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Review

Brain Metastasis Treatment: The Place of Tyrosine Kinase Inhibitors and How to Facilitate Their Diffusion across the Blood–Brain Barrier

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Abstract: The incidence of brain metastases has been increasing constantly for the last 20 years, because of better control of metastases outside the brain, and the failure of most drugs to cross the blood–brain barrier at relevant pharmacological concentrations. Recent advances in the molecular biology of cancer have led to the identification of numerous molecular alterations, some of them targetable with the development of specific targeted therapies, including tyrosine kinase inhibitors. In this narrative review, we set out to describe the state-of-the-art in the use of tyrosine kinase inhibitors for the treatment of melanoma, lung cancer, and breast cancer brain metastases. We also report preclinical and clinical pharmacological data on brain exposure to tyrosine kinase inhibitors after oral administration and describe the most recent advances liable to facilitate their penetration of the blood–brain barrier at relevant concentrations and limit their physiological efflux.

Keywords: brain metastases; blood–brain barrier; tyrosine kinase inhibitors; pharmacokinetic

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1. Introduction

Brain metastases occur in 9 to 17% of all cancer patients [1], with a short survival [2,3]. Among the different cancer types, melanoma, breast and lung cancers are responsible for 6 to 56% of brain metastases [1].

Recent advances in the molecular biology of cancer have led to the identification of numerous molecular alterations, some of them targetable with the development of specific targeted therapies, including tyrosine kinase inhibitors (TKIs). For various cancer types, this new treatment era has considerably improved the prognosis for metastatic patients, with durable complete response [4–6]. This is particularly true for metastases that develop outside the central nervous system (CNS). In contrast, brain metastases, while usually sharing common gene alterations with extra-CNS metastases [7–23], are less sensitive to most anticancer agents. Indeed, diffusion into the brain parenchyma remains a pharmaceutical challenge because of the highly selective blood–brain barrier, combined with protective efflux systems limiting brain exposure to most xenobiotics [24].

Indeed, diffusion into the brain parenchyma remains a pharmaceutical challenge because of the highly selective blood–brain barrier, combined with protective efflux systems limiting brain exposure to most xenobiotics, two important topics that our research team has recently reviewed in [24,25].

Recently, next-generation TKIs have been approved for the treatment of metastatic breast cancer, lung cancer and melanoma, including patients with brain metastases, with promising response rates on CNS localizations. Thus, this topic has aroused growing interest, particularly over the last 5 years.

In this narrative review, we set out to describe the state-of-the-art in the use of TKIs for the treatment of brain metastases, as well as recent advances liable to facilitate their penetration of the blood–brain barrier.

2. Tyrosine Kinase Inhibitors for the Treatment of Breast Cancer Brain Metastases

For the literature search on the Pubmed database, we applied the following algorithm: ("Tyrosine Kinase Inhibitor") AND ("Brain Neoplasms" [MeSH] OR "Brain Metastases") AND ("Lung Neoplasms" [MeSH] OR "Breast Neoplasms" [MeSH] OR "Melanoma" [MeSH]) (Figure 1).

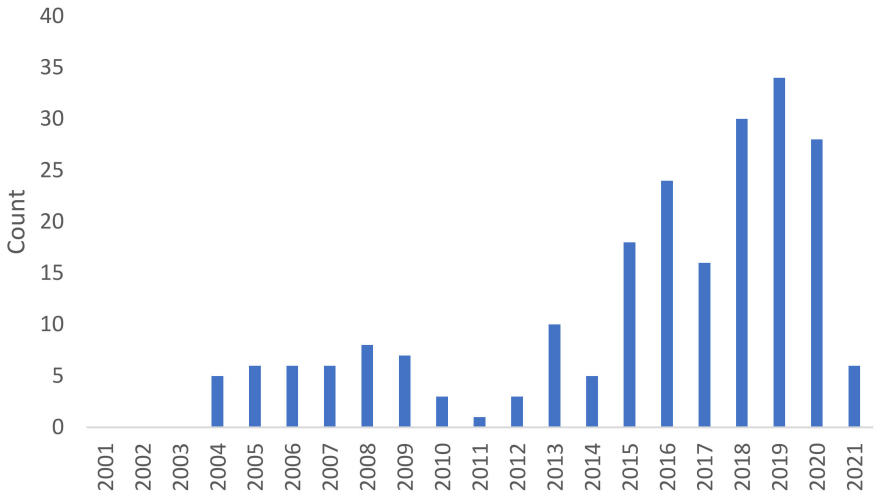

Figure 1. Publication trend since 2001 for kinase inhibitors and brain metastases from breast cancer, lung cancer and melanoma.

Breast cancers are divided into three subgroups: (i) hormone-dependent breast cancers expressing estrogen and/or progesterone receptors; (ii) human epidermal receptor 2 (HER2) breast cancers with *HER2-neu* gene amplification and HER2 membrane receptor overexpression; and (iii) triple-negative breast cancers which overexpress neither hormone nor HER2 receptors. Among metastatic breast cancers, the incidence of brain metastases is much higher for the triple-negative or HER2 subtypes. For the HER2 subtype, since 2001, several anti-HER2-targeted therapies have been approved [26–28], providing a durable complete response for 30% of metastatic patients. However, other patients will systematically develop resistance to anti-HER2 treatment, and up to 37% of these patients will develop brain metastases and die because of the limited efficacy of drugs on these localizations [29,30]. There is little preclinical and clinical pharmacological data on the blood–brain barrier passage by anti-HER2 antibodies. When available, the cerebrospinal fluid-to-blood concentration ratio is usually very low, less than 1% [24]. In contrast, brain exposure is higher for anti-HER2 TKIs than for therapeutic antibodies, including lapatinib, neratinib and tucatinib. Given the difficulty in obtaining brain samples, it remains difficult to accurately assess drug concentrations in the brain parenchyma after intravenous administration, the most pharmacologically relevant method being the measurement of the free brain/free plasma ratio, called Kpuu [31]. Most studies still report the CSF/plasma concentration ratio, which probably overestimates the actual intracerebral concentration [32].

Lapatinib is an oral TKI reversibly blocking phosphorylation of the human epidermal growth factor receptor (EGFR) 1, HER2 and HER4, extracellular signal-regulated kinase 1 and 2 (ERK-1, 2), and protein kinase B (PKB/AKT). Lapatinib, combined with capecitabine, is currently approved for the treatment of metastatic breast cancer progressing after trastuzumab therapy [33] (Table 1).

In mice that developed brain metastases after intra-cardiac injection of HER2 cancer cell lines, concomitant intravenous injection of lapatinib significantly decreased the surface

area of brain metastases, and this was associated with decreased HER2 phosphorylation of cancer cells [34]. In another murine orthotopic model of HER2 breast cancer brain metastases, after oral administration of (^{14}C)lapatinib, the concentrations were seven to nine times higher in brain metastases than in normal brain parenchyma, suggesting greater diffusion across the altered blood–brain barrier. However, lapatinib concentrations remained five to ten times lower in brain metastases than in extra-CNS metastatic localizations [35]. Finally, various preclinical studies in mice have reported low CSF/plasma or brain/plasma ratios after lapatinib oral administration in mice [35–38] (Table 2). Even if the low molecular weight of lapatinib theoretically enables its brain penetration, lapatinib is quickly effluxed from the brain to blood via P-glycoprotein (P-Gp, coded by the *MDR1a/b* gene) and breast cancer resistance protein (BCRP, coded by the *BCRP1* gene) transporters. Using a triple knock-out mouse model for *MDR1a/b* and *BCRP1*, lapatinib brain concentrations were 40 times higher than in wild-type mice of the same genetic strain [39].

In patients, the benefit of using lapatinib alone for the treatment of HER2 breast cancer brain metastases is modest. In a pooled analysis of 12 studies and 799 patients, the use of lapatinib combined with capecitabine provided a brain response rate of 29.2% [40] (Table 1).

In a single pharmacological study, 12 patients with metastatic breast cancer had surgical resection of at least one brain metastasis after a single dose of lapatinib at 1250 mg given orally 2–5 days before surgery. Considerable variations in brain uptake of the drug were observed, between patients and within one and the same patient between different brain metastases [38] (Table 1).

Neratinib is an oral irreversible pan-HER TKI and a P-Gp inhibitor of low molecular weight. In a clinical phase III NEfERT-T study comparing the association of paclitaxel-neratinib with paclitaxel-trastuzumab for the first-line treatment of HER2 metastatic breast cancer, the neratinib arm was associated with a significant decrease in brain recurrence (8.3% versus 17.3%, $p = 0.002$) [41]. A phase II study was then conducted to specifically assess the benefit of using capecitabine and neratinib in the treatment of refractory HER2 breast cancer brain metastases. Thirty patients out of 49 achieved an objective response on brain metastases [42,43] (Table 1). To date, there is no preclinical pharmacological data for neratinib diffusion into the brain. In humans, one study reported brain and cerebro-spinal fluid pharmacological concentrations of neratinib in three patients after a daily dose of 250 mg for 7 to 21 days before surgical resection of HER2 brain metastases. At the time of craniotomy, cerebro-spinal fluid concentrations of neratinib were below the detection limit, while plasma concentrations were detectable. For one patient, the concentration of neratinib was measured in different parts of the resected brain metastasis, and neratinib concentrations were 1 to 10 times higher than plasma concentrations [44] (Table 2).

Tucatinib is the latest generation of anti-HER2 TKI to be developed, and it has recently been approved for the treatment of HER2 metastatic breast cancer, including patients with refractory brain metastases.

In an orthotopic brain model of nude mice grafted with HER2 breast cancer, 75% of the tucatinib-treated mice were alive 22 days after grafting, whereas all animals were dead in the control groups treated with lapatinib alone or with placebo. In addition, in mice treated with tucatinib, there was a significant reduction in phosphorylated HER2 in the brain metastases, suggesting a direct inhibitory effect of tucatinib on HER2-overexpressing cancer cells [45].

In heavily pre-treated women with HER2 metastatic breast cancer, the HER2CLIMB trial demonstrated a considerable benefit of associating tucatinib with trastuzumab and capecitabine, with overall survival of 44.9% at 2 years [46]. In the sub-group of 291 patients with brain metastases, adding tucatinib reduced the risk of brain progression or death by 68% [47], with a median overall survival of 18.1 months (Table 1).

