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Review Article

Molecular markers and targeted therapy in central nervous system metastases of ovarian cancer: a review

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Abstract: Brain metastases of ovarian cancer are a rare occurrence, most often presenting in advanced stages of disease. The incidence of brain metastases of ovarian cancer appears to be increasing in recent years, prompting the search for markers that predict metastatic disease in the brain and development of more effective treatment methods. Current treatment methods include surgical resection, systemic therapy, and radiation, and studies show that a combination of treatment methods is most effective in treating brain metastases. Targeted therapy has become increasingly important in the treatment of brain metastases across various tumor types. Identification of driver genetic alterations, or differential RNA and protein expression involved in ovarian cancer brain metastases would allow for the development of individualized treatment methods with improved intracranial access. Genetic analysis of primary ovarian tumors that metastasized to the brain provides information on the molecular profile of the tumor itself as well as tumor microenvironment that predispose some ovarian cancers to more likely metastasize to the brain.

Keywords: Ovarian cancer, brain metastasis, targeted therapy, blood-brain barrier

Introduction

Ovarian cancer is the fifth leading cause of cancer deaths among women, and accounts for more deaths than any other gynecologic cancer. An estimated 1.3% of women will be diagnosed with ovarian cancer at some point in their lifetime [1]. It was previously estimated that in 2016 there would be 22,280 new cases of ovarian cancer in the United States, and 14,240 disease-related deaths [2]. The disease can present itself with a number of symptoms, including bloating, abdominal pain, frequent urination, and difficulty eating [3]. Awareness of symptoms is important, as early diagnosis significantly increases survival. Unfortunately, upon diagnosis the majority of cases (85%) present with advanced stage III/IV disease [4]. Treatment typically consists of surgical debulking, followed by platinum and taxane chemotherapy. After completing primary treatment, the average progression-free survival is approximately 18 months, and 75% of patients then experience a recurrence. The five-year overall survival for advanced stage ovarian cancer is approximately 30% [5].

Ovarian cancer metastases tend to be localized in the abdomen or pelvis, with up to 85% of cases presenting with local recurrence [6]. Distal metastases are less frequent, most commonly occurring in the pleura, liver, and lung [7]. Brain metastases (BM) of ovarian cancer are a rare and late occurrence, with recent estimates of 0.5-12% of cases [7]. Difficulty in establishing true incidence is largely due to the fact that brain imaging is not a part of routine follow-up for ovarian cancer patients. Brain metastases most commonly occur in advanced stage, platinum-sensitive serous ovarian cancer, and most patients present with extracranial metastases at time of diagnosis [8-10]. Ovarian cancer brain metastases may present with isolated or multiple lesions, with symptoms depending on the site of the lesion. They most commonly present in the brain parenchyma, with a small percentage of cases (8%) presenting with leptomeningeal spread [11]. Sites of ovarian cancer

brain metastasis most commonly include the cerebellum (30%), followed by frontal, parietal, and occipital lobes [12]. Notably, the incidence of brain metastases appears to be rising in recent years, most likely due to prolonged survival as a result of improved treatment methods such as surgical resection combined with platinum-based chemotherapy [13, 14].

Brain metastases most frequently occur within 1-2 years following diagnosis of ovarian cancer, and, as reported by past literature, median survival after diagnosis of brain metastasis is 4-5 months [14]. However, as treatment and diagnosis methods have improved over the years, the patient survival after diagnosis of brain metastasis of ovarian cancer has significantly increased. Due to the rarity of brain metastasis in ovarian cancer, treatment options are limited, and defined treatment methods have not been established. Treatment is particularly challenging for a number of reasons, including the difficulty of overcoming the blood-brain barrier, genetic divergence of brain metastases from the primary tumor and other extracranial metastases, and the build-up of chemotherapy resistance from repeated exposure to chemotherapy [15]. These factors make brain metastases of special interest, particularly in the era of molecularly targeted agents. By characterizing the molecular composition of the primary tumor and tumor microenvironment of ovarian cancers that metastasize to the brain, one can establish prognostic biomarkers and develop individualized treatments for patients with brain metastasis. The development of future targeted molecular therapy agents involves identifying clinically actionable genetic mutations and proteins associated with metastasis to the brain, and improving the penetration of small molecule agents across the blood-brain barrier.

