; 17:935–944.

47. Palmieri D, Bronder JL, Herring JM, et al. Her-2 overexpression increases the metastatic outgrowth of breast cancer cells in the brain. *Cancer Res* 2007; 67:4190–4198.

48. Stemmler HJ, Schmitt M, Willems A, et al. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood–brain barrier. *Anticancer Drugs* 2007; 18:23–28.

49. Gaedcke J, Traub F, Milde S, et al. Predominance of the basal type and HER-2/neu type in brain metastasis from breast cancer. *Mod Pathol* 2007; 20:864–870.

50. Dawood S, Gonzalez-Angulo AM, Albarracin C, et al. Prognostic factors of survival in the trastuzumab era among women with breast cancer and brain metastases who receive whole brain radiotherapy: a single-institution review. *Cancer* 2010; 116:3084–3092.
51. Le Scodan R, Jouanneau L, Massard C, et al. Brain metastases from breast cancer: prognostic significance of HER-2 overexpression, effect of trastuzumab and cause of death. *BMC Cancer* 2011; 11:395.
- 52*. Xu Z, Marko NF, Chao ST, et al. Relationship between HER2 status and prognosis in women with brain metastases from breast cancer. *Int J Radiat Oncol Biol Phys* 2012; 82:e739–e747.
A study confirming that patients with HER2-positive breast tumors and brain metastases have improved survival when continuing trastuzumab treatment.
53. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2008; 26:1993–1999.
54. Lin NU, Diéras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 2009; 15:1452–1459.
55. Boccardo F, Kaufman B, Baselga J, et al. Evaluation of lapatinib (Lap) plus capecitabine (Cap) in patients with brain metastases (BM) from HER2+ breast cancer (BC) enrolled in the Lapatinib Expanded Access Program (LEAP) and French Authorization Temporaire d'Utilisation (ATU). *J Clin Oncol* 2008; 26:1094(abstract).
56. Sutherland S, Ashley S, Miles D, et al. Treatment of HER2-positive metastatic breast cancer with lapatinib and capecitabine in the lapatinib expanded access programme, including efficacy in brain metastases – the UK experience. *Br J Cancer* 2010; 102:995–1002.
- 57*. Metro G, Foglietta J, Russillo M, et al. Clinical outcome of patients with brain metastases from HER2-positive breast cancer treated with lapatinib and capecitabine. *Ann Oncol* 2011; 22:625–630.
An interesting study reporting the response of brain metastases from HER2-positive breast cancer patients to lapatinib plus capecitabine.
- 58*. Lin NU, Eierman W, Greil R, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. *J Neurooncol* 2011; 105:613–620.
An interesting study reporting the response of brain metastases from HER2-positive breast cancer patients to lapatinib plus capecitabine and the inefficacy of topotecan associated with lapatinib.
- 59*. Bachelot TD, Romieu G, Campone M, et al. LANDSCAPE: an FNCLCC Phase II study with lapatinib (L) and capecitabine (C) in patients with brain metastases (BM) from HER2-positive (+) breast cancer (MBC) before whole-brain radiotherapy (WBR). *J Clin Oncol* 2011; 29:509(abstract).
The first phase II study reporting the efficacy of lapatinib plus capecitabine in newly diagnosed brain metastases from HER2-positive breast cancer patients.
60. Lin NU, Ramakrishna N, Younger WJ, et al. Phase I study of lapatinib (L) in combination with whole-brain radiation therapy (WBRT) in patients (pts) with brain metastases from HER2-positive breast cancer. *J Clin Oncol* 2010; 28:1154(abstract).
- 61*. Minami CA, Chung DU, Chang HR, et al. Management options in triple-negative breast cancer. *Breast Cancer* 2011; 5:175–199.
A detailed review of therapeutic options in triple-negative breast cancer.
62. O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 2011; 364:205–214.