3. Tyrosine Kinase Inhibitors for the Treatment of Lung Cancer Brain Metastases

For this literature search on the Pubmed database, we applied the following algorithm: (tyrosine kinase inhibitor) AND (Brain Neoplasms [MeSH] OR brain metastases) AND (Lung Neoplasms [MeSH]) (Figure 1).

Lung cancer is the most common cancer in the world and the leading cause of death from cancer [48]. In the last two decades, targetable gene alterations have been identified in about 45% of patients with non-small-cell lung cancers (NSCLC) [49]. In particular, *EGFR* mutations or *ALK-EML4* translocations are identified in up to 50% of non-smokers or Asian patients with NSCLC of the adenocarcinoma histological sub-type [50].

NSCLC with *EGFR* mutations seems to be associated with an increased risk of brain metastases compared to patients with *EGFR* wild-type status [51]. In addition, the type of *EGFR* mutation could determine the phenotype of brain metastases, as exon 19 deletion is associated with more numerous small-sized metastases compared to exon 21 mutation and to *EGFR* wild-type genotype [52].

The first-generation EGFR TKIs, erlotinib and gefitinib, have been approved since 2005 for the treatment of metastatic NSCLC with activating *EGFR* mutations [53–56]. They are orally administered small molecules of less than 500g/mol kDa, reversibly inhibiting the adenosine triphosphate (ATP) binding site for EGFR tyrosine kinase, and thus the anti-apoptotic Ras signal transduction cascade. In vivo, preclinical pharmacokinetic studies of EGFR TKI distribution into the brain have shown a highly variable blood–brain barrier penetration of molecules, from 9 to 86% in normal mice [57,58] (Table 2). After oral administration, gefitinib brain concentrations are dose-dependent, reaching a peak at 1 h and rapidly decreasing as a result of P-Gp-mediated efflux [58]. In patients with NSCLC brain metastases treated with gefitinib, there is also dose-dependent cerebro-spinal fluid penetration, but it is very low, with a peak cerebro-spinal fluid /plasma ratio of 1.87% [59]. Significant brain metastasis responses have been obtained with erlotinib in lung cancers [60], up to 87% in a Japanese study [61] (Table 1).

The second-generation EGFR-TKIs, afatinib and dacomitinib, irreversibly bind to the tyrosine kinase domain of *EGFR*, and also to other ErbB-family members. Afatinib is an oral irreversible TKI that has been developed to specifically target *EGFR exon 19* deletion and *L658R* mutation. Afatinib treatment led to a significant progression-free survival improvement in patients with *EGFR*-mutated NSCLC, compared to platine-based chemotherapy (LUX-Lung 3 and LUX-Lung 6 clinical trials). A combined analysis of these two trials for the subgroup of patients with brain metastases showed improved progression-free survival (8.2 versus 5.4 months $p = 0.03$) [62]. In another study on patients with lung cancer brain metastases, afatinib provided a brain response rate of 81.1% [63] (Table 1).

Despite excellent CNS response rates for first- and second-generation TKIs, the prognosis of patients with *EGFR*-mutated lung cancer is linked to acquired resistance mutations, such as the *T790M* mutation [64]. After first- or second-generation TKIs, more than 30% of patients with NSCLC experience brain disease progression. Limited genomic data on surgically resected metastases has also evidenced acquired *EGFR* resistance mutations [64–66].

Osimertinib is a potent oral irreversible EGFR TKI developed to specifically target *EGFR T790M* resistance mutation. In preclinical murine models, osimertinib achieved a relevant brain exposure with a maximum brain-to-blood ratio of 2.2 at 60 min post-administration. Distribution was maintained in the brain up to 21 days after a single dose, osimertinib being then effluxed via P-Gp or BCRP blood–brain barrier transporters [67] (Table 2). In the phase III clinical trial FLAURA leading to FDA and European approval, osimertinib demonstrated its superiority compared to first- and second-generation TKIs [68,69]. A pooled analysis of data from 50 patients with brain metastases and *EGFR T790M* mutations reported a response rate of 54%, independent of prior brain radiotherapy [70] (Table 1). To our knowledge, there is no pharmacological data for osimertinib brain penetration in humans.

Anaplastic lymphoma kinase (*ALK*) gene rearrangements are associated with a high risk of brain metastases, occurring in up to 50–60% of patients in the course of their dis-

ease [71]. Crizotinib was the first ALK inhibitor approved for the treatment of metastatic *ALK*-mutated NSCLCs, with an improvement in survival compared to standard platine-based chemotherapy [72]. However, the intracranial efficacy of crizotinib is limited, because of its poor blood–brain barrier penetration. Three clinical cases report a cerebro-spinal fluid/plasma ratio of 0.06 to 0.3% after daily oral administration of crizotinib [73,74] (Table 2). After first-line treatment using crizotinib, all *ALK*-mutated NSCLC patients developed secondary resistance within 12 months, mainly due to acquired *ALK* mutations [75].

The second-generation ALK inhibitors alectinib and brigatinib were thus developed to efficaciously target these acquired *ALK* mutations. In addition, they have been associated with better survival results compared to crizotinib in first-line settings for metastatic ALK-mutated NSCLCs [76,77]. For brain metastases, alectinib provides high response rates ranging from 52 to 59% [78], and brigatinib provides even higher response rates of 78% [77] (Table 1).

More recently, lorlatinib, a third-generation *ALK* and c-ros oncogene 1 (*ROS1*), was developed for ALK-mutated NSCLCs harboring resistance mutations. During preclinical development, lorlatinib was optimized for a good cerebro-spinal fluid /plasma ratio [79] (Table 2). In a phase III study of 293 patients with ALK-positive metastatic NSCLC, lorlatinib was compared to crizotinib. At 12 months, 78% of the patients were alive in the lorlatinib groups versus 39% in the crizotinib group. Among patients with measurable brain metastases, 82% of the patients in the lorlatinib group exhibited intracranial response versus 23% in the crizotinib group. Seventy-one percent of the patients who received lorlatinib had complete intracranial response [80] (Table 1).

4. Tyrosine Kinase Inhibitors for the Treatment of Melanoma Brain Metastases

For the literature search on the Pubmed database, we applied the following algorithm: (tyrosine kinase inhibitor) AND (Brain Neoplasms [MeSH] OR brain metastases) AND (Melanoma [MeSH]) (Figure 1).

Among all cancers, melanoma is the third most common cause of brain metastasis [81]. About 50% of patients with cutaneous melanoma harbor the *BRAFV600E* hotspot mutation [82], which has led to the development of specific inhibitors, the first one being vemurafenib. In a phase II study of 90 patients with previously untreated brain metastases and *BRAFV600* mutation, treatment with vemurafenib yielded a brain response rate of 18% [83] (Table 1). More recently, combinations of BRAF inhibitors and MEK inhibitors (dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib) have been approved for the treatment of patients with metastatic *BRAF*-mutated melanoma [84] but with little data on brain metastasis efficacy. In a prospective phase II study of 146 patients with brain metastases, monotherapy with a BRAF inhibitor (vemurafenib or dabrafenib) was compared to a combination of BRAF and MEK inhibitors (dabrafenib and trametinib). The median time to brain progression was not different between the two treatment arms, and it was under 6 months in both cases [85] (Table 1).

Table 1. Clinical trials on TKIs in different cancer types with brain metastases.

Cancer Type	Molecule	Sequence	CNS ORR (%)	PFS (Month)	OS (Months)	Trial Type	Reference
Breast cancer with HER2 amplification	Lapatinib	Lapatinib + capecitabine	29.2	4.1	11.2	MA	[40]
		lapatinib + capecitabine	20	6.4	NR	II	[86]
		Lapatinib	6	3.6	6.4	II	[86]
		Lapatinib + capecitabine	66	5.5	17	II	[87]
		Lapatinib + capecitabine	33	5.5	11	II	[88]
	Neratinib	Neratinib + paclitaxel	CNS PFS: NR	12.9	NA	III	[41]
		Neratinib + capecitabine	49	5.5	13.3	II	[42]
		Neratinib + capecitabine	33	3.1	15.1	II	[42]
		Neratinib + capecitabine	49	5.5	13.5	II	[43]
	Tucatinib	Tucatinib + trastuzumab + capecitabine	47.3	33.1	44.9	III	[46,47]
Lung cancer with EGFR mutation	Afatinib	Afatinib	70	NS	NS	II	[89]
		Afatitnib + vinorelbine	66	NS	NS	II	[89]
	Gefitinib	Gefitinib	87.8	14.5	21.9	II	[61]
	Erlotinib	Erlotinib + WBRT	86	-	-	II	[60]
		Gefitinib or erlotinib	-	vs. 10.2	vs. 31.6	II–III	[69,70]
	Afatinib	Afatinib	-	8.2	22.4	III	[62]
		Afatinib	81.1	-	-	R	[63]
	Osimertinib	Osimertinib	54	18.9	38.6	II–III	[69,70]
Lung cancer ALK-positive	Crizotinib	Crizotinib	12	-	-	I-II	[90]
		Crizotinib	23	39	NR	III	[80]
		Crizotinib	29	43	NA	III	[77]
	Lorlatinib	Lorlatinib	64	-	-	I–II	[90]
		Lorlatinib	82	78	NR	III	[80]
	Alectinib	Alectinib	54.2	9.6	-	III	[91]
		Alectinib	57	8.9	-	II	[92]
		Alectinib	75	-	-	II	[93]
	Brigatinib	Brigatinib	78	67	NA	III	[77]
BRAF mutated melanoma	Vemurafenib	Vemurafenib	18	-	8.9	II	[83]
		Vemurafenib	3.7	4	5.7	R	[85]
	Dabrafenib	Dabrafenib + trametinib	5.8 (median intracranial PFS)	7.3	11.2	R	[85]
		Dabrafenib	5.6	5.8	8.8	R	[85]

CNS Central Nervous System; ORR Objective Response Rate; PFS Progression Free Survival; OS Overall Survival; MA Meta-Analysis; IC Investigator's choice; WBRT whole brain radiation therapy; R: Retrospective study; NR not reached; NA non available.

Table 2. Clinical and preclinical pharmacokinetic brain data for different TKIs.