In addition to ovarian brain metastases, increased incidence of brain metastases has been noted across various other cancer types, due largely to increased efficacy of systemic therapies [14-16]. Patient survival has significantly improved, and CNS involvement becomes increasingly likely in later stages of disease progression [17]. Introduction of targeted therapy and immunotherapy has increased survival with metastatic melanoma, and it is expected that the incidence of melanoma brain metastases will increase in upcoming years as the patients live longer with the primary disease [18, 19]. In non-small cell lung cancer, the use of EGFR tyrosine kinase inhibitors has resulted in significantly prolonged survival. Interestingly, it has been found that patients with an *EGFR* mutation have a significantly higher incidence of brain metastasis [16, 20, 21]. Recently, newly developed ALK inhibitors with increased intracranial efficacy have further improved overall survival in non-small cell lung cancer [22, 23]. A mutated *ALK* gene is present in 5% of NSCLC cases, and can be treated more successfully with an ALK inhibitor such as crizotinib [24]. However, the lack of penetration of the blood-brain barrier by crizotinib, and development of resistance to treatment has resulted in frequent cases of brain metastasis [24-26]. The use of newly developed ALK inhibitors post-crizotinib therapy significantly increases overall survival, with a median overall survival of 89.6 months after diagnosis of metastatic disease, compared to 28.2 months with other therapeutic agents [27, 28].

Blood-brain barrier (BBB) disruption

The difficulty of treatment of ovarian brain metastases can be attributed to the lack of blood brain barrier penetration by systemic therapy, as well as the molecular divergence of brain metastases from the primary tumor and other extracranial metastases. The efficacy of BBB disruption in treatment of ovarian brain metastasis has been studied in clinical trials and animal models. One method for the treatment of ovarian carcinoma brain metastases is intraarterial delivery (IA) of chemotherapy agents in combination with temporary blood brain barrier disruption [29]. Of the five ovarian cancer patients with brain metastases, four received IA with BBB disruption, while one received IA without BBB disruption [29]. Four patients had complete response, and two of the five patients with complete response remained in complete response after 34.1 and 27.8 months [29]. Another study involving a mouse model examined the effects of multidrug efflux transporters BRCP and P-gp on the oral availability and brain penetrance of rucaparib, a PARP inhibitor recently approved for the treatment of advanced breast and ovarian cancer [30]. ABC transporters such as P-gp and BRCP have high expression in the blood-brain barrier, and affect the intracranial availability of therapeutic agents [31, 32]. The results of the study showed that rucaparib is a substrate of the ATP-binding cassette transporters BRCP

(breast cancer resistance protein) and P-glycoprotein, and that P-gp and BRCP significantly restrict brain penetrance of the PARP inhibitor [30]. Blocking specific multidrug efflux transporters at the blood brain barrier, may temporarily permeate the BBB to allow entry of targeted molecular agents or chemotherapy agents.

Blood-brain barrier circumvention

To increase the intracranial availability of small molecules or chemotherapy agents, drug delivery can be combined with a method of blood brain barrier circumvention. Various strategies of BBB circumvention have been studied in clinical trials and animal models. A study done on mice investigated the selective permeation of the blood brain barrier at sites of brain metastases by using tumor necrosis factor (TNF) to transiently permeate tumor vasculature [33]. TNFR1 and TNFR2 are endogenous receptors of TNF that are found in tumor vasculature and the tumor microenvironment, but do not appear in normal brain tissue [33]. TNFR1 staining was found to be concentrated on the vascular endothelium, while TNFR2 was co-localized with microglia and leukocytes in the tumor microenvironment [33]. Results showed that applying TNF caused significant blood-brain barrier permeation at sites of brain metastases, but not in other regions of the brain [33]. In six cases of human brain metastases, similar expression of TNFR1 and TNFR2 was found, although no clinical trials have been conducted with TNF [33]. Other methods for BBB circumvention include delivering focused ultrasound in combination with microbubbles directly to the site of brain metastasis, and coupling receptor-mediated uptake mechanisms at the blood-brain barrier to a therapeutic agent [34]. Future strategies for blood brain barrier circumvention may involve identifying specific targetable surface proteins at the BBB vasculature that can be used for transcytosis of molecular agents [35].

Current treatment approaches for metastatic disease in the brain depend on tumor number, location and size, and can include radiation therapy, systemic therapy, surgical resection, and stereotactic radiosurgery [9]. *Marcetti et al.* reported that survival rates improved with multimodal vs. unimodal treatment, with median survival rates of 22 months vs. 5 months, respectively [10].

Whole-brain radiation therapy (WBRT)

WBRT, with or without chemotherapy, is commonly used for treatment of multiple brain metastases. However, it is associated with neurocognitive deterioration and decline in quality of life [36, 37]. One study found that whole-brain radiation markedly reduces hippocampal neurogenesis, and hippocampal avoidance during radiotherapy may be effective in reducing negative consequences of radiation to the brain [38]. The hippocampus is involved in memory formation, spatial navigation, and mood, and its proper function is critical to cognitive health.

