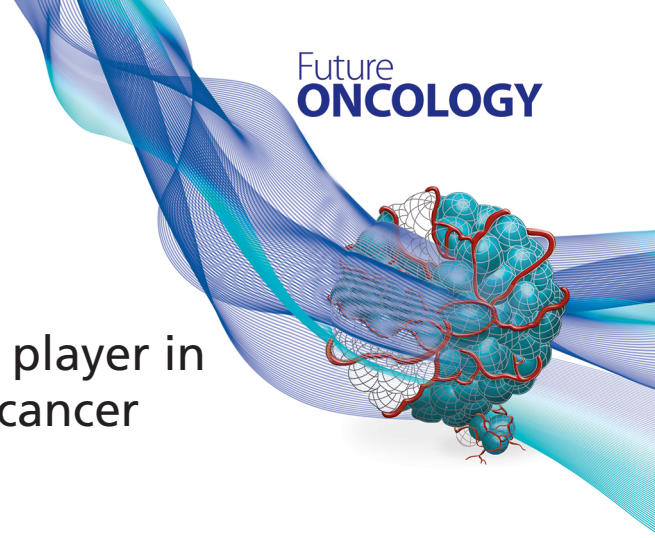
Drug Evaluation

For reprint orders, please contact: reprints@futuremedicine.com

Future ONCOLOGY



Neratinib: the emergence of a new player in the management of HER2+ breast cancer brain metastasis

Azadeh Nasrazadani[1] & Adam Brufsky*,[2]
[1]UPMC Hillman Cancer Center, University of Pittsburgh, 5115 Centre Ave, Pittsburgh, PA 15232, USA
[2]UPMC Hillman Cancer Center, Magee Women's Hospital, Suite 4628, 300 Halket Street, Pittsburgh, PA 15213, USA
*Author for correspondence: brufskyam@upmc.edu

HER2-positive (HER2+) breast cancer has become an effectively treatable disease in the era of targeted therapies, and outcomes have improved such that prognosis of this subtype is demonstrated to be superior to HER2-negative disease. Despite these advances, durable responses in HER2+ metastatic disease are challenged by the increased risk for brain metastasis. Neratinib is an irreversible pan-HER kinase inhibitor that has emerged as an effective agent when combined with capecitabine for the management of HER2+ metastatic breast cancer patients with brain metastasis. The randomized, Phase III, NALA trial compares neratinib plus capecitabine to a currently prevailing regimen of lapatinib plus capecitabine and is provided herein. Analysis of NALA portends meaningful changes on the horizon for the management of HER2+ metastatic breast cancer.

First draft submitted: 6 November 2019; Accepted for publication: 15 January 2020; Published online: 14 February 2020

Keywords: breast • metastasis • molecular oncology • novel therapy

A once formidable diagnosis, HER2-positive (HER2+) breast cancer has become an effectively treatable disease in the era of targeted therapies. With the approval of trastuzumab, a recombinant monoclonal antibody against HER2, outcomes have improved such that prognosis of this subtype is demonstrated to be superior to HER2-negative disease [1,2]. Despite these advances, durable responses are challenged by the increased risk for brain metastasis encountered in HER2+ breast cancer. The estimated incidence of symptomatic brain metastasis among women with metastatic breast cancer (MBC) regardless of HER2 status is reported to be 10–16% [3], and up to 24% by a more recent study [4], but have even been described as occurring after diagnosis of early stage I disease [5].