Cancer	Drug	Molar Mass (g/mol)	Species	CSF/Plasma Ratio or Brain/Plasma Ratio	Time	Reference
Breast	Lapatinib	581	Mice	0.03	steady state	[39]
			Mice	0.02	2 h	[35]
			Mice	0.03	12 h	[35]
			Mice	0.05	$AUC_{0–16\ h}$	[37]
			Mice	0.04	$AUC_{0–16\ h}$	[37]
	Neratinib	557	Humans	<LOD	steady state	[44]
	Erlotinib	393	Mice	0.01	1 h	[57]
			Rats	0.14	$AUC_{0–16\ h}$	[94]
Lung	Gefitinib	447	Mice	0.01	1 h	[57]
			Mice	0.4	$AUC_{0–48\ h}$	[58]
			Mice	0.7	$AUC_{0–48\ h}$	[58]
			Humans	0.01	Day 30	[59]
	Afatinib	486	Rats	0.12	$AUC_{0–16\ h}$	[94]
			Rats	0.2	$AUC_{0–16\ h}$	[94]
	Osimertinib	163	Rats	6.09	$AUC_{0–16\ h}$	[94]
			Humans	3.8 (mean)	$AUC_{0\text{-}90\ min}$	[95]
	Crizotinib	450	Humans	0.001	5 h	[74]
			Humans	0.0006	5 h	[73]
	Lorlatinib	406	Rats	0.6	$AUC_{0\text{-}24h}$	[79]
Melanoma	Vemurafenib	490	Humans	0.28–1.39	NA	[96]
			Mice	<0.1	4 h	[97]
	Dabrafenib	520	Mice	0.02	$AUC_{0\text{-}2h}$	[98]
	Trametinib	615	Mice	0.1	$AUC_{0\text{-}48h}$	[99]
	Cobimetinib	531	Mice	0.02	6 h	[100]
	Encorafenib	540	Mice	4.10–3	2 h	[101]

CSF cerebrospinal fluid; AUC Area Under the Curve; LOD Limit of Detection.

5. How to Facilitate Brain Diffusion of Anti-Cancer Tyrosine Kinase Inhibitors

To improve brain diffusion, drugs need to cross the blood–brain barrier without being effluxed from the brain to the blood. Several other approaches have been developed to increase drug penetration of the BBB [24] and therefore increase influx. In particular,

the intranasal route of administration seems the most promising for small-sized molecules, and there is also promising data for the use of bi-specific antibodies of the angiopeps family.

5.1. Nanoparticle Formulation

Among different nanoparticles developed for blood–brain barrier penetration, most performant are polymeric nanoparticles, gold nanoparticles, and liposomes [102–111]. These nanoparticles have several advantages: (i) because of their small size, which normally does not exceed 100 nm, and their lipophilicity, they can cross the blood–brain barrier and accumulate at the tumor site as a result of the enhanced permeability and retention (EPR) effect; (ii) they can be loaded with different drugs. (iii) Finally, liposomes and polymeric nanoparticles ensure elimination of the product and limited toxicity because they are biodegradable [112,113].

In addition to these properties, several nanoparticles have been designed and engineered as "Trojan horses" to facilitate the crossing of the blood–brain barrier by TKIs. "Trojan horses" usually refer to bi-specific antibodies or systems using a ligand of physiological receptors located on the blood side of endothelial cells (reviewed in reference [24]).

In a study using murine models, lapatinib loaded on human serum albumin (HSA) nanoparticles had a 5-fold increased diffusion into the brain compared to lapatinib alone. This facilitated passage of the blood–brain barrier was explained by an increased passive diffusion of nanoparticles but also by active penetration using physiological albumin receptors [114]. Eight hours post-administration, the nanoparticle was almost absent from tissues. For gefitinib, two liposomal formulations have been tested using in vitro blood–brain barrier models. One formulation combined glutathione and polysorbate 80, known to be two ligands of physiological receptors in the blood–brain barrier, and another formulation used liposomes functionalized with RF, a cell-penetrating peptide. Both formulations showed an enhanced uptake across bEnd.3 cells, partially through clathrin-mediated endocytosis for RF-liposomes [115]. None of these molecules has been approved by the FDA to date.

5.2. Use of Ultrasound to Disrupt the Blood–Brain Barrier

This method combines the use of ultrasound with micro-bubbles. When excited by ultrasounds, micro-bubbles expand and exert a mechanical force on endothelial cells in the blood–brain barrier, thus disrupting tight junctions. This approach seems to not only have a mechanical effect but also to affect tight junction protein expression. Indeed, in murine models, mRNA and protein expression of CLAUDIN-5, OCCLUDIN, and ZONA OCLLUDENS-1 decreased in endothelial cells in the blood–brain barrier 3 h after low-frequency-focused ultrasound application. This biological effect of ultrasound could be explained by the tridimensional conformation change of tight junctions [116]. This approach has evidenced an enhanced brain penetration of drugs in preclinical and clinical studies [117–119]. For TKIs, one preclinical study explored the brain distribution of ^{11}C-erlotinib in healthy rats after intravenous injection of micro-bubbles combined with brain application of ultrasound but was unsuccessful [120].

6. How to Reduce the Brain Efflux of Anti-Cancer Tyrosine Kinase Inhibitors

After diffusion into the brain parenchyma, physiological efflux systems expressed in the endothelial cells of the blood–brain barrier ensure the elimination of drugs from the brain to the blood. These protective efflux systems, by preventing drugs from reaching relevant and also potentially toxic concentrations in the brain parenchyma, also explain the limited efficacy of anti-cancer drugs on brain metastases. Among them, the ATP-binding cassette (ABC) transporters are ubiquitously expressed. They use energy from ATP hydrolysis to transport substrates across membranes. The most widely studied ABC efflux transporters at the blood–brain barrier are the P-glycoprotein (P-Gp), the breast cancer resistance protein (BCRP) and the multidrug resistance protein (MRP) [121].

All TKIs are substrates of ABC transporters, limiting their brain accumulation at relevant concentrations [99,122–128]. Using efflux transporter inhibitors might be a way to sig-

nificantly enhance brain accumulations of anticancer drugs (reviewed in [25]), with promising preclinical data [97,129–133]. P-Gp inhibitors have failed in clinical trials. Indeed, next-generation inhibitors such as lorlatinib or osimertinib have been chemically engineered not to be recognized by the P-Gp-family efflux pumps.

7. Optimal Chemical Design of New Tyrosine Kinase Inhibitors

Lorlatinib was designed and structurally optimized in silico and in vitro for maximum brain penetration, and a minimum P-Gp efflux ratio [79]. Using in silico structure-based drug design, a macrocyclic template has been developed with a good brain penetration capacity. Then, using in vitro blood–brain barrier models with P-Gp-overexpressing cell lines, drugs have been optimized for a minimum efflux ratio. Typically, compounds that exhibited efflux ratios of under 2.5 were not retained, considered to have a low probability of achieving pharmacologically relevant brain concentrations in humans. A low molecular weight, high lipophilicity, and a low hydrogen bond donor count were independent factors for ratio performance.

The same methodological approach was used for osimertinib development [134], with a promising in silico prediction model of brain exposure [31,135], based on a quantitative structure–activity relationship (QSAR) model. Among 15 TKIs, osimertinib was identified to be the weakest substrate for blood–brain barrier efflux transporters in vitro, harboring fewer rotatable bonds for a more rigid molecule [136]. The free brain-to-plasma ratio (Kpuu) has been used to assess the BBB penetration by compounds and is the best predictor of brain penetration. It uses the in vivo brain-to-plasma ratio (Kp) combined with the in vitro determined fraction unbound in brain (fub) and in plasma (fup) (Kpuu = Kp × fub/fup). Among different compounds, all of those with an in vivo-estimated Kpuu > 0.3 were retained. In *cynomolgus* monkeys, ^{11}C-osimertinib administered orally achieved a significant brain distribution from Positron Emission Tomography imaging [94].

8. Conclusions and Perspectives

Despite major improvements in the control of extra-CNS metastases, the treatment of brain metastases remains a pharmacological challenge due to the highly selective and protective blood–brain barrier. Different ways to overcome this limitation have been explored, such as nanoparticle formulations or the use of ultrasounds to disrupt the blood–brain barrier. Other possibilities have yet to be explored to enhance the delivery of TKIs to the brain at pharmacologically relevant concentrations and thus efficaciously treat brain metastases. In particular, one could imagine the use of the intranasal route of administration or the engineering of bispecific molecules combining TKIs with angiopeps. The main challenge remains the way in which to limit TKI brain efflux after brain penetration. Next-generation TKIs have been chemically designed to facilitate their penetration into the brain and to overcome efflux pumps, with promising clinical responses. These formulations need to be further improved.