Systemic therapy

Though chemotherapy is largely ineffective in treating brain metastases due to difficulty of overcoming the blood-brain barrier, newly developed small-molecule targeted agents and immunotherapies are increasingly effective in treating brain metastases and systemic disease. Targeted therapies have been effective in treating systemic cancer, and show increased intracranial efficacy compared to standard chemotherapy [39]. Currently used targeted therapy and immunotherapy in melanoma includes BRAF and MEK inhibitors, as well as anti-PD-1 and anti-CTLA-4 therapy [40, 41]. In non-small cell lung cancer, targeted therapy includes EGFR inhibitors and ALK inhibitors [23, 24, 42]. The use of BRAF inhibitors in the treatment of melanoma brain metastases has resulted in improved survival of 7.9 months after diagnosis of brain metastasis, compared to 2-4 months without targeted therapy [19, 43]. The delivery of targeted therapy in conjunction with radiotherapy has also shown promising results [44]. In one study, non-small cell lung cancer and breast cancer patients were treated with WBRT in combination with lapatinib, an EGFR and HER2 tyrosine kinase inhibitor that has been shown to be active in brain metastases, and sensitizes tumor cells to radiation [45]. Of the 43 patients with volumetric assessment before and after treatment, 62.8% has partial responses, and 32.9% had stable disease post-treatment [45].

Driver mutations in ovarian cancer brain metastases

The development of targeted agents for treatment of brain metastasis of ovarian cancer

Table 1. Ovarian cancer driver mutations

Primary ovarian cancer	Gene alterations	Brain metastasis Gene alterations
Low grade, endometrioid, borderline	*BRAF*	
	KRAS	
	ERBB2	
High grade	PI3K/AKT pathway	*BRCA1/2*
	CDKN2A/B	*ATM*
	RB1	*CHEK2*
	BRCA1/2	
	AKT2	

Modified from: *Lengyel* [5].

begins with identifying driver genetic alterations or proteins that can be successfully targeted with a molecular agent. Potentially actionable mutations may be selected from previously identified driver mutations of primary ovarian cancer, as well as driver genetic alterations in intracranial metastases of ovarian cancer (**Table 1**). Literature on the brain metastasis of ovarian cancer does not typically specify whether the brain metastasis developed from a high-grade or low-grade ovarian carcinoma. Although brain metastases are known to more frequently develop from high-grade ovarian carcinoma, there are likely cases of brain metastasis from low-grade ovarian cancer. Next-generation sequencing of samples of ovarian cancer brain metastases has identified frequent mutations in DNA repair genes *BRCA1/2*, *ATM*, and *CHEK2*, *BRCA1* being the most commonly altered gene [46]. Other studies comparing primary ovarian cancer and brain metastases have found differential expression in *MDR-1*, *FGFR-1*, and *MYC* [47]. Another gene of interest is *ERBB2*, which was found to have increased expression in the brain metastases of an ovarian cancer patient [47]. *ERBB2* is also notable for its significantly increased expression in breast cancer brain metastases [48]. Due to the limitation of small sample size in studies of ovarian cancer brain metastases, additional studies are needed to determine if these molecules are significant biomarkers.

RNA sequencing

Differential RNA expression has been identified in various cancers that commonly metastasize to the brain, including melanoma, lung cancer, and breast cancer [49, 50]. RNA sequencing of non-small cell lung cancer brain metastases has identified a critical gene for the process of brain metastasis [51] Expression of ACTN4, which has been found to promote metastasis and chemoresistance across various histologies, including ovarian cancer, was found to have significantly increased expression in the brain metastases of a lung cancer patient [51-53].

Differential protein expression

On a protein level, androgen receptors (AR) and estrogen receptors have been found to have significantly decreased expression in brain metastases compared to primary tumor samples of ovarian cancer [7]. Patients with AR-negative ovarian cancer were almost ten times more likely to develop brain metastasis [7]. In addition, one study found differential expression in ENO1, TPI-1, and TAGLN2, when comparing primary and metastatic ovarian tumors [54]. ENO1 and TPI-1 are enzymes involved in the glycolytic pathway, while TAGLN2 acts to suppress the metastatic activity of tumors [54]. Yet another study showed that increased expression of CD133 in primary ovarian cancer is associated with poorer survival and greater risk of developing intracranial metastases [55].