Within the HER2+ MBC population, central nervous system (CNS) metastasis is seen in a reported 34–37% of patients [6,7]. In the recently reported SystHERs prospective registry of newly diagnosed patients with HER2+ MBC, 8.9% present with CNS metastasis at diagnosis, with an additional 21.7% of patients developing CNS metastasis after diagnosis [8]. CNS metastasis occurs with a higher likelihood in younger patients, in those with hormone receptor negative disease, and in patients with a higher disease burden; implicating a more aggressive subpopulation [6–9]. While trastuzumab does improve survival in these patients, many are diagnosed with brain metastasis within the initial six months of treatment, suggesting a higher incidence of occult disease not appreciated on initial diagnosis [6,7,10]. Prior to the availability of many of our current therapeutic options, median survival in patients developing recurrence in the CNS in MBC was estimated to be only 4 months [9], although this has been extended to 20.3–27 months with use of trastuzumab, chemotherapy or surgery [7].

Surgical & radiation centered management

En bloc surgical resection is certainly desirable when possible; however, this relies on the presence of limited sites of disease that are surgically accessible in patients with an otherwise reasonable functional status [11,12]. Stereotactic radiosurgery (SRS) is an attractive alternative that delivers photon radiation with high precision to achieve local control, but is associated with high rates of complications, namely neurological and varying depending on whether functional brain regions are involved [13]. It is generally favored over whole brain radiation (WBRT), which is

Future Medicine

considered in more diffuse CNS disease, although used unenthusiastically due to its well appreciated adverse effects on cognitive function and quality of life [14]. The most recent ESO-ESMO International Consensus guidelines for advanced breast cancer (ABC 4) provide level IB recommendations for resection of small and potentially resectable brain metastasis and a level IC recommendation for consideration of subsequent WBRT upon discussion with the patient [15]. SRS is preferred to WBRT especially in patients with HER2+ disease given the potential for otherwise durable responses to therapy in this population and a desire to minimize toxicity. Ultimately, surgical or radiation based therapies are most effective in cases in which the disease is well controlled systemically, necessitating us to look toward systemic therapies [13]. Specific to cases in which recurrence of HER2+ disease occurs in the brain only, ABC 4 guidelines notably recommend against addition of chemotherapy given its anticipated lack of effect on the course of disease [15].

Systemic therapies for management of brain metastasis

The penetrance of chemotherapy to the CNS is limited by the blood–brain barrier (BBB) – as with other pharmacologic agents – although, it is suggested that there are deficits in barrier integrity in the case of primary and metastatic brain tumors with subsequent increased permeability in the BBB [16]. As compared with other solid tumors, breast cancer brain metastases are thought to be intermediately chemosensitive with response rates of 0–58% across various chemotherapy agents or combinations of therapies [17,18]. Objective responses in brain metastasis have been demonstrated in roughly half of a population treated with cyclophosphamide and 5-fluorouracil, or methotrexate and vincristine, and correlates with extracranial disease control. However, only one in six patients (17%) had a response to cyclophosphamide and doxorubicin [19]. In a separate study, response was noted in 59% of patients treated with cyclophosphamide and 5-fluorouriacil, and either methotrexate or doxorubicin, with reported objective tumor regression in 76% after two courses of chemotherapy [20]. Conversely, prior treatment with docetaxel has been associated with an increased incidence of brain metastasis vs metastasis at other sites [21]. The literature available notably does not make distinctions for HER2+ populations as many of these studies either predate biomarker testing or contain small cohorts inadequate for statistical comparisons. Congruent with findings observed in patient cohorts, *in vivo* models have confirmed the poor distribution of paclitaxel and doxorubicin in the CNS upon tail vein introduction in mice despite increased BBB permeability [22].

HER2-directed therapies

Among HER2 directed therapies, trastuzumab has been noted to significantly increase the risk of developing CNS metastasis across multiple studies including patients with stage I–III HER2+ invasive breast cancer [23,24]. Improved outcomes in patients with HER2+ disease treated with trastuzumab serves as a confounding factor in this regard. The development of CNS recurrence may in actuality be reflecting an overall improved systemic control of the disease and the lesser extent of its efficacy in control of CNS metastasis. An exploratory analysis of the Phase III CLEOPATRA trial demonstrated a delay in onset of CNS disease with the addition of pertuzumab to trastuzumab and docetaxel in HER2+ MBC [25]. This potentially indicates some level of BBB penetrance with this combination versus more likely effective control of systemic disease leading to fewer circulating tumor cells available to metastasize. In *in vivo* studies reported by Terrell-Hall *et al.*, radiolabeled trastuzumab injected intra-cardiac in mice harboring HER2+ brain metastases demonstrate only roughly 5% of the injected dose reaching the tumor [26].