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References

1. Nayak, L.; Lee, E.Q.; Wen, P.Y. Epidemiology of Brain Metastases. *Curr. Oncol. Rep.* **2012**, *14*, 48–54. [CrossRef]
2. Lowery, F.J.; Yu, D. Brain Metastasis: Unique Challenges and Open Opportunities. *Biochim. Biophys. Acta Rev. Cancer* **2017**, *1867*, 49–57. [CrossRef]
3. Cagney, D.N.; Martin, A.M.; Catalano, P.J.; Redig, A.J.; Lin, N.U.; Lee, E.Q.; Wen, P.Y.; Dunn, I.F.; Bi, W.L.; Weiss, S.E.; et al. Incidence and Prognosis of Patients with Brain Metastases at Diagnosis of Systemic Malignancy: A Population-Based Study. *Neuro-Oncology* **2017**, *19*, 1511–1521. [CrossRef] [PubMed]
4. Zhao, D.; Chen, X.; Qin, N.; Su, D.; Zhou, L.; Zhang, Q.; Li, X.; Zhang, X.; Jin, M.; Wang, J. The Prognostic Role of EGFR-TKIs for Patients with Advanced Non-Small Cell Lung Cancer. *Sci. Rep.* **2017**, *7*, 40374. [CrossRef]
5. Schlam, I.; Swain, S.M. HER2-Positive Breast Cancer and Tyrosine Kinase Inhibitors: The Time Is Now. *NPJ Breast Cancer* **2021**, *7*, 56. [CrossRef] [PubMed]
6. Popescu, A.; Anghel, R.M. Tyrosine-Kinase Inhibitors Treatment in Advanced Malignant Melanoma. *Maedica* **2017**, *12*, 293–296.
7. Tyran, M.; Carbuccia, N.; Garnier, S.; Guille, A.; Adelaïde, J.; Finetti, P.; Touzlian, J.; Viens, P.; Tallet, A.; Goncalves, A.; et al. A Comparison of DNA Mutation and Copy Number Profiles of Primary Breast Cancers and Paired Brain Metastases for Identifying Clinically Relevant Genetic Alterations in Brain Metastases. *Cancers* **2019**, *11*, 665. [CrossRef] [PubMed]
8. Lee, J.Y.; Park, K.; Lim, S.H.; Kim, H.S.; Yoo, K.H.; Jung, K.S.; Song, H.-N.; Hong, M.; Do, I.-G.; Ahn, T.; et al. Mutational Profiling of Brain Metastasis from Breast Cancer: Matched Pair Analysis of Targeted Sequencing between Brain Metastasis and Primary Breast Cancer. *Oncotarget* **2015**, *6*, 43731. [CrossRef]
9. Lee, J.Y.; Park, K.; Lee, E.; Ahn, T.; Jung, H.H.; Lim, S.H.; Hong, M.; Do, I.-G.; Cho, E.Y.; Kim, D.-H.; et al. Gene Expression Profiling of Breast Cancer Brain Metastasis. *Sci. Rep.* **2016**, *6*, 28623. [CrossRef]
10. Varešlija, D.; Priedigkeit, N.; Fagan, A.; Purcell, S.; Cosgrove, N.; O'Halloran, P.J.; Ward, E.; Cocchiglia, S.; Hartmaier, R.; Castro, C.A.; et al. Transcriptome Characterization of Matched Primary Breast and Brain Metastatic Tumors to Detect Novel Actionable Targets. *J. Natl. Cancer Inst.* **2019**, *111*, 388–398. [CrossRef] [PubMed]
11. Schrijver, W.A.; Selenica, P.; Lee, J.Y.; Ng, C.K.Y.; Burke, K.; Piscuoglio, S.; Berman, S.H.; Reis-Filho, J.S.; Weigelt, B.; Van Diest, P.J.; et al. Mutation Profiling of Key Cancer Genes in Primary Breast Cancers and Their Distant Metastases. *Cancer Res.* **2018**, *78*, 3112–3121. [CrossRef]
12. Da Silva, L.; Simpson, P.T.; Smart, C.E.; Cocciardi, S.; Waddell, N.; Lane, A.; Morrison, B.J.; Vargas, A.C.; Healey, S.; Beesley, J.; et al. HER3 and Downstream Pathways Are Involved in Colonization of Brain Metastases from Breast Cancer. *Breast Cancer Res.* **2010**, *12*, R46. [CrossRef]
13. Bollig-Fischer, A.; Michelhaugh, S.K.; Wijesinghe, P.; Dyson, G.; Kruger, A.; Palanisamy, N.; Choi, L.; Alosh, B.; Ali-Fehmi, R.; Mittal, S. Cytogenomic Profiling of Breast Cancer Brain Metastases Reveals Potential for Repurposing Targeted Therapeutics. *Oncotarget* **2015**, *6*, 14614. [CrossRef]
14. Schulten, H.-J.; Bangash, M.; Karim, S.; Dallol, A.; Hussein, D.; Merdad, A.; Al-Thoubaity, F.K.; Al-Maghrabi, J.; Jamal, A.; Al-Ghamdi, F.; et al. Comprehensive Molecular Biomarker Identification in Breast Cancer Brain Metastases. *J. Transl. Med.* **2017**, *15*, 269. [CrossRef]
15. Priedigkeit, N.; Hartmaier, R.J.; Chen, Y.; Vareslija, D.; Basudan, A.; Watters, R.J.; Thomas, R.; Leone, J.P.; Lucas, P.C.; Bhargava, R.; et al. Intrinsic Subtype Switching and Acquired *ERBB2/HER2* Amplifications and Mutations in Breast Cancer Brain Metastases. *JAMA Oncol.* **2017**, *3*, 666. [CrossRef]
16. Paik, P.K.; Shen, R.; Won, H.; Rekhtman, N.; Wang, L.; Sima, C.S.; Arora, A.; Seshan, V.; Ladanyi, M.; Berger, M.F.; et al. Next-Generation Sequencing of Stage IV Squamous Cell Lung Cancers Reveals an Association of PI3K Aberrations and Evidence of Clonal Heterogeneity in Patients with Brain Metastases. *Cancer Discov.* **2015**, *5*, 610–621. [CrossRef] [PubMed]
17. Wang, H.; Ou, Q.; Li, D.; Qin, T.; Bao, H.; Hou, X.; Wang, K.; Wang, F.; Deng, Q.; Liang, J.; et al. Genes Associated with Increased Brain Metastasis Risk in Non–Small Cell Lung Cancer: Comprehensive Genomic Profiling of 61 Resected Brain Metastases versus Primary Non–Small Cell Lung Cancer (Guangdong Association Study of Thoracic Oncology 1036). *Cancer* **2019**, *125*, 3535–3544. [CrossRef] [PubMed]
18. Li, F.; Sun, L.; Zhang, S. Acquirement of DNA Copy Number Variations in Non-Small Cell Lung Cancer Metastasis to the Brain. *Oncol. Rep.* **2015**, *34*, 1701–1707. [CrossRef] [PubMed]
19. Chen, G.; Chakravarti, N.; Aardalen, K.; Lazar, A.J.; Tetzlaff, M.T.; Wubbenhorst, B.; Kim, S.-B.; Kopetz, S.; Ledoux, A.A.; Gopal, Y.N.V.; et al. Molecular Profiling of Patient-Matched Brain and Extracranial Melanoma Metastases Implicates the PI3K Pathway as a Therapeutic Target. *Clin. Cancer Res.* **2014**, *20*, 5537–5546. [CrossRef]
20. Fischer, G.M.; Jalali, A.; Kircher, D.A.; Lee, W.-C.; McQuade, J.L.; Haydu, L.E.; Joon, A.Y.; Reuben, A.; De Macedo, M.P.; Carapeto, F.C.L.; et al. Molecular Profiling Reveals Unique Immune and Metabolic Features of Melanoma Brain Metastases. *Cancer Discov.* **2019**, *9*, 628–645. [CrossRef]
21. Ferguson, S.D.; Zheng, S.; Xiu, J.; Zhou, S.; Khasraw, M.; Brastianos, P.K.; Kesari, S.; Hu, J.; Rudnick, J.; Salacz, M.E.; et al. Profiles of Brain Metastases: Prioritization of Therapeutic Targets: Profiling Brain Metastases. *Int. J. Cancer* **2018**, *143*, 3019–3026. [CrossRef]
22. Brastianos, P.K.; Carter, S.L.; Santagata, S.; Cahill, D.P.; Taylor-Weiner, A.; Jones, R.T.; Van Allen, E.M.; Lawrence, M.S.; Horowitz, P.M.; Cibulskis, K.; et al. Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. *Cancer Discov.* **2015**, *5*, 1164–1177. [CrossRef]