- 63*. Capper D, Preusser M, Habel A, et al. Assessment of BRAF V600E mutation status by immunohistochemistry with a mutation-specific monoclonal antibody. *Acta Neuropathol* 2011; 122:11–19.
The study reporting on the development of VE1 monoclonal antibody recognizing BRAF V600E mutations.
- 64*. Capper D, Berghoff AS, Magerle M, et al. Immunohistochemical testing of BRAF V600E status in 1,120 tumor tissue samples of patients with brain metastases. *Acta Neuropathol* 2012; 123:223–233.
An immunohistochemical investigation of BRAF 600E mutations in a large sample of brain metastases.
- 65**. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364:2507–2516.
The first study reporting a significant impact of vemurafenib in advanced melanoma.
- 66*. Dummer R Jr, Goldinger SM, Wagner I, et al. An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases. *J Clin Oncol* 2011; 29:8548(abstract).
Preliminary results of a phase II study on vemurafenib in brain metastases from melanoma.
- 67*. Rochet NM, Kottschade LA, Markovic SN. Vemurafenib for melanoma metastases to the brain. *N Engl J Med* 2011; 365:2439–2441.
The first case of brain metastases from melanoma in a pediatric patient responding to vemurafenib.
68. Long GV, Kefford RF, Carr PJA, et al. Phase 1/2 study of GSK2118436, a selective inhibitor of V600 mutant BRAF kinase: evidence of activity in melanoma brain metastases (LBA27). *Ann Oncol* 2010; 21:viii12 (abstract).
69. Fong L, Small EJ. Anticytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. *J Clin Oncol* 2008; 26:5275–5283
70. Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. *Cancer Immunol Immunother* 2009; 58:823–830.
- 71**. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363:711–723.
A phase III trial demonstrating the efficacy of ipilimumab in metastatic melanoma.
- 72**. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; 364:2517–2526.
A phase III trial demonstrating the efficacy of ipilimumab plus dacarbazine in metastatic melanoma.
73. Downey SG, Klapper JA, Smith FO, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin Cancer Res* 2007; 13:6681–6688.
74. Hodi FS, Oble DA, Drappatz J, et al. CTLA-4 blockade with ipilimumab induces significant clinical benefit in a female with melanoma metastases to the CNS. *Nat Clin Pract Oncol* 2008; 5:557–561.
75. Scharitz NE, Farges C, Madelaine I, et al. Complete regression of a previously untreated melanoma brain metastasis with ipilimumab. *Melanoma Res* 2010; 20:247–250.
- 76*. Weber JS, Amin A, Minor D, et al. Safety and clinical activity of ipilimumab in melanoma patients with brain metastases: retrospective analysis of data from a phase 2 trial. *Melanoma Res* 2011; 21:530–534.
This retrospective study clearly confirms the activity of ipilimumab in brain metastases from melanoma.
- 77**. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol* 2012; 13:459–465.
The first phase II trial demonstrating the efficacy of ipilimumab in patients with brain metastases from melanoma.