Upon progression with trastuzumab containing regimens, lapatinib became of increasing interest based on preclinical studies demonstrating activity against breast cancer brain metastasis in a murine model [27]. Lapatinib is a reversible EGFR(HER1)/ErbB2(HER2) inhibitor that is US FDA approved for the treatment of MBC overexpressing HER2 for use in combination with capecitabine in patients previously treated with standard therapies [28]. In the Phase II EGF105084 study, lapatinib monotherapy demonstrated an over 20% volumetric reduction in CNS lesions in 21% of patients, increased to over 40% of patients in combination with capecitabine [29]. In the subsequent Phase II LANDSCAPE trial, an objective response of over 50% volumetric reduction was reported in 65.9% treated with lapatinib and capecitabine, which similarly included heavily pretreated patients previously on trastuzumab based therapy although without prior radiation therapy [30]. Note that while RECIST 1.1 criteria considers partial response to be an at least 30% reduction in the sum of diameters in target lesions [31], a 30% unidimensional reduction in a perfect sphere would correspond to a 65% volumetric reduction. Across multiple studies, however, a 20% volumetric reduction is considered clinically meaningful [32,33]. An extension of median overall survival (OS) to 27.9 months from time of brain metastasis development in patients treated with lapatinib

and capecitabine was separately reported, as compared with 16.7 months in patients continued on trastuzumab based therapies [34].

A portion of patients remain, however, that either do not respond to lapatinib or do not sustain responses due to the eventual development of resistance mechanisms, including upregulation of compensatory mechanisms, mutations in the HER2 TK domain, or select gene amplifications [35]. Trastuzumab emtansine (T-DM1), an anti-HER2 antibody–drug conjugate has notably demonstrated superior outcomes in HER2+ MBC patients when compared with the lapatinib and capecitabine combination in the KATHERINE trial [36]. However, patients with symptomatic or recently treated CNS metastases were excluded, and outcomes with regards to development of brain metastasis were not described.

Neratinib

Neratinib is a chloroanilino-quinazoline inhibitor of HER2 [37], and similar to lapatinib is a type II kinase inhibitor, which binds the ATP kinase domain in its inactive conformation, thus accessing an adjacent allosteric binding pocket that confers greater selectivity. It has received FDA approval in the adjuvant setting for extended treatment of early stage HER2+ breast cancer following trastuzumab-based therapy. In contrast to lapatinib, neratinib is a less selective irreversible inhibitor considered to be a pan-HER kinase inhibitor, additionally targeting EGFR (HER1) and HER4 [38]. In preclinical *in vitro* models, neratinib (referred to by its chemical compound name HKI-272) potently and selectively inhibited the proliferation of HER2 overexpressing breast cancer cell lines. On a more mechanistic level, HKI-272 was found to reduce HER2 receptor autophosphorylation, ultimately leading to hindered downstream MAPK and AKT phosphorylation [39]. In breast cancer cell lines with acquired trastuzumab resistance, neratinib not only decreased HER2 and HER3 phosphorylation, but also inhibited growth both alone and synergistically with trastuzumab [40].