23. Saunus, J.M.; Quinn, M.C.; Patch, A.-M.; Pearson, J.V.; Bailey, P.J.; Nones, K.; McCart Reed, A.E.; Miller, D.; Wilson, P.J.; Al-Ejeh, F.; et al. Integrated Genomic and Transcriptomic Analysis of Human Brain Metastases Identifies Alterations of Potential Clinical Significance: Integrated Genomic and Transcriptomic Analysis of Brain Metastases. *J. Pathol.* **2015**, *237*, 363–378. [CrossRef] [PubMed]
24. Angeli, E.; Nguyen, T.T.; Janin, A.; Bousquet, G. How to Make Anticancer Drugs Cross the Blood-Brain Barrier to Treat Brain Metastases. *Int. J. Mol. Sci.* **2020**, *21*, 22. [CrossRef] [PubMed]
25. Paris, J.; Angeli, E.; Bousquet, G. The Pharmacology of Xenobiotics after Intracerebro Spinal Fluid Administration: Implications for the Treatment of Brain Tumors. *Int. J. Mol. Sci.* **2021**, *22*, 1281. [CrossRef] [PubMed]
26. Swain, S.M.; Kim, S.-B.; Cortés, J.; Ro, J.; Semiglazov, V.; Campone, M.; Ciruelos, E.; Ferrero, J.-M.; Schneeweiss, A.; Knott, A.; et al. Pertuzumab, Trastuzumab, and Docetaxel for HER2-Positive Metastatic Breast Cancer (CLEOPATRA Study): Overall Survival Results from a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study. *Lancet Oncol.* **2013**, *14*, 461–471. [CrossRef]
27. Verma, S.; Miles, D.; Gianni, L.; Krop, I.E.; Welslau, M.; Baselga, J.; Pegram, M.; Oh, D.-Y.; Diéras, V.; Guardino, E.; et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. *N. Engl. J. Med.* **2012**, *367*, 1783–1791. [CrossRef]
28. Modi, S.; Saura, C.; Yamashita, T.; Park, Y.H.; Kim, S.-B.; Tamura, K.; Andre, F.; Iwata, H.; Ito, Y.; Tsurutani, J.; et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N. Engl. J. Med.* **2020**, *382*, 610–621. [CrossRef]
29. Brufsky, A.M.; Mayer, M.; Rugo, H.S.; Kaufman, P.A.; Tan-Chiu, E.; Tripathy, D.; Tudor, I.C.; Wang, L.I.; Brammer, M.G.; Shing, M.; 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. [CrossRef]
30. Hurvitz, S.A.; O'Shaughnessy, J.; Mason, G.; Yardley, D.A.; Jahanzeb, M.; Brufsky, A.; Rugo, H.S.; Swain, S.M.; Kaufman, P.A.; Tripathy, D.; et al. Central Nervous System Metastasis in Patients with HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from SystHERs. *Clin. Cancer Res.* **2019**, *25*, 2433–2441. [CrossRef]
31. Fridén, M.; Winiwarter, S.; Jerndal, G.; Bengtsson, O.; Wan, H.; Bredberg, U.; Hammarlund-Udenaes, M.; Antonsson, M. Structure-Brain Exposure Relationships in Rat and Human Using a Novel Data Set of Unbound Drug Concentrations in Brain Interstitial and Cerebrospinal Fluids. *J. Med. Chem.* **2009**, *52*, 6233–6243. [CrossRef]
32. Pardridge, W.M. Blood-Brain Barrier and Delivery of Protein and Gene Therapeutics to Brain. *Front. Aging Neurosci.* **2020**, *11*, 373. [CrossRef]
33. Geyer, C.E.; Forster, J.; Lindquist, D.; Chan, S.; Romieu, C.G.; Pienkowski, T.; Jagiello-Gruszfeld, A.; Crown, J.; Chan, A.; Kaufman, B.; et al. Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer. *N. Engl. J. Med.* **2006**, *355*, 2733–2743. [CrossRef]
34. Gril, B.; Palmieri, D.; Bronder, J.L.; Herring, J.M.; Vega-Valle, E.; Feigenbaum, L.; Liewehr, D.J.; Steinberg, S.M.; Merino, M.J.; Rubin, S.D.; et al. Effect of Lapatinib on the Outgrowth of Metastatic Breast Cancer Cells to the Brain. *J. Natl. Cancer Inst.* **2008**, *100*, 1092–1103. [CrossRef]
35. Taskar, K.S.; Rudraraju, V.; Mittapalli, R.K.; Samala, R.; Thorsheim, H.R.; Lockman, J.; Gril, B.; Hua, E.; Palmieri, D.; Polli, J.W.; et al. Lapatinib Distribution in HER2 Overexpressing Experimental Brain Metastases of Breast Cancer. *Pharm. Res.* **2012**, *29*, 770–781. [CrossRef] [PubMed]
36. Scheffler, M.; Di Gion, P.; Doroshyenko, O.; Wolf, J.; Fuhr, U. Clinical Pharmacokinetics of Tyrosine Kinase Inhibitors: Focus on 4-Anilinoquinazolines. *Clin. Pharmacokinet.* **2011**, *50*, 371–403. [CrossRef]
37. Hudachek, S.F.; Gustafson, D.L. Physiologically Based Pharmacokinetic Model of Lapatinib Developed in Mice and Scaled to Humans. *J. Pharmacokinet. Pharmacodyn.* **2013**, *40*, 157–176. [CrossRef]
38. Morikawa, A.; Peereboom, D.M.; Thorsheim, H.R.; Samala, R.; Balyan, R.; Murphy, C.G.; Lockman, P.R.; Simmons, A.; Weil, R.J.; Tabar, V.; et al. Capecitabine and Lapatinib Uptake in Surgically Resected Brain Metastases from Metastatic Breast Cancer Patients: A Prospective Study. *Neuro-Oncology* **2015**, *17*, 289–295. [CrossRef] [PubMed]
39. Polli, J.W.; Olson, K.L.; Chism, J.P.; John-Williams, L.S.; Yeager, R.L.; Woodard, S.M.; Otto, V.; Castellino, S.; Demby, V.E. An Unexpected Synergist Role of P-Glycoprotein and Breast Cancer Resistance Protein on the Central Nervous System Penetration of the Tyrosine Kinase Inhibitor Lapatinib (N-{3-Chloro-4-[(3-Fluorobenzyl)Oxy]Phenyl}-6-[5-({[2-(Methylsulfonyl)Ethyl]Amino}methyl)-2-Furyl]-4-Quinazolinamine; GW572016). *Drug Metab. Dispos. Biol. Fate Chem.* **2009**, *37*, 439–442. [CrossRef] [PubMed]
40. Petrelli, F.; Ghidini, M.; Lonati, V.; Tomasello, G.; Borgonovo, K.; Ghilardi, M.; Cabiddu, M.; Barni, S. The Efficacy of Lapatinib and Capecitabine in HER-2 Positive Breast Cancer with Brain Metastases: A Systematic Review and Pooled Analysis. *Eur. J. Cancer* **2017**, *84*, 141–148. [CrossRef]
41. Awada, A.; Colomer, R.; Inoue, K.; Bondarenko, I.; Badwe, R.A.; Demetriou, G.; Lee, S.-C.; Mehta, A.O.; Kim, S.-B.; Bachelot, T.; et al. Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial. *JAMA Oncol.* **2016**, *2*, 1557. [CrossRef]
42. Stirrups, R. Neratinib and Capecitabine for Breast Cancer Brain Metastases. *Lancet Oncol.* **2019**, *20*, e197. [CrossRef]
43. Freedman, R.A.; Gelman, R.S.; Anders, C.K.; Melisko, M.E.; Parsons, H.A.; Cropp, A.M.; Silvestri, K.; Cotter, C.M.; Componeschi, K.P.; Marte, J.M.; et al. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients with Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases. *J. Clin. Oncol.* **2019**, *37*, 1081–1089. [CrossRef]
44. Freedman, R.A.; Gelman, R.S.; Agar, N.Y.R.; Santagata, S.; Randall, E.C.; Gimenez-Cassina Lopez, B.; Connolly, R.M.; Dunn, I.F.; Van Poznak, C.H.; Anders, C.K.; et al. Pre- and Postoperative Neratinib for HER2-Positive Breast Cancer Brain Metastases: Translational Breast Cancer Research Consortium 022. *Clin. Breast Cancer* **2020**, *20*, 145–151. [CrossRef] [PubMed]

45. Dinkel, V.; Anderson, D.; Winski, S.; Winkler, J.; Koch, K.; Lee, P.A. Abstract 852: ARRY-380, a potent, small molecule inhibitor of ErbB2, increases survival in intracranial ErbB2+ xenograft models in mice. In Proceedings of the AACR 103rd Annual Meeting 2012, Chicago, IL, USA, 31 March–4 April 2012. Unpublished Data.
46. Murthy, R.K.; Loi, S.; Okines, A.; Paplomata, E.; Hamilton, E.; Hurvitz, S.A.; Lin, N.U.; Borges, V.; Abramson, V.; Anders, C.; et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N. Engl. J. Med.* **2020**, *382*, 597–609. [CrossRef]
47. Lin, N.U.; Borges, V.; Anders, C.; Murthy, R.K.; Paplomata, E.; Hamilton, E.; Hurvitz, S.; Loi, S.; Okines, A.; Abramson, V.; et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2020**, *38*, 2610–2619. [CrossRef]
48. De Groot, P.M.; Wu, C.C.; Carter, B.W.; Munden, R.F. The Epidemiology of Lung Cancer. *Transl. Lung Cancer Res.* **2018**, *7*, 220–233. [CrossRef] [PubMed]
49. Tsao, A.S.; Scagliotti, G.V.; Bunn, P.A.; Carbone, D.P.; Warren, G.W.; Bai, C.; De Koning, H.J.; Yousaf-Khan, A.U.; McWilliams, A.; Tsao, M.S.; et al. Scientific Advances in Lung Cancer 2015. *J. Thorac. Oncol.* **2016**, *11*, 613–638. [CrossRef]
50. Chevallier, M.; Borgeaud, M.; Addeo, A.; Friedlaender, A. Oncogenic Driver Mutations in Non-Small Cell Lung Cancer: Past, Present and Future. *World J. Clin. Oncol.* **2021**, *12*, 217–237. [CrossRef]
51. Li, L.; Luo, S.; Lin, H.; Yang, H.; Chen, H.; Liao, Z.; Lin, W.; Zheng, W.; Xie, X. Correlation between EGFR Mutation Status and the Incidence of Brain Metastases in Patients with Non-Small Cell Lung Cancer. *J. Thorac. Dis.* **2017**, *9*, 2510–2520. [CrossRef]
52. Sekine, A.; Kato, T.; Hagiwara, E.; Shinohara, T.; Komagata, T.; Iwasawa, T.; Satoh, H.; Tamura, K.; Kasamatsu, T.; Hayashihara, K.; et al. Metastatic Brain Tumors from Non-Small Cell Lung Cancer with EGFR Mutations: Distinguishing Influence of Exon 19 Deletion on Radiographic Features. *Lung Cancer* **2012**, *77*, 64–69. [CrossRef]
53. Lynch, T.J.; Bell, D.W.; Sordella, R.; Gurubhagavatula, S.; Okimoto, R.A.; Brannigan, B.W.; Harris, P.L.; Haserlat, S.M.; Supko, J.G.; Haluska, F.G.; et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. *N. Engl. J. Med.* **2004**, *350*, 2129–2139. [CrossRef]
54. Paez, J.G.; Jänne, P.A.; Lee, J.C.; Tracy, S.; Greulich, H.; Gabriel, S.; Herman, P.; Kaye, F.J.; Lindeman, N.; Boggon, T.J.; et al. EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy. *Science* **2004**, *304*, 1497–1500. [CrossRef] [PubMed]
55. Mok, T.S.; Wu, Y.-L.; Thongprasert, S.; Yang, C.-H.; Chu, D.-T.; Saijo, N.; Sunpaweravong, P.; Han, B.; Margono, B.; Ichinose, Y.; et al. Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. *N. Engl. J. Med.* **2009**, *361*, 947–957. [CrossRef]
56. Mitsudomi, T.; Morita, S.; Yatabe, Y.; Negoro, S.; Okamoto, I.; Tsurutani, J.; Seto, T.; Satouchi, M.; Tada, H.; Hirashima, T.; et al. Gefitinib versus Cisplatin plus Docetaxel in Patients with Non-Small-Cell Lung Cancer Harbouring Mutations of the Epidermal Growth Factor Receptor (WJTOG3405): An Open Label, Randomised Phase 3 Trial. *Lancet Oncol.* **2010**, *11*, 121–128. [CrossRef]
57. Tan, J.; Li, M.; Zhong, W.; Hu, C.; Gu, Q.; Xie, Y. Tyrosine Kinase Inhibitors Show Different Anti-Brain Metastases Efficacy in NSCLC: A Direct Comparative Analysis of Icotinib, Gefitinib, and Erlotinib in a Nude Mouse Model. *Oncotarget* **2017**, *8*, 98771–98781. [CrossRef] [PubMed]
58. Chen, Y.; Wang, M.; Zhong, W.; Zhao, J. Pharmacokinetic and Pharmacodynamic Study of Gefitinib in a Mouse Model of Non-Small-Cell Lung Carcinoma with Brain Metastasis. *Lung Cancer* **2013**, *82*, 313–318. [CrossRef]
59. Zeng, Y.-D.; Liao, H.; Qin, T.; Zhang, L.; Wei, W.-D.; Liang, J.-Z.; Xu, F.; Dinglin, X.-X.; Ma, S.-X.; Chen, L.-K. Blood-Brain Barrier Permeability of Gefitinib in Patients with Brain Metastases from Non-Small-Cell Lung Cancer before and during Whole Brain Radiation Therapy. *Oncotarget* **2015**, *6*, 8366–8376. [CrossRef] [PubMed]
60. Welsh, J.W.; Komaki, R.; Amini, A.; Munsell, M.F.; Unger, W.; Allen, P.K.; Chang, J.Y.; Wefel, J.S.; McGovern, S.L.; Garland, L.L.; et al. Phase II Trial of Erlotinib plus Concurrent Whole-Brain Radiation Therapy for Patients with Brain Metastases from Non-Small-Cell Lung Cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2013**, *31*, 895–902. [CrossRef] [PubMed]
61. Iuchi, T.; Shingyoji, M.; Sakaida, T.; Hatano, K.; Nagano, O.; Itakura, M.; Kageyama, H.; Yokoi, S.; Hasegawa, Y.; Kawasaki, K.; et al. Phase II Trial of Gefitinib Alone without Radiation Therapy for Japanese Patients with Brain Metastases from EGFR-Mutant Lung Adenocarcinoma. *Lung Cancer* **2013**, *82*, 282–287. [CrossRef] [PubMed]
62. Schuler, M.; Wu, Y.-L.; Hirsh, V.; O'Byrne, K.; Yamamoto, N.; Mok, T.; Popat, S.; Sequist, L.V.; Massey, D.; Zazulina, V.; et al. First-Line Afatinib versus Chemotherapy in Patients with Non–Small Cell Lung Cancer and Common Epidermal Growth Factor Receptor Gene Mutations and Brain Metastases. *J. Thorac. Oncol.* **2016**, *11*, 380–390. [CrossRef]
63. Wei, Y.-F.; Lim, C.-K.; Tsai, M.-S.; Huang, M.-S.; Chen, K.-Y. Intracranial Responses to Afatinib at Different Doses in Patients With EGFR-Mutated Non-Small-Cell Lung Carcinoma and Brain Metastases. *Clin. Lung Cancer* **2019**, *20*, e274–e283. [CrossRef] [PubMed]
64. Oxnard, G.R.; Arcila, M.E.; Sima, C.S.; Riely, G.J.; Chmielecki, J.; Kris, M.G.; Pao, W.; Ladanyi, M.; Miller, V.A. Acquired Resistance to EGFR Tyrosine Kinase Inhibitors in EGFR-Mutant Lung Cancer: Distinct Natural History of Patients with Tumors Harboring the T790M Mutation. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2011**, *17*, 1616–1622. [CrossRef] [PubMed]
65. Mujoomdar, A.; Austin, J.H.M.; Malhotra, R.; Powell, C.A.; Pearson, G.D.N.; Shiau, M.C.; Raftopoulos, H. Clinical Predictors of Metastatic Disease to the Brain from Non-Small Cell Lung Carcinoma: Primary Tumor Size, Cell Type, and Lymph Node Metastases. *Radiology* **2007**, *242*, 882–888. [CrossRef]
66. Heon, S.; Yeap, B.Y.; Britt, G.J.; Costa, D.B.; Rabin, M.S.; Jackman, D.M.; Johnson, B.E. Development of Central Nervous System Metastases in Patients with Advanced Non-Small Cell Lung Cancer and Somatic EGFR Mutations Treated with Gefitinib or Erlotinib. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2010**, *16*, 5873–5882. [CrossRef]