With limited information on the development on brain metastases of ovarian cancer, it is useful to analyze the brain metastases of cancers that more frequently metastasize to the brain. Genes and proteins frequently implicated in the brain metastasis of lung cancer, melanoma, and breast cancer are generally involved with blood-brain barrier penetration, angiogenesis, cell migration/motility, and cell adhesion [56]. Pathways and gene networks frequently implicated in the development of BM across various histologies include the PI3K-AKT-mTOR pathway, HER2- and GABA-receptor signaling, CDK pathway, and DNA double-strand break repair [56, 57] (**Table 2**). In a clinical example, a patient with ERBB2-amplified brain metastases who was initially determined to be HER2-negative, was offered HER2-targeted treatment and is now alive with stable metastatic disease [57]. Other commonly altered genes include

Table 2. Brain metastasis (BM) driver mutations

BM primary cancer	Mutated genes	Genes with greater expression in BM	Genes with decreased expression in BM
NSCLC	*AKT1*	*C-MET*	
	PI3KCA		
Breast	*PI3KCA*	*ERBB2*	*PTEN*
	MAP3K4	*PI3KCA*	*ITPR1*
	COL5A1	*ST6GALNAC5FOXM1*	*ESR1*
		FGFR1	
Melanoma	*NRAS*	PI3K pathway	*CDKN2A*
	KIT		*PTEN*
	BRAF		
Lung	*KRAS*	*PI3KCA*	*KRAS*
	NRAS	*FGFR1*	*CDKN2A*
	BRAF	*BRAF*	*CDK6*
		KRAS	*EGFR*
			MET
			AKT1
Ovarian	*BRCA1/2*	*ERBB2*	
	ATM		
	CHEK2		

Modified from: [46, 48, 56, 57, 61-64].

HER3 and HER4, which were highly expressed in brain metastasis from multiple primary cancer types [57].

Response assessment/imaging

Following the delivery of treatment, the next step for successful treatment of brain metastases is accurate assessment of response to treatment. Response assessment for brain metastasis post-treatment is composed of brain imaging and measurement of patient cognitive performance. Common challenges encountered during brain imaging include differentiating between pseudo-progression or pseudo-response caused by chemotherapy or radiation, and true tumor growth or response [58, 59]. Pseudo-progression is an increase in contrast enhancement that is observed in 10-30% of patients immediately after chemotherapy treatment [58]. Other agents may cause pseudo-response, characterized by a decrease in contrast enhancement immediately after initiation of therapy [58]. To address these issues, a group of physicians have established the Response Assessment in Neuro-Oncology (RANO) criteria, which may help to eliminate discrepancies and to increase agreement between observers [58]. Discrepancies in assessment are also encountered during clinician observation of patient performance. The standard method for measurement of functional performance during routine follow-up is the Karnofsky performance test. The new Neurologic Assessment in Neuro-Oncology (NANO) scale is a quantifiable assessment of patient performance, that improves consistency and accuracy in assessment between observers [58, 60].

Conclusion

Treatment of brain metastasis of ovarian cancer is particularly difficult due to the challenge of crossing the blood-brain barrier, as well as the molecular divergence of brain metastases from the primary tumor and other metastatic sites. A multimodal treatment approach has been shown to be most effective in treating brain metastases, though better response may be achieved through targeted therapy, with or without blood-brain barrier circumvention. Recently, genetic alterations and differential protein expression have been shown to be associated with ovarian cancer brain metastasis. However, due to the rarity of intracranial metastasis in ovarian cancer, there is limited information on the molecular profile of brain metastasis and why some ovarian cancers metastasize to the brain. With information on driver genetic alterations associated with brain metastasis of cancers that more frequently metastasize to this site, some insight may be gained on pathways or genes likely to be involved in brain metastasis of ovarian cancer. Genotyping and RNA sequencing of ovarian cancer primary tumor and corresponding brain metastases may also reveal up-regulated or down-regulated proteins that can be targeted with a small molecule agent. Additional molecular analysis of ovarian cancer intracranial metastases as well as the molecular profile of the primary tumor and tumor microenvironment is necessary for the development of individualized therapy for patients who face this devastating prognosis. Methods of blood-brain barrier circumvention may be combined with targeted therapy to improve the access of systemic therapy to the brain.

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References

[1] Reid BM, Permuth JB and Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med 2017; 14: 9-32.

[2] Bax HJ, Josephs DH, Pellizzari G, Spicer JF, Montes A and Karagiannis SN. Therapeutic targets and new directions for antibodies developed for ovarian cancer. MAbs 2016; 8: 1437-1455.

[3] Freij M, Al Qadire M, Khadra M, M AL, Tuqan W, Al Faqih M, Innabi A, Batiha AM, Alhalaiqa F and Abd El-Razek A. Awareness and knowledge of ovarian cancer symptoms and risk factors: a survey of Jordanian women. Clin Nurs Res 2017; 1054773817704749.