Orthotopic tumor growth and brain metastasis is significantly impaired with neratinib treatment in the syngeneic TBCP-1 murine model for HER2+ breast cancer, and uniquely demonstrates caspase-independent ferroptosis not observed with other tyrosine kinase inhibitors (TKIs) [41]. In nude mice xenografted with multidrug resistant (MDR) cells which overexpress ATP binding cassette (ABC) transporters, neratinib overcomes resistance to paclitaxel, as well as enhances accumulation of doxorubicin within resistant cells. ABC transporters are integral to maintaining protective barriers such as the BBB and preventing penetrance of antineoplastic therapies. Neratinib specifically binds the drug-binding cavity of the p-glycoprotein (Pg-P) ABCB1, thereby reducing drug efflux and enhancing drug sensitivity particularly in sanctuary sites such as the CNS [42]. This distinctively positions neratinib as a promising agent for breast cancer brain metastasis treatment.

Clinical trials

Daily dosing of neratinib was established at 240 mg in early development studies using the maximum tolerated dose approach increases in levels and a roughly 14-h half-life. The maximum tolerated dose was 320 mg with grade 3 diarrhea causing dose-limiting toxicity [43]. Phase II studies with neratinib in the advanced or metastatic disease setting demonstrated a median progression-free survival (PFS) of 22.3 weeks, and objective response rate (ORR) of 24% in patients previously treated with trastuzumab. PFS and ORR were significantly higher at 39.6 weeks and 56%, respectively, in a trastuzumab naïve cohort, although patients with active CNS were notably excluded from this trial [44]. This is contrasted to early studies with trastuzumab in chemotherapy refractory patients with HER2+ MBC reporting ORR of 15% [45], increased to 24% when combined with cisplatin [46].

In a separate Phase II study specifically evaluating patients with HER2+ MBC with brain metastasis, TBCRC 022 reported low CNS ORR in 8% with neratinib monotherapy in a pretreated population [47]. In direct comparison to lapatinib plus capecitabine, neratinib monotherapy wasn't found to be non-inferior, but also wasn't inferior in advanced and HER2+ MBC, and revealed progression of symptomatic CNS lesions in 9% vs 13% in the lapatinib plus capecitabine regimen [48]. The addition of neratinib to paclitaxel similarly lowered incidence of CNS recurrence and delayed time to CNS metastasis in NEfERT-T when compared with trastuzumab plus paclitaxel (relative risk 0.48 and hazard ratio 0.45, respectively). PFS was otherwise equivalent at 12.9 months [49].

Given the encouraging findings from the aforementioned studies, the combination of neratinib with capecitabine was evaluated in a HER2+ MBC cohort with a remarkable ORR of 57% in patients previously treated with lapatinib and 64% in patients without prior lapatinib exposure [50]. TBCRC 022 Cohort 3A and 3B arms evaluated this combination in patients with brain metastasis without and with prior lapatinib exposure, respectively. CNS ORR indicating a reduction of over 50% of target lesion volumes was demonstrated in 49% of those without