67. Ballard, P.; Yates, J.W.T.; Yang, Z.; Kim, D.-W.; Yang, J.C.-H.; Cantarini, M.; Pickup, K.; Jordan, A.; Hickey, M.; Grist, M.; et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. *Clin. Cancer Res.* **2016**, *22*, 5130–5140. [CrossRef] [PubMed]
68. Soria, J.-C.; Ohe, Y.; Vansteenkiste, J.; Reungwetwattana, T.; Chewaskulyong, B.; Lee, K.H.; Dechaphunkul, A.; Imamura, F.; Nogami, N.; Kurata, T.; et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *378*, 113–125. [CrossRef] [PubMed]
69. Ramalingam, S.S.; Vansteenkiste, J.; Planchard, D.; Cho, B.C.; Gray, J.E.; Ohe, Y.; Zhou, C.; Reungwetwattana, T.; Cheng, Y.; Chewaskulyong, B.; et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N. Engl. J. Med.* **2020**, *382*, 41–50. [CrossRef] [PubMed]
70. Goss, G.; Tsai, C.-M.; Shepherd, F.A.; Ahn, M.-J.; Bazhenova, L.; Crinò, L.; De Marinis, F.; Felip, E.; Morabito, A.; Hodge, R.; 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*, 687–693. [CrossRef]
71. Zhang, I.; Zaorsky, N.G.; Palmer, J.D.; Mehra, R.; Lu, B. Targeting Brain Metastases in ALK-Rearranged Non-Small-Cell Lung Cancer. *Lancet Oncol.* **2015**, *16*, e510–e521. [CrossRef]
72. Solomon, B.J.; Mok, T.; Kim, D.-W.; Wu, Y.-L.; Nakagawa, K.; Mekhail, T.; Felip, E.; Cappuzzo, F.; Paolini, J.; Usari, T.; et al. First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. *N. Engl. J. Med.* **2014**, *371*, 2167–2177. [CrossRef] [PubMed]
73. Costa, D.B.; Kobayashi, S.; Pandya, S.S.; Yeo, W.-L.; Shen, Z.; Tan, W.; Wilner, K.D. CSF Concentration of the Anaplastic Lymphoma Kinase Inhibitor Crizotinib. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2011**, *29*, e443–e445. [CrossRef] [PubMed]
74. Metro, G.; Lunardi, G.; Floridi, P.; Pascali, J.P.; Marcomigni, L.; Chiari, R.; Ludovini, V.; Crinò, L.; Gori, S. CSF Concentration of Crizotinib in Two ALK-Positive Non-Small-Cell Lung Cancer Patients with CNS Metastases Deriving Clinical Benefit from Treatment. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2015**, *10*, e26–e27. [CrossRef] [PubMed]
75. Ricciuti, B.; De Giglio, A.; Mecca, C.; Arcuri, C.; Marini, S.; Metro, G.; Baglivo, S.; Sidoni, A.; Bellezza, G.; Crinò, L.; et al. Precision Medicine against ALK-Positive Non-Small Cell Lung Cancer: Beyond Crizotinib. *Med. Oncol.* **2018**, *35*, 72. [CrossRef]
76. Peters, S.; Camidge, D.R.; Shaw, A.T.; Gadgeel, S.; Ahn, J.S.; Kim, D.-W.; Ou, S.-H.I.; Pérol, M.; Dziadziuszko, R.; Rosell, R.; et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2017**, *377*, 829–838. [CrossRef] [PubMed]
77. Camidge, D.R.; Kim, H.R.; Ahn, M.-J.; Yang, J.C.-H.; Han, J.-Y.; Lee, J.-S.; Hochmair, M.J.; Li, J.Y.-C.; Chang, G.-C.; Lee, K.H.; et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *379*, 2027–2039. [CrossRef]
78. Tomasini, P.; Egea, J.; Souquet-Bressand, M.; Greillier, L.; Barlesi, F. Alectinib in the Treatment of ALK-Positive Metastatic Non-Small Cell Lung Cancer: Clinical Trial Evidence and Experience with a Focus on Brain Metastases. *Ther. Adv. Respir. Dis.* **2019**, *13*, 1753466619831906. [CrossRef]
79. Johnson, T.W.; Richardson, P.F.; Bailey, S.; Brooun, A.; Burke, B.J.; Collins, M.R.; Cui, J.J.; Deal, J.G.; Deng, Y.-L.; Dinh, D.; et al. Discovery of (10R)-7-Amino-12-Fluoro-2,10,16-Trimethyl-15-Oxo-10,15,16,17-Tetrahydro-2H-8,4-(Metheno)Pyrazolo[4,3-h][2,5,11]-Benzoxadiazacyclotetradecine-3-Carbonitrile (PF-06463922), a Macrocyclic Inhibitor of Anaplastic Lymphoma Kinase (ALK) and c-Ros Oncogene 1 (ROS1) with Preclinical Brain Exposure and Broad-Spectrum Potency against ALK-Resistant Mutations. *J. Med. Chem.* **2014**, *57*, 4720–4744. [CrossRef]
80. Shaw, A.T.; Bauer, T.M.; De Marinis, F.; Felip, E.; Goto, Y.; Liu, G.; Mazieres, J.; Kim, D.-W.; Mok, T.; Polli, A.; et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. *N. Engl. J. Med.* **2020**, *383*, 2018–2029. [CrossRef]
81. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer Statistics, 2015. *CA Cancer J. Clin.* **2015**, *65*, 5–29. [CrossRef]
82. Colombino, M.; Capone, M.; Lissia, A.; Cossu, A.; Rubino, C.; De Giorgi, V.; Massi, D.; Fonsatti, E.; Staibano, S.; Nappi, O.; et al. *BRAF/NRAS* Mutation Frequencies Among Primary Tumors and Metastases in Patients with Melanoma. *J. Clin. Oncol.* **2012**, *30*, 2522–2529. [CrossRef]
83. McArthur, G.A.; Maio, M.; Arance, A.; Nathan, P.; Blank, C.; Avril, M.-F.; Garbe, C.; Hauschild, A.; Schadendorf, D.; Hamid, O.; 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*, 634–641. [CrossRef]
84. Long, G.V.; Stroyakovskiy, D.; Gogas, H.; Levchenko, E.; De Braud, F.; Larkin, J.; Garbe, C.; Jouary, T.; Hauschild, A.; Grob, J.J.; et al. Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. *N. Engl. J. Med.* **2014**, *371*, 1877–1888. [CrossRef]
85. Geukes Foppen, M.H.; Boogerd, W.; Blank, C.U.; Van Thienen, J.V.; Haanen, J.B.; Brandsma, D. Clinical and Radiological Response of BRAF Inhibition and MEK Inhibition in Patients with Brain Metastases from BRAF-Mutated Melanoma. *Melanoma Res.* **2018**, *28*, 126–133. [CrossRef] [PubMed]
86. Lin, N.U.; Diéras, V.; Paul, D.; Lossignol, D.; Christodoulou, C.; Stemmler, H.-J.; Roché, H.; Liu, M.C.; Greil, R.; Ciruelos, E.; et al. Multicenter Phase II Study of Lapatinib in Patients with Brain Metastases from HER2-Positive Breast Cancer. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2009**, *15*, 1452–1459. [CrossRef] [PubMed]
87. Bachelot, T.; Romieu, G.; Campone, M.; Diéras, V.; Cropet, C.; Dalenc, F.; Jimenez, M.; Le Rhun, E.; Pierga, J.-Y.; Gonçalves, A.; et al. Lapatinib plus Capecitabine in Patients with Previously Untreated Brain Metastases from HER2-Positive Metastatic Breast Cancer (LANDSCAPE): A Single-Group Phase 2 Study. *Lancet Oncol.* **2013**, *14*, 64–71. [CrossRef]
88. Shawky, H.; Tawfik, H. All-Oral Combination of Lapatinib and Capecitabine in Patients with Brain Metastases from HER2-Positive Breast Cancer—A Phase II Study. *J. Egypt. Natl. Cancer Inst.* **2014**, *26*, 187–194. [CrossRef] [PubMed]