[4] Ross JS, Ali SM, Wang K, Palmer G, Yelensky R, Lipson D, Miller VA, Zajchowski D, Shawver LK and Stephens PJ. Comprehensive genomic profiling of epithelial ovarian cancer by next generation sequencing-based diagnostic assay reveals new routes to targeted therapies. Gynecol Oncol 2013; 130: 554-559.

[5] Lengyel E. Ovarian cancer development and metastasis. Am J Pathol 2010; 177: 1053-1064.

[6] Choi N, Chang JH, Kim S and Kim HJ. Radiation for persistent or recurrent epithelial ovarian cancer: a need for reassessment. Radiat Oncol J 2017; 35: 144-152.

[7] Mittica G, Senetta R, Scotto G, Aglietta M, Maggiorotto F, Ghisoni E, Genta S, Boldorini R, Manini C, Morra I, Buosi R, Sapino A, Cassoni P and Valabrega G. Androgen receptor status predicts development of brain metastases in ovarian cancers. Oncotarget 2017; 8: 41143-41153.

[8] Sehouli J, Pietzner K, Harter P, Munstedt K, Mahner S, Hasenburg A, Camara O, Wimberger P, Boehmer D, Buehling KJ, Richter R, El Khalfaoui K and Oskay-Ozcelik G. Prognostic role of platinum sensitivity in patients with brain metastases from ovarian cancer: results of a German multicenter study. Ann Oncol 2010; 21: 2201-2205.

[9] Gressel GM, Lundsberg LS, Altwerger G, Katchi T, Azodi M, Schwartz PE, Ratner ES and Damast S. Factors predictive of improved survival in patients with brain metastases from gynecologic cancer: a single institution retrospective study of 47 cases and review of the literature. Int J Gynecol Cancer 2015; 25: 1711-1716.

[10] Marchetti C, Ferrandina G, Cormio G, Gambino A, Cecere S, Lorusso D, De Giorgi U, Bogliolo S, Fagotti A, Mammoliti S, Narducci F, Bergamini A, Scollo P, Biglia N, Breda E, Tamberi S, Marinaccio M, Angioli R, Salerno L, Eusebi MC, Loizzi V, Scambia G and Panici PB. Brain metastases in patients with EOC: clinico-pathological and prognostic factors. A multicentric retrospective analysis from the MITO group (MITO 19). Gynecol Oncol 2016; 143: 532-538.

[11] Bangham M, Goldstein R, Walton H and Ledermann JA. Olaparib treatment for BRCA-mutant ovarian cancer with leptomeningeal disease. Gynecol Oncol Rep 2016; 18: 22-24.

[12] Pakneshan S, Safarpour D, Tavassoli F and Jabbari B. Brain metastasis from ovarian cancer: a systematic review. J Neurooncol 2014; 119: 1-6.

[13] Piura E and Piura B. Brain metastases from ovarian carcinoma. ISRN Oncol 2011; 2011: 527453.

[14] Pectasides D, Pectasides M and Economopoulos T. Brain metastases from epithelial ovarian cancer: a review of the literature. Oncologist 2006; 11: 252-260.

[15] Gampa G, Vaidhyanathan S, Sarkaria JN and Elmquist WF. Drug delivery to melanoma brain metastases: can current challenges lead to new opportunities? Pharmacol Res 2017; 123: 10-25.

[16] Stanic K, Zwitter M, Hitij NT, Kern I, Sadikov A and Cufer T. Brain metastases in lung adenocarcinoma: impact of EGFR mutation status on incidence and survival. Radiol Oncol 2014; 48: 173-183.

[17] Franceschini D, Franzese C, Navarria P, Ascolese AM, De Rose F, Del Vecchio M, Santoro A and Scorsetti M. Radiotherapy and immunotherapy: can this combination change the prognosis of patients with melanoma brain metastases? Cancer Treat Rev 2016; 50: 1-8.

[18] Gaudy-Marqueste C, Dussouil AS, Carron R, Troin L, Malissen N, Loundou A, Monestier S, Mallet S, Richard MA, Regis JM and Grob JJ. Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery. Eur J Cancer 2017; 84: 44-54.

[19] Spagnolo F, Picasso V, Lambertini M, Ottaviano V, Dozin B and Queirolo P. Survival of patients with metastatic melanoma and brain metastases in the era of MAP-kinase inhibitors and immunologic checkpoint blockade antibodies: a systematic review. Cancer Treat Rev 2016; 45: 38-45.