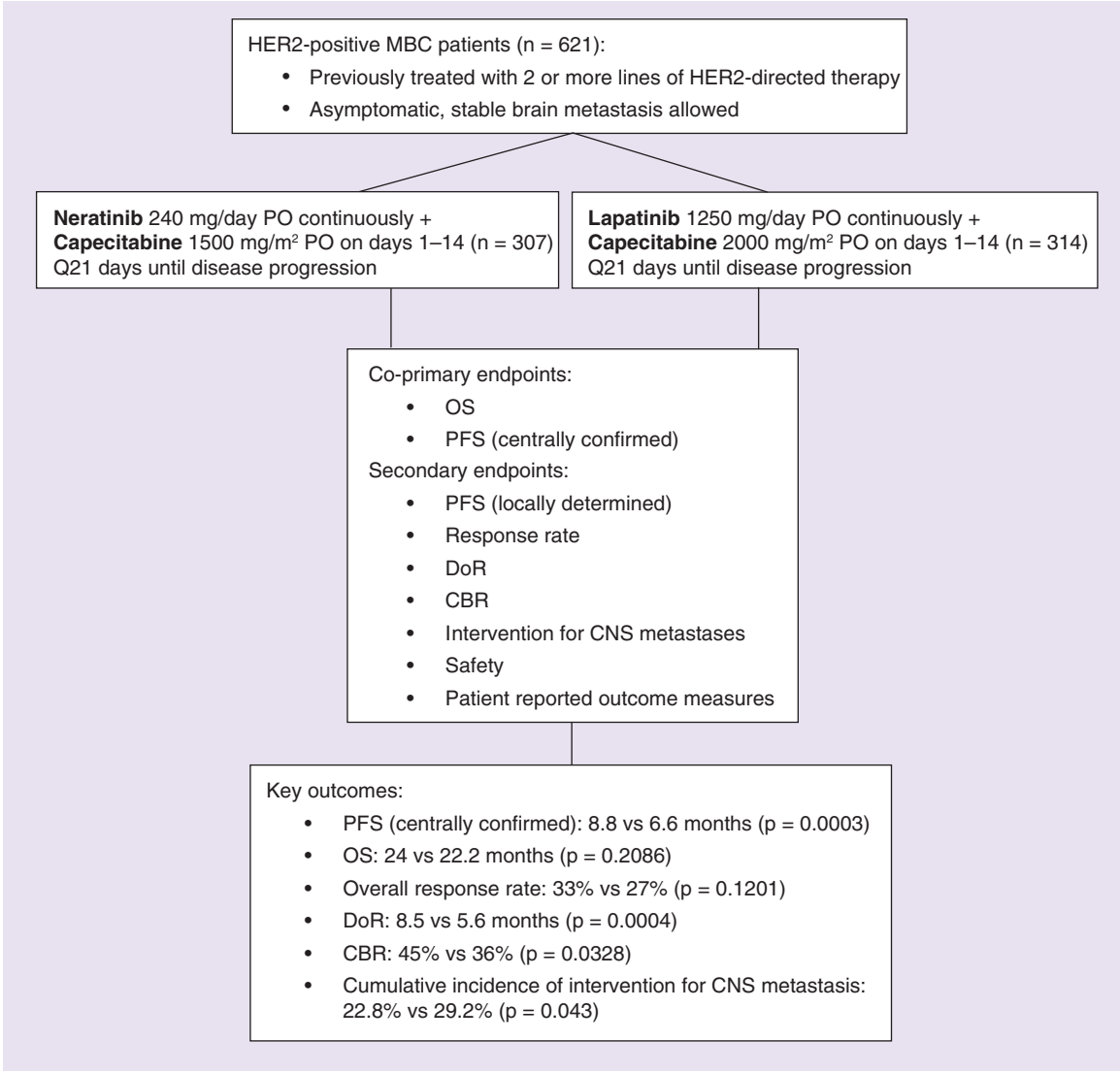


Figure 1. Design of the NALA Study.
CBR: Clinical benefit rate; CNS: Central nervous system; DoR: Duration of response; MBC: Metastatic breast cancer; OS: Overall survival; PFS: Progression-free survival; PO: Per os.

prior lapatinib exposure and 33% with prior exposure, resulting in a median survival of 13.3 and 15.1 months, respectively [51].

Collectively, the efforts of preceding trials have culminated in the initiation of the Phase III, randomized NALA trial, which directly compares neratinib plus capecitabine to lapatinib plus capecitabine in patients with HER2+ MBC previously treated with at least two prior lines of HER2-directed therapies (Figure 1). Preliminary analysis revealed a 24% reduction in the risk of disease progression and a trend toward improved survival in the neratinib combination [52]. More pertinently, time to intervention for symptomatic CNS disease was also delayed, portending meaningful changes on the horizon in the management of metastatic HER2+ breast cancer.

Novel HER2-directed therapies

The recently reported results from the Phase II DESTINY-BREAST01 trial present trastuzumab deruxtecan (DS-8201) as an effective agent in patients previously treated with T-DM1 [53]. DS-8201, similar to T-DM1, is conjugated to a cytotoxic agent, and demonstrates an impressive response rate of 60.9% in a cohort of patients treated with a median of six prior therapies. PFS was reported to be 16.4 months in the intention to treat population, and higher at 18.1 months in the 24 patients enrolled with history of treated or asymptomatic brain metastasis.