89. Cortés, J.; Dieras, V.; Ro, J.; Barriere, J.; Bachelot, T.; Hurvitz, S.; Le Rhun, E.; Espié, M.; Kim, S.-B.; Schneeweiss, A.; et al. Afatinib Alone or Afatinib plus Vinorelbine versus Investigator's Choice of Treatment for HER2-Positive Breast Cancer with Progressive Brain Metastases after Trastuzumab, Lapatinib, or Both (LUX-Breast 3): A Randomised, Open-Label, Multicentre, Phase 2 Trial. *Lancet Oncol.* **2015**, *16*, 1700–1710. [CrossRef] [PubMed]
90. Shaw, A.T.; Solomon, B.J.; Chiari, R.; Riely, G.J.; Besse, B.; Soo, R.A.; Kao, S.; Lin, C.-C.; Bauer, T.M.; Clancy, J.S.; 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**, *20*, 1691–1701. [CrossRef]
91. Novello, S.; Mazières, J.; Oh, I.-J.; De Castro, J.; Migliorino, M.R.; Helland, Å.; Dziadziuszko, R.; Griesinger, F.; Kotb, A.; Zeaiter, A.; 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. Off. J. Eur. Soc. Med. Oncol.* **2018**, *29*, 1409–1416. [CrossRef]
92. Ou, S.-H.I.; Ahn, J.S.; De Petris, L.; Govindan, R.; Yang, J.C.-H.; Hughes, B.; Lena, H.; Moro-Sibilot, D.; Bearz, A.; Ramirez, S.V.; et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2016**, *34*, 661–668. [CrossRef]
93. Shaw, A.T.; Gandhi, L.; Gadgeel, S.; Riely, G.J.; Cetnar, J.; West, H.; Camidge, D.R.; Socinski, M.A.; Chiappori, A.; Mekhail, T.; et al. Alectinib in ALK-Positive, Crizotinib-Resistant, Non-Small-Cell Lung Cancer: A Single-Group, Multicentre, Phase 2 Trial. *Lancet Oncol.* **2016**, *17*, 234–242. [CrossRef]
94. Colclough, N.; Chen, K.; Johnström, P.; Strittmatter, N.; Yan, Y.; Wrigley, G.L.; Schou, M.; Goodwin, R.; Varnäs, K.; Adua, S.J.; et al. Preclinical Comparison of the Blood–Brain Barrier Permeability of Osimertinib with Other EGFR TKIs. *Clin. Cancer Res.* **2021**, *27*, 189–201. [CrossRef]
95. Varrone, A.; Varnäs, K.; Jucaite, A.; Cselényi, Z.; Johnström, P.; Schou, M.; Vazquez-Romero, A.; Moein, M.M.; Halldin, C.; Brown, A.P.; et al. A PET Study in Healthy Subjects of Brain Exposure of 11C-Labelled Osimertinib—A Drug Intended for Treatment of Brain Metastases in Non-Small Cell Lung Cancer. *J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* **2020**, *40*, 799–807. [CrossRef] [PubMed]
96. Sakji-Dupré, L.; Le Rhun, E.; Templier, C.; Desmedt, E.; Blanchet, B.; Mortier, L. Cerebrospinal Fluid Concentrations of Vemurafenib in Patients Treated for Brain Metastatic BRAF-V600 Mutated Melanoma. *Melanoma Res.* **2015**, *25*, 305. [CrossRef]
97. Durmus, S.; Sparidans, R.W.; Wagenaar, E.; Beijnen, J.H.; Schinkel, A.H. Oral Availability and Brain Penetration of the B-RAFV600E Inhibitor Vemurafenib Can Be Enhanced by the P-GLYCOprotein (ABCB1) and Breast Cancer Resistance Protein (ABCG2) Inhibitor Elacridar. *Mol. Pharm.* **2012**, *9*, 3236–3245. [CrossRef] [PubMed]
98. Mittapalli, R.K.; Vaidhyanathan, S.; Dudek, A.Z.; Elmquist, W.F. Mechanisms Limiting Distribution of the Threonine-Protein Kinase B-RaF(V600E) Inhibitor Dabrafenib to the Brain: Implications for the Treatment of Melanoma Brain Metastases. *J. Pharmacol. Exp. Ther.* **2013**, *344*, 655–664. [CrossRef]
99. Vaidhyanathan, S.; Mittapalli, R.K.; Sarkaria, J.N.; Elmquist, W.F. Factors Influencing the CNS Distribution of a Novel MEK-1/2 Inhibitor: Implications for Combination Therapy for Melanoma Brain Metastases. *Drug Metab. Dispos. Biol. Fate Chem.* **2014**, *42*, 1292–1300. [CrossRef] [PubMed]
100. Choo, E.F.; Ly, J.; Chan, J.; Shahidi-Latham, S.K.; Messick, K.; Plise, E.; Quiason, C.M.; Yang, L. Role of P-Glycoprotein on the Brain Penetration and Brain Pharmacodynamic Activity of the MEK Inhibitor Cobimetinib. *Mol. Pharm.* **2014**, *11*, 4199–4207. [CrossRef]
101. Wang, J.; Gan, C.; Sparidans, R.W.; Wagenaar, E.; Van Hoppe, S.; Beijnen, J.H.; Schinkel, A.H. P-Glycoprotein (MDR1/ABCB1) and Breast Cancer Resistance Protein (BCRP/ABCG2) Affect Brain Accumulation and Intestinal Disposition of Encorafenib in Mice. *Pharmacol. Res.* **2018**, *129*, 414–423. [CrossRef] [PubMed]
102. Gulyaev, A.E.; Gelperina, S.E.; Skidan, I.N.; Antropov, A.S.; Kivman, G.Y.; Kreuter, J. Significant Transport of Doxorubicin into the Brain with Polysorbate 80-Coated Nanoparticles. *Pharm. Res.* **1999**, *16*, 1564–1569. [CrossRef] [PubMed]
103. Gelperina, S.E.; Khalansky, A.S.; Skidan, I.N.; Smirnova, Z.S.; Bobruskin, A.I.; Severin, S.E.; Turowski, B.; Zanella, F.E.; Kreuter, J. Toxicological Studies of Doxorubicin Bound to Polysorbate 80-Coated Poly(Butyl Cyanoacrylate) Nanoparticles in Healthy Rats and Rats with Intracranial Glioblastoma. *Toxicol. Lett.* **2002**, *126*, 131–141. [CrossRef]
104. Nunes, T.; Pons, T.; Hou, X.; Van Do, K.; Caron, B.; Rigal, M.; Di Benedetto, M.; Palpant, B.; Leboeuf, C.; Janin, A.; et al. Pulsed-Laser Irradiation of Multifunctional Gold Nanoshells to Overcome Trastuzumab Resistance in HER2-Overexpressing Breast Cancer. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 306. [CrossRef] [PubMed]
105. Gromnicova, R.; Davies, H.A.; Sreekanthreddy, P.; Romero, I.A.; Lund, T.; Roitt, I.M.; Phillips, J.B.; Male, D.K. Glucose-Coated Gold Nanoparticles Transfer across Human Brain Endothelium and Enter Astrocytes In Vitro. *PLoS ONE* **2013**, *8*, e81043. [CrossRef] [PubMed]
106. Jensen, S.A.; Day, E.S.; Ko, C.H.; Hurley, L.A.; Luciano, J.P.; Kouri, F.M.; Merkel, T.J.; Luthi, A.J.; Patel, P.C.; Cutler, J.I.; et al. Spherical Nucleic Acid Nanoparticle Conjugates as an RNAi-Based Therapy for Glioblastoma. *Sci. Transl. Med.* **2013**, *5*, 209ra152. [CrossRef] [PubMed]
107. Karim, R.; Palazzo, C.; Evrard, B.; Piel, G. Nanocarriers for the Treatment of Glioblastoma Multiforme: Current State-of-the-Art. *J. Control. Release* **2016**, *227*, 23–37. [CrossRef] [PubMed]
108. Koukourakis, M.I.; Koukouraki, S.; Fezoulidis, I.; Kelekis, N.; Kyrias, G.; Archimandritis, S.; Karkavitsas, N. High Intratumoural Accumulation of Stealth®Liposomal Doxorubicin (Caelyx®) in Glioblastomas and in Metastatic Brain Tumours. *Br. J. Cancer* **2000**, *83*, 1281–1286. [CrossRef] [PubMed]