[20] Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, Beal K, Amini A, Patil T, Kavanagh BD, Camidge DR, Braunstein SE, Boreta LC, Balasubramanian SK, Ahluwalia

MS, Rana NG, Attia A, Gettinger SN, Contessa JN, Yu JB and Chiang VL. 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 2017; 35: 1070-1077.

[21] McGranahan T and Nagpal S. A neuro-oncologist's perspective on management of brain metastases in patients with EGFR mutant non-small cell lung cancer. Curr Treat Options Oncol 2017; 18: 22.

[22] Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, Novello S, Bearz A, Gautschi O, Mok T, Nishio M, Scagliotti G, Spigel DR, Deudon S, Zheng C, Pantano S, Urban P, Massacesi C, Viraswami-Appanna K and Felip E. 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; 18: 874-886.

[23] Kwok WC, Tam TC, Lui MM, Lam DC and Ho JC. Control of brain metastases with alectinib in anaplastic lymphoma kinase-rearranged lung cancer. Respirol Case Rep 2017; 5: e00224.

[24] Le T and Gerber DE. ALK alterations and inhibition in lung cancer. Semin Cancer Biol 2017; 42: 81-88.

[25] Waqar SN, Morgensztern D and Govindan R. Systemic treatment of brain metastases. Hematol Oncol Clin North Am 2017; 31: 157-176.

[26] Zhang I, Zaorsky NG, Palmer JD, Mehra R and Lu B. Targeting brain metastases in ALK-rearranged non-small-cell lung cancer. Lancet Oncol 2015; 16: e510-521.

[27] Duruisseaux M, Besse B, Cadranel J, Perol M, Mennecier B, Bigay-Game L, Descourt R, Dansin E, Audigier-Valette C, Moreau L, Hureaux J, Veillon R, Otto J, Madroszyk-Flandin A, Cortot A, Guichard F, Boudou-Rouquette P, Langlais A, Missy P, Morin F and Moro-Sibilot D. Overall survival with crizotinib and next-generation ALK inhibitors in ALK-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study. Oncotarget 2017; 8: 21903-21917.

[28] Costa DB. Ascending role of next-generation ALK inhibitors. Lancet Oncol 2017; 18: 837-839.

[29] Fortin D, Gendron C, Boudrias M and Garant MP. Enhanced chemotherapy delivery by intra-arterial infusion and blood-brain barrier disruption in the treatment of cerebral metastasis. Cancer 2007; 109: 751-760.

[30] Durmus S, Sparidans RW, van Esch A, Wagenaar E, Beijnen JH and Schinkel AH. Breast cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P-GP/ABCB1) restrict oral availability and brain accumulation of the PARP inhibitor rucaparib (AG-014699). Pharm Res 2015; 32: 37-46.

[31] Iorio AL, Ros M, Fantappie O, Lucchesi M, Facchini L, Stival A, Becciani S, Guidi M, Favre C, Martino M, Genitori L and Sardi I. Blood-brain barrier and breast cancer resistance protein: a limit to the therapy of CNS tumors and neurodegenerative diseases. Anticancer Agents Med Chem 2016; 16: 810-815.

[32] Kort A, Sparidans RW, Wagenaar E, Beijnen JH and Schinkel AH. Brain accumulation of the EML4-ALK inhibitor ceritinib is restricted by P-glycoprotein (P-GP/ABCB1) and breast cancer resistance protein (BCRP/ABCG2). Pharmacol Res 2015; 102: 200-207.

[33] Connell JJ, Chatain G, Cornelissen B, Vallis KA, Hamilton A, Seymour L, Anthony DC and Sibson NR. Selective permeabilization of the blood-brain barrier at sites of metastasis. J Natl Cancer Inst 2013; 105: 1634-1643.

[34] Kobus T, Zervantonakis IK, Zhang Y and McDannold NJ. Growth inhibition in a brain metastasis model by antibody delivery using focused ultrasound-mediated blood-brain barrier disruption. J Control Release 2016; 238: 281-288.

[35] van Tellingen O, Yetkin-Arik B, de Gooijer MC, Wesseling P, Wurdinger T and de Vries HE. Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. Drug Resist Updat 2015; 19: 1-12.

[36] Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, Marosi C, Metellus P, Radbruch A, Villa Freixa SS, Brada M, Carapella CM, Preusser M, Le Rhun E, Ruda R, Tonn JC, Weber DC and Weller M. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro Oncol 2017; 19: 162-174.

[37] McTyre E, Scott J and Chinnaiyan P. Whole brain radiotherapy for brain metastasis. Surg Neurol Int 2013; 4: S236-244.