78. Wilson EH, Weninger W, Hunter CA. Trafficking of immune cells in the central nervous system. *J Clin Invest* 2010; 120:1368–1379.
79. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; 15:7412–1720.
80. Di Giacomo AM, Ascierto PA, Pittiglio E, et al. A phase II study combining ipilimumab and fotemustine in patients with metastatic melanoma – the NIBIT M1 trial. *Eur J Cancer* 2011; 47:9305(abstract).
- 81*. Shapiro DG, Samlowski WE. Management of melanoma brain metastases in the era of targeted therapy. *J Skin Cancer* 2011; 2011:845–863.
A thorough review of the management of brain metastases from melanoma.
- 82*. Fisher R, Larkin J. Treatment of brain metastases in patients with melanoma. *Lancet Oncol* 2012; 13:434–435.(comment).
A clear overview of future perspectives in the treatment of brain metastases from melanoma.
- 83**. Steeg PS, Camphausen KA, Smith QR. Brain metastases as preventive and therapeutic targets. *Nat Rev Cancer* 2011; 11:352–363.
An exhaustive review of molecular targets in brain metastases for treatment and prevention studies.
84. Lockman PR, Mittapalli RK, Taskar KS, et al. Heterogeneous blood–tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. *Clin Cancer Res* 2010; 16:5664–5678.
- 85*. Taskar KS, Rudraraju V, Mittapalli RK, et al. Lapatinib distribution in HER2 overexpressing experimental brain metastases of breast cancer. *Pharm Res* 2012; 29:770–781.
The first study analyzing the distribution of lapatinib in experimental brain metastases from breast cancer.
- 86*. Agarwal S, Sane R, Gallardo JL, et al. Distribution of gefitinib to the brain is limited by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2)-mediated active efflux. *J Pharmacol Exp Ther* 2010; 334:147–155.
This study provides an excellent demonstration of role of multiple BBB efflux transporters in restricting the brain distribution of chemotherapeutic drugs.
87. Lagas J, van Waterschoot RA, Sparidans RW, et al. Breast cancer resistance protein and P-glycoprotein limit sorafenib brain accumulation. *Mol Cancer Ther* 2010; 9:319–326.
- 88*. Trinh VA, Hwu WJ. Chemoprevention for brain metastases. *Curr Oncol Rep* 2012; 14:63–69.
A detailed review analyzing the different chemoprevention strategies.
89. Kienast Y, von Baumgarten L, Fuhrmann M, et al. Real-time imaging reveals the single steps of brain metastasis formation. *Nat Med* 2010; 16:116–122.
- 90*. Kienast Y, Winkler F. Therapy and prophylaxis of brain metastases. *Expert Rev Anticancer Ther* 2010; 10:1763–1777.
An exhaustive review of treatment and prevention of brain metastases.
91. Yin JJ, Zhang L, Munasinghe J, et al. Cediranib/AZD2171 inhibits bone and brain metastasis in a preclinical model of advanced prostate cancer. *Cancer Res* 2010; 70:8662–8673.
- 92*. Gril B, Palmieri D, Bronder JL, et al. Effect of lapatinib on the outgrowth of metastatic breast cancer cells to the brain. *J Natl Cancer Inst* 2008; 100:1092–1103.
This is the first demonstration that a molecular therapeutic can prevent HER2-positive experimental brain metastases.

93. Palmieri D, Lockman PR, Thomas FC, et al. Vorinostat inhibits brain metastatic colonization in a model of triple-negative breast cancer and induces DNA double-strand breaks. *Clin Cancer Res* 2009; 15:6148–6157.
- 94*. Gril B, Palmieri D, Qian Y, et al. Pazopanib reveals a role for tumor cell B-Raf in the prevention of HER2+ breast cancer brain metastasis. *Clin Cancer Res* 2011; 17:142–153.
An experimental study showing a preventive efficacy of pazopanib toward metastasization of breast tumor cells in the brain.
95. Qian Y, Hua E, Bisht K, et al. Inhibition of Polo-like kinase 1 prevents the growth of metastatic breast cancer cells in the brain. *Clin Exp Metastasis* 2010; 28:899–908.
96. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat* 2008; 112:533–543.
97. Heon S, Yeap BY, Britt GJ, et al. Development of central nervous system metastases in patients with advanced nonsmall cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. *Clin Cancer Res* 2010; 16:5873–5882.
98. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer* 2010; 116:1272–1280.
99. Massard C, Zonierek J, Gross-Goupil M, et al. Incidence of brain metastases in renal cell carcinoma treated with sorafenib. *Ann Oncol* 2010; 21:1027–1031.
- 100*. Verma J, Jonasch E, Allen P, et al. Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma. *Cancer* 2011; 117:4958–4965.
An exhaustive review of targeted agents in the prevention setting of renal cell carcinoma.
- 101*. Peereboom DM. Clinical trial design in brain metastasis: approaches for a unique patient population. *Curr Oncol Rep* 2012; 14:91–96.
An exhaustive review on methodological issues in designing clinical trials in brain metastases.
102. Reardon DA, Galanis E, DeGroot JF, et al. Clinical trial end points for high-grade glioma: the evolving landscape. *Neuro Oncol* 2011; 13:353–361.
103. Berry DA. Adaptive clinical trials: the promise and the caution. *J Clin Oncol* 2011; 29:606–609.
104. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010; 28:1963–1972.