While it is not yet known how DS-8201 compares to other HER-directed agents in delaying the incidence of brain metastasis, there is reason for optimism given the reported 86.2% survival rate in treated patients reported at 12 months from initiation of therapy.

Tucatinib, similar to neratinib, is a HER2-selective oral TKI, recently evaluated in HER2CLIMB. The addition of tucatinib to trastuzumab and capecitabine in patients with HER2+ MBC with progression on trastuzumab, pertuzumab and T-DMI resulted in a near doubling of OS at 2 years from 26.6 to 44.9% [54]. Unique to this trial, over 40% of enrolled patients had either untreated or a prior history of treated brain metastasis, which was roughly twice that enrolled in DESTINY-BREAST01. In this sub-population, PFS at 1 year was improved to 24.9 versus 0% with the addition of tucatinib vs placebo.

Regulatory affairs

Neratinib (NERLYNX, Puma Biotechnology, Inc.) initially obtained FDA approval on July 17, 2017 for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. A supplemental New Drug Application (sNDA) has been submitted for use of neratinib in combination with capecitabine for the third-line treatment of patients with HER2+ metastatic disease, with a reported action date of late April, 2020. At present, neratinib has obtained orphan drug designation for the treatment of patients with breast cancer who have brain metastases.

Conclusion

In recent years, multiple novel HER2-directed agents have become available to patients with metastatic HER2+ breast cancer. NALA poises the combination of neratinib and capecitabine as an attractive option among currently approved agents for use in the third line metastatic setting upon progression after T-DM1. On the heels of NALA, DESTINY-BREAST01 and HER2CLIMB offer evidence to also consider DS-8201 and tucatinib, respectively, in the third line metastatic setting. While direct head-to-head comparisons between these novel agents are lacking, combinatorial strategies may add to the individual efficacy achieved with each therapy. Currently, the addition of tucatinib to T-DM1 in T-DM1 naïve patients is actively being evaluated [55]. DESTINY-BREAST03 directly compares DS-8201 to T-DM1 (ClinicalTrials.gov identifier: NCT03529110), results of which may lead to a range of combinations performed in earlier line metastatic settings. Collectively, these studies may reframe our current treatment patterns and offer patients more durable responses to treatment. As we become more sophisticated with the sequencing of our targeted therapies, we are better able to control breast cancer brain metastasis, which at present remains our most challenging obstacle in the management of metastatic HER2+ disease.

Executive summary

Background

- Brain metastasis occurs at a higher incidence in metastatic breast cancer (MBC) patients with HER2-positive (HER2+) disease, which limits our ability to otherwise achieve durable responses with HER2-directed therapies.

Systemic therapies for management of brain metastasis

- While central nervous system (CNS) penetration of chemotherapy and HER2-directed therapies are suboptimal, improved systemic control of HER2+ MBC with novel agents has led to improved outcomes with regards to development and progression of brain metastasis.

Neratinib

- The combination of neratinib with capecitabine in HER2+ MBC delays time to intervention of CNS metastasis as compared with a leading combination of lapatinib plus capecitabine.

Novel HER2-directed therapies

- NALA, DESTINY-BREAST01 and HER2CLIMB support the use of combinations including neratinib, DS-8201 and tucatinib, respectively in the third line setting for management of HER2+ MBC.