[38] Redmond KJ, Hales RK, Anderson-Keightly H, Zhou XC, Kummerlowe M, Sair HI, Duhon M, Kleinberg L, Rosner GL and Vannorsdall T. Prospective study of hippocampal-sparing prophylactic cranial irradiation in limited-stage small cell lung cancer. Int J Radiat Oncol Biol Phys 2017; 98: 603-611.

[39] Miller JA, Kotecha R, Ahluwalia MS, Mohammadi AM, Chao ST, Barnett GH, Murphy ES, Vogelbaum MA, Angelov L, Peereboom DM and Suh JH. Overall survival and the response to radiotherapy among molecular subtypes of

breast cancer brain metastases treated with targeted therapies. Cancer 2017; 123: 2283-2293.
[40] Kourie HR, Kanaan H, Awada G and Awada AH. Checkpoint inhibitors in the treatment of brain metastases of non-small-cell lung cancer and melanoma. Future Oncol 2017; 13: 1097-1103.
[41] Westphal D, Glitza Oliva IC and Niessner H. Molecular insights into melanoma brain metastases. Cancer 2017; 123: 2163-2175.
[42] Shtivelman E, Davies MQ, Hwu P, Yang J, Lotem M, Oren M, Flaherty KT and Fisher DE. Pathways and therapeutic targets in melanoma. Oncotarget 2014; 5: 1701-1752.
[43] Chukwueke U, Batchelor T and Brastianos P. Management of brain metastases in patients with melanoma. J Oncol Pract 2016; 12: 536-542.
[44] Choong ES, Lo S, Drummond M, Fogarty GB, Menzies AM, Guminski A, Shivalingam B, Clarke K, Long GV and Hong AM. Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies. Eur J Cancer 2017; 75: 169-178.
[45] Christodoulou C, Kalogera-Fountzila A, Karavasilis V, Kouvatseas G, Papandreou CN, Samantas E, Varaki K, Papadopoulos G, Bobos M, Rallis G, Razis E, Goudopoulou A, Kalogeras KT, Syrigos KN and Fountzilas G. Lapatinib with whole brain radiotherapy in patients with brain metastases from breast and non-small cell lung cancer: a phase II study of the Hellenic cooperative oncology group (HeCOG). J Neurooncol 2017; 134: 443-451.
[46] Balendran S, Liebmann-Reindl S, Berghoff AS, Reischer T, Popitsch N, Geier CB, Kenner L, Birner P, Streubel B and Preusser M. Next-generation sequencing-based genomic profiling of brain metastases of primary ovarian cancer identifies high number of BRCA-mutations. J Neurooncol 2017; 133: 469-476.
[47] Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, Van Allen EM, Lawrence MS, Horowitz PM, Cibulskis K, Ligon KL, Tabernero J, Seoane J, Martinez-Saez E, Curry WT, Dunn IF, Paek SH, Park SH, McKenna A, Chevalier A, Rosenberg M, Barker FG, 2nd, Gill CM, Van Hummelen P, Thorner AR, Johnson BE, Hoang MP, Choueiri TK, Signoretti S, Sougnez C, Rabin MS, Lin NU, Winer EP, Stemmer-Rachamimov A, Meyerson M, Garraway L, Gabriel S, Lander ES, Beroukhim R, Batchelor TT, Baselga J, Louis DN, Getz G and Hahn WC. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. Cancer Discov 2015; 5: 1164-1177.
[48] Priedigkeit N, Hartmaier RJ, Chen Y, Vareslija D, Basudan A, Watters RJ, Thomas R, Leone JP, Lucas PC, Bhargava R, Hamilton RL, Chmielecki J, Puhalla SL, Davidson NE, Oesterreich S, Brufsky AM, Young L and Lee AV. Intrinsic subtype switching and acquired ERBB2/HER2 amplifications and mutations in breast cancer brain metastases. JAMA Oncol 2017; 3: 666-671.
[49] Debeb BG, Lacerda L, Anfossi S, Diagaradjane P, Chu K, Bambhroliya A, Huo L, Wei C, Larson RA, Wolfe AR, Xu W, Smith DL, Li L, Ivan C, Allen PK, Wu W, Calin GA, Krishnamurthy S, Zhang XH, Buchholz TA, Ueno NT, Reuben JM and Woodward WA. miR-141-mediated regulation of brain metastasis from breast cancer. J Natl Cancer Inst 2016; 108.
[50] Hanniford D, Zhong J, Koetz L, Gaziel-Sovran A, Lackaye DJ, Shang S, Pavlick A, Shapiro R, Berman R, Darvishian F, Shao Y, Osman I and Hernando E. A miRNA-based signature detected in primary melanoma tissue predicts development of brain metastasis. Clin Cancer Res 2015; 21: 4903-4912.
[51] Gao Y, Li G, Sun L, He Y, Li X, Sun Z, Wang J, Jiang Y and Shi J. ACTN4 and the pathways associated with cell motility and adhesion contribute to the process of lung cancer metastasis to the brain. BMC Cancer 2015; 15: 277.
[52] Liu X and Chu KM. alpha-Actinin-4 promotes metastasis in gastric cancer. Lab Invest 2017; 97: 1084-1094.
[53] Honda K. The biological role of actinin-4 (ACTN4) in malignant phenotypes of cancer. Cell Biosci 2015; 5: 41.
[54] Yoshida A, Okamoto N, Tozawa-Ono A, Koizumi H, Kiguchi K, Ishizuka B, Kumai T and Suzuki N. Proteomic analysis of differential protein expression by brain metastases of gynecological malignancies. Hum Cell 2013; 26: 56-66.
[55] Liu BL, Liu SJ, Baskys A, Cheng H, Han Y, Xie C, Song H, Li J and Xin XY. Platinum sensitivity and CD133 expression as risk and prognostic predictors of central nervous system metastases in patients with epithelial ovarian cancer. BMC Cancer 2014; 14: 829.
[56] Weidle UH, Birzele F, Kollmorgen G and Ruger R. Dissection of the process of brain metastasis reveals targets and mechanisms for molecular-based intervention. Cancer Genomics Proteomics 2016; 13: 245-258.
[57] Saunus JM, Quinn MC, Patch AM, Pearson JV, Bailey PJ, Nones K, McCart Reed AE, Miller D, Wilson PJ, Al-Ejeh F, Mariasegaram M, Lau Q, Withers T, Jeffree RL, Reid LE, Da Silva L, Matsika A, Niland CM, Cummings MC, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Wani S, Anderson MJ, Fink JL, Holmes O, Kazakoff S, Leonard C,