109. Shaw, T.K.; Mandal, D.; Dey, G.; Pal, M.M.; Paul, P.; Chakraborty, S.; Ali, K.A.; Mukherjee, B.; Bandyopadhyay, A.K.; Mandal, M. Successful Delivery of Docetaxel to Rat Brain Using Experimentally Developed Nanoliposome: A Treatment Strategy for Brain Tumor. *Drug Deliv.* **2017**, *24*, 346–357. [CrossRef]
110. Mohammad, A.S.; Griffith, J.I.; Adkins, C.E.; Shah, N.; Sechrest, E.; Dolan, E.L.; Terrell-Hall, T.B.; Hendriks, B.S.; Lee, H.; Lockman, P.R. Liposomal Irinotecan Accumulates in Metastatic Lesions, Crosses the Blood-Tumor Barrier (BTB), and Prolongs Survival in an Experimental Model of Brain Metastases of Triple Negative Breast Cancer. *Pharm. Res.* **2018**, *35*, 1–10. [CrossRef]
111. Lee, H.; Shields, A.F.; Siegel, B.A.; Miller, K.D.; Krop, I.; Ma, C.X.; LoRusso, P.M.; Munster, P.N.; Campbell, K.; Gaddy, D.F.; et al. ^{64} Cu-MM-302 Positron Emission Tomography Quantifies Variability of Enhanced Permeability and Retention of Nanoparticles in Relation to Treatment Response in Patients with Metastatic Breast Cancer. *Clin. Cancer Res.* **2017**, *23*, 4190–4202. [CrossRef]
112. Niza, E.; Ocaña, A.; Castro-Osma, J.A.; Bravo, I.; Alonso-Moreno, C. Polyester Polymeric Nanoparticles as Platforms in the Development of Novel Nanomedicines for Cancer Treatment. *Cancers* **2021**, *13*, 3387. [CrossRef]
113. Kashapov, R.; Ibragimova, A.; Pavlov, R.; Gabdrakhmanov, D.; Kashapova, N.; Burilova, E.; Zakharova, L.; Sinyashin, O. Nanocarriers for Biomedicine: From Lipid Formulations to Inorganic and Hybrid Nanoparticles. *Int. J. Mol. Sci.* **2021**, *22*, 7055. [CrossRef]
114. Wan, X.; Zheng, X.; Pang, X.; Pang, Z.; Zhao, J.; Zhang, Z.; Jiang, T.; Xu, W.; Zhang, Q.; Jiang, X. Lapatinib-Loaded Human Serum Albumin Nanoparticles for the Prevention and Treatment of Triple-Negative Breast Cancer Metastasis to the Brain. *Oncotarget* **2016**, *7*, 34038–34051. [CrossRef] [PubMed]
115. Lin, K.-H.; Hong, S.-T.; Wang, H.-T.; Lo, Y.-L.; Lin, A.M.-Y.; Yang, J.C.-H. Enhancing Anticancer Effect of Gefitinib across the Blood-Brain Barrier Model Using Liposomes Modified with One α-Helical Cell-Penetrating Peptide or Glutathione and Tween 80. *Int. J. Mol. Sci.* **2016**, *17*, 1998. [CrossRef] [PubMed]
116. Shang, X.; Wang, P.; Liu, Y.; Zhang, Z.; Xue, Y. Mechanism of Low-Frequency Ultrasound in Opening Blood-Tumor Barrier by Tight Junction. *J. Mol. Neurosci.* **2011**, *43*, 364–369. [CrossRef] [PubMed]
117. Arvanitis, C.D.; Askoxylakis, V.; Guo, Y.; Datta, M.; Kloepper, J.; Ferraro, G.B.; Bernabeu, M.O.; Fukumura, D.; McDannold, N.; Jain, R.K. Mechanisms of Enhanced Drug Delivery in Brain Metastases with Focused Ultrasound-Induced Blood–Tumor Barrier Disruption. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E8717–E8726. [CrossRef]
118. Carpentier, A.; Canney, M.; Vignot, A.; Reina, V.; Beccaria, K.; Horodyckid, C.; Karachi, C.; Leclercq, D.; Lafon, C.; Chapelon, J.-Y.; et al. Clinical Trial of Blood-Brain Barrier Disruption by Pulsed Ultrasound. *Sci. Transl. Med.* **2016**, *8*, 343re2. [CrossRef]
119. Goldwirt, L.; Canney, M.; Horodyckid, C.; Poupon, J.; Mourah, S.; Vignot, A.; Chapelon, J.-Y.; Carpentier, A. Enhanced Brain Distribution of Carboplatin in a Primate Model after Blood–Brain Barrier Disruption Using an Implantable Ultrasound Device. *Cancer Chemother. Pharmacol.* **2016**, *77*, 211–216. [CrossRef] [PubMed]
120. Goutal, S.; Gerstenmayer, M.; Auvity, S.; Caillé, F.; Mériaux, S.; Buvat, I.; Larrat, B.; Tournier, N. Physical Blood-Brain Barrier Disruption Induced by Focused Ultrasound Does Not Overcome the Transporter-Mediated Efflux of Erlotinib. *J. Control. Release* **2018**, *292*, 210–220. [CrossRef]
121. Chen, Z.; Shi, T.; Zhang, L.; Zhu, P.; Deng, M.; Huang, C.; Hu, T.; Jiang, L.; Li, J. Mammalian Drug Efflux Transporters of the ATP Binding Cassette (ABC) Family in Multidrug Resistance: A Review of the Past Decade. *Cancer Lett.* **2016**, *370*, 153–164. [CrossRef]
122. De Vries, N.A.; Buckle, T.; Zhao, J.; Beijnen, J.H.; Schellens, J.H.M.; Van Tellingen, O. Restricted Brain Penetration of the Tyrosine Kinase Inhibitor Erlotinib Due to the Drug Transporters P-Gp and BCRP. *Investig. New Drugs* **2012**, *30*, 443–449. [CrossRef] [PubMed]
123. Agarwal, S.; Sane, R.; Ohlfest, J.R.; Elmquist, W.F. The Role of the Breast Cancer Resistance Protein (ABCG2) in the Distribution of Sorafenib to the Brain. *J. Pharmacol. Exp. Ther.* **2011**, *336*, 223–233. [CrossRef]
124. Traxl, A.; Mairinger, S.; Filip, T.; Sauberer, M.; Stanek, J.; Poschner, S.; Jäger, W.; Zoufal, V.; Novarino, G.; Tournier, N.; et al. Inhibition of ABCB1 and ABCG2 at the Mouse Blood-Brain Barrier with Marketed Drugs To Improve Brain Delivery of the Model ABCB1/ABCG2 Substrate [11C]Erlotinib. *Mol. Pharm.* **2019**, *16*, 1282–1293. [CrossRef]
125. Van Hoppe, S.; Jamalpoor, A.; Rood, J.J.M.; Wagenaar, E.; Sparidans, R.W.; Beijnen, J.H.; Schinkel, A.H. Brain Accumulation of Osimertinib and Its Active Metabolite AZ5104 Is Restricted by ABCB1 (P-Glycoprotein) and ABCG2 (Breast Cancer Resistance Protein). *Pharmacol. Res.* **2019**, *146*, 104297. [CrossRef]
126. Tournier, N.; Goutal, S.; Auvity, S.; Traxl, A.; Mairinger, S.; Wanek, T.; Helal, O.-B.; Buvat, I.; Soussan, M.; Caillé, F.; et al. Strategies to Inhibit ABCB1- and ABCG2-Mediated Efflux Transport of Erlotinib at the Blood-Brain Barrier: A PET Study on Nonhuman Primates. *J. Nucl. Med. Off. Publ. Soc. Nucl. Med.* **2017**, *58*, 117–122. [CrossRef] [PubMed]
127. Van Hoppe, S.; Sparidans, R.W.; Wagenaar, E.; Beijnen, J.H.; Schinkel, A.H. Breast Cancer Resistance Protein (BCRP/ABCG2) and P-Glycoprotein (P-Gp/ABCB1) Transport Afatinib and Restrict Its Oral Availability and Brain Accumulation. *Pharmacol. Res.* **2017**, *120*, 43–50. [CrossRef] [PubMed]
128. Li, W.; Sparidans, R.W.; Wang, Y.; Lebre, M.C.; Wagenaar, E.; Beijnen, J.H.; Schinkel, A.H. P-Glycoprotein (MDR1/ABCB1) Restricts Brain Accumulation and Cytochrome P450-3A (CYP3A) Limits Oral Availability of the Novel ALK/ROS1 Inhibitor Lorlatinib. *Int. J. Cancer* **2018**, *143*, 2029–2038. [CrossRef]
129. Dai, H.; Marbach, P.; Lemaire, M.; Hayes, M.; Elmquist, W.F. Distribution of STI-571 to the Brain Is Limited by P-Glycoprotein-Mediated Efflux. *J. Pharmacol. Exp. Ther.* **2003**, *304*, 1085–1092. [CrossRef] [PubMed]
130. Tang, S.C.; Lagas, J.S.; Lankheet, N.A.G.; Poller, B.; Hillebrand, M.J.; Rosing, H.; Beijnen, J.H.; Schinkel, A.H. Brain Accumulation of Sunitinib Is Restricted by P-Glycoprotein (ABCB1) and Breast Cancer Resistance Protein (ABCG2) and Can Be Enhanced by Oral Elacridar and Sunitinib Coadministration. *Int. J. Cancer* **2012**, *130*, 223–233. [CrossRef] [PubMed]

131. Karbownik, A.; Sobańska, K.; Płotek, W.; Grabowski, T.; Klupczynska, A.; Plewa, S.; Grześkowiak, E.; Szałek, E. The Influence of the Coadministration of the P-Glycoprotein Modulator Elacridar on the Pharmacokinetics of Lapatinib and Its Distribution in the Brain and Cerebrospinal Fluid. *Investig. New Drugs* **2020**, *38*, 574–583. [CrossRef] [PubMed]
132. Tang, S.C.; Nguyen, L.N.; Sparidans, R.W.; Wagenaar, E.; Beijnen, J.H.; Schinkel, A.H. Increased Oral Availability and Brain Accumulation of the ALK Inhibitor Crizotinib by Coadministration of the P-Glycoprotein (ABCB1) and Breast Cancer Resistance Protein (ABCG2) Inhibitor Elacridar. *Int. J. Cancer* **2014**, *134*, 1484–1494. [CrossRef] [PubMed]
133. Agarwal, S.; Sane, R.; Gallardo, J.L.; Ohlfest, J.R.; Elmquist, W.F. 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. [CrossRef] [PubMed]
134. Colclough, N.; Chen, K.; Johnström, P.; Fridén, M.; McGinnity, D.F. Building on the Success of Osimertinib: Achieving CNS Exposure in Oncology Drug Discovery. *Drug Discov. Today* **2019**, *24*, 1067–1073. [CrossRef] [PubMed]
135. Varadharajan, S.; Winiwarter, S.; Carlsson, L.; Engkvist, O.; Anantha, A.; Kogej, T.; Fridén, M.; Stålring, J.; Chen, H. Exploring in Silico Prediction of the Unbound Brain-to-Plasma Drug Concentration Ratio: Model Validation, Renewal, and Interpretation. *J. Pharm. Sci.* **2015**, *104*, 1197–1206. [CrossRef]
136. Zeng, Q.; Wang, J.; Cheng, Z.; Chen, K.; Johnström, P.; Varnäs, K.; Li, D.Y.; Yang, Z.F.; Zhang, X. Discovery and Evaluation of Clinical Candidate AZD3759, a Potent, Oral Active, Central Nervous System-Penetrant, Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2015**, *58*, 8200–8215. [CrossRef]