Financial & competing interests disclosure

A Brufsky is a Consultant for Puma, Seattle Genetics and Roche/Genentech, Daiichi and AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Company review disclosure

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Slamon DJ, Leyland-Jones B, Shak S *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* 344(11), 783–792 (2001).
2. Kast K, Schoffer O, Link T *et al.* Trastuzumab and survival of patients with metastatic breast cancer. *Arch. Gynecol. Obstet.* 296(2), 303–312 (2017).
3. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J. Clin. Oncol.* 22(17), 3608–3617 (2004).
4. Rostami R, Mittal S, Rostami P, Tavassoli F, Jabbari B. Brain metastasis in breast cancer: a comprehensive literature review. *J. Neurooncol.* 127(3), 407–414 (2016).
5. DiStefano A, Yong Yap Y, Hortobagyi GN, Blumenschein GR. The natural history of breast cancer patients with brain metastases. *Cancer* 44(5), 1913–1918 (1979).
6. Bendell JC, Domchek SM, Burstein HJ *et al.* Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 97(12), 2972–2977 (2003).
7. Brufsky AM, Mayer M, Rugo HS *et al.* Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. *Clin. Cancer Res.* 17(14), 4834–4843 (2011).
8. Hurvitz SA, O'Shaughnessy J, Mason G *et al.* Central nervous system metastasis in patients with HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from SystHERs. *Clin. Cancer Res.* 25(8), 2433–2441 (2019).
9. Pestalozzi BC, Zahrieh D, Price KN *et al.* Identifying breast cancer patients at risk for central nervous system (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). *Ann. Oncol.* 17(6), 935–44 (2006).
10. Tonyali O, Coskun U, Yuksel S *et al.* Risk factors for brain metastasis as a first site of disease recurrence in patients with HER2 positive early stage breast cancer treated with adjuvant trastuzumab. *Breast* 25, 22–6 (2016).
11. Hatiboglu MA, Wildrick DM, Sawaya R. The role of surgical resection in patients with brain metastases. *Ecancermedicalscience* 7, 308 (2013).
12. Leone JP, Leone BA. Breast cancer brain metastases: the last frontier. *Exp. Hematol. Oncol.* 4, 33 (2015).
13. Williams BJ, Suki D, Fox BD *et al.* Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications. *J. Neurosurg.* 111(3), 439–448 (2009).
14. Franchino F, Ruda R, Soffietti R. Mechanisms and therapy for cancer metastasis to the brain. *Front. Oncol.* 8, 161 (2018).
15. Cardoso F, Senkus E, Costa A *et al.* 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) dagger. *Ann. Oncol.* 29(8), 1634–1657 (2018).
16. Deeken JF, Loscher W. The blood–brain barrier and cancer: transporters, treatment, and Trojan horses. *Clin. Cancer Res.* 13(6), 1663–1674 (2007).
17. Soffietti R, Ruda R, Trevisan E. Brain metastases: current management and new developments. *Curr. Opin. Oncol.* 20(6), 676–684 (2008).
18. Tosoni A, Ermani M, Brandes AA. The pathogenesis and treatment of brain metastases: a comprehensive review. *Crit. Rev. Oncol. Hematol.* 52(3), 199–215 (2004).
19. Rosner D, Nemoto T, Lane WW. Chemotherapy induces regression of brain metastases in breast carcinoma. *Cancer* 58(4), 832–839 (1986).
20. Boogerd W, Dalesio O, Bais EM, van der Sande JJ. Response of brain metastases from breast cancer to systemic chemotherapy. *Cancer* 69(4), 972–980 (1992).
21. Bernatz S, Ilina EI, Devraj K *et al.* Impact of Docetaxel on blood–brain barrier function and formation of breast cancer brain metastases. *J. Exp. Clin. Cancer Res.* 38(1), 434 (2019).
22. Lockman PR, Mittapalli RK, Taskar KS *et al.* Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. *Clin. Cancer Res.* 16(23), 5664–5678 (2010).
23. Musolino A, Ciccolallo L, Panebianco M *et al.* Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. *Cancer* 117(9), 1837–1846 (2011).

24. Moja L, Tagliabue L, Balduzzi S *et al.* Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst. Rev.* (4), CD006243 (2012).