Newell F, Taylor D, Waddell N, Wood S, Xu Q, Kassahn KS, Narayanan V, Taib NA, Teo SH, Chow YP, kConFab, Jat PS, Brandner S, Flanagan AM, Khanna KK, Chenevix-Trench G, Grimmond SM, Simpson PT, Waddell N and Lakhani SR. Integrated genomic and transcriptomic analysis of human brain metastases identifies alterations of potential clinical significance. J Pathol 2015; 237: 363-378.

[58] Wen PY, Chang SM, Van den Bent MJ, Vogelbaum MA, Macdonald DR and Lee EQ. Response assessment in neuro-oncology clinical trials. J Clin Oncol 2017; 35: 2439-2449.

[59] Leclercq D, Trunet S, Bertrand A, Galanaud D, Lehericy S, Dormont D and Drier A. Cerebral tumor or pseudotumor? Diagn Interv Imaging 2014; 95: 906-916.

[60] Nayak L, DeAngelis LM, Brandes AA, Peereboom DM, Galanis E, Lin NU, Soffietti R, Macdonald DR, Chamberlain M, Perry J, Jaeckle K, Mehta M, Stupp R, Muzikansky A, Pentsova E, Cloughesy T, Iwamoto FM, Tonn JC, Vogelbaum MA, Wen PY, van den Bent MJ and Reardon DA. The neurologic assessment in neuro-oncology (NANO) scale: a tool to assess neurologic function for integration into the response assessment in neuro-oncology (RANO) criteria. Neuro Oncol 2017; 19: 625-635.

[61] Bollig-Fischer A, Michelhaugh SK, Wijesinghe P, Dyson G, Kruger A, Palanisamy N, Choi L, Alosh B, Ali-Fehmi R and Mittal S. Cytogenomic profiling of breast cancer brain metastases reveals potential for repurposing targeted therapeutics. Oncotarget 2015; 6: 14614-14624.

[62] Eisele SC, Gill CM, Shankar GM and Brastianos PK. PLEKHA5: a key to unlock the blood-brain barrier? Clin Cancer Res 2015; 21: 1978-1980.

[63] Neagu MR, Gill CM, Batchelor TT and Brastianos PK. Genomic profiling of brain metastases: current knowledge and new frontiers. Chin Clin Oncol 2015; 4: 22.

[64] Marzese DM, Scolyer RA, Roque M, Vargas-Roig LM, Huynh JL, Wilmott JS, Murali R, Buckland ME, Barkhoudarian G, Thompson JF, Morton DL, Kelly DF and Hoon DS. DNA methylation and gene deletion analysis of brain metastases in melanoma patients identifies mutually exclusive molecular alterations. Neuro Oncol 2014; 16: 1499-1509.