25. Swain SM, Baselga J, Miles D *et al.* Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized Phase III study CLEOPATRA. *Ann. Oncol.* 25(6), 1116–1121 (2014).

- **NefERT-T demonstrated a lowered incidence of central nervous system (CNS) recurrence and delayed time to CNS metastasis with neratinib plus paclitacel versus trastuzumab plus paclitaxel.**

26. Terrell-Hall TB, Nounou MI, El-Amrawy F, Griffith JIG, Lockman PR. Trastuzumab distribution in an *in-vivo* and *in-vitro* model of brain metastases of breast cancer. *Oncotarget* 8(48), 83734–83744 (2017).

27. Gril B, Palmieri D, Bronder JL *et al.* Effect of lapatinib on the outgrowth of metastatic breast cancer cells to the brain. *J. Natl Cancer Inst.* 100(15), 1092–1103 (2008).

28. Ryan Q, Ibrahim A, Cohen MH *et al.* FDA drug approval summary: lapatinib in combination with capecitabine for previously treated metastatic breast cancer that overexpresses HER-2. *Oncologist* 13(10), 1114–1119 (2008).

29. Lin NU, Dieras V, Paul D *et al.* Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin. Cancer Res.* 15(4), 1452–1459 (2009).

30. Bachelot T, Romieu G, Campone M *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.* 14(1), 64–71 (2013).

- **Lapatinib plus capecitabine led to a significant volumetric reduction in CNS metastases in a heavily pretreated population.**

31. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45(2), 228–247 (2009).

32. Lin NU, Lee EQ, Aoyama H *et al.* Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol.* 16(6), e270–e278 (2015).

33. Soffietti R, Chiavazza C, Ruda R. Imaging and clinical end points in brain metastases trials. *CNS Oncol.* 6(4), 243–246 (2017).

34. Metro G, Foglietta J, Russillo M *et al.* Clinical outcome of patients with brain metastases from HER2-positive breast cancer treated with lapatinib and capecitabine. *Ann. Oncol.* 22(3), 625–630 (2011).

35. D'Amato V, Raimondo L, Formisano L *et al.* Mechanisms of lapatinib resistance in HER2-driven breast cancer. *Cancer Treat. Rev.* 41(10), 877–883 (2015).

36. Verma S, Miles D, Gianni L *et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. *N. Engl. J. Med.* 367(19), 1783–1791 (2012).

37. Tsou HR, Overbeek-Klumpers EG, Hallett WA *et al.* Optimization of 6,7-disubstituted-4-(arylamino)quinoline-3-carbonitriles as orally active, irreversible inhibitors of human epidermal growth factor receptor-2 kinase activity. *J. Med. Chem.* 48(4), 1107–1131 (2005).

38. Collins DM, Conlon NT, Kannan S *et al.* Preclinical characteristics of the irreversible Pan-HER kinase inhibitor neratinib compared with lapatinib: implications for the treatment of HER2-positive and HER2-mutated breast cancer. *Cancers (Basel)* 11(6), pii: E737 (2019).

39. Rabindran SK, Discafani CM, Rosfjord EC *et al.* Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. *Cancer Res.* 64(11), 3958–3965 (2004).

40. Canonici A, Gijsen M, Mullooly M *et al.* Neratinib overcomes trastuzumab resistance in HER2 amplified breast cancer. *Oncotarget* 4(10), 1592–1605 (2013).

41. Nagpal A, Redvers RP, Ling X *et al.* Neoadjuvant neratinib promotes ferroptosis and inhibits brain metastasis in a novel syngeneic model of spontaneous HER2(+ve) breast cancer metastasis. *Breast Cancer Res.* 21(1), 94 (2019).

42. Zhao XQ, Xie JD, Chen XG *et al.* Neratinib reverses ATP-binding cassette B1-mediated chemotherapeutic drug resistance *in vitro, in vivo,* and *ex vivo*. *Mol. Pharmacol.* 82(1), 47–58 (2012).

- **Describes neratinib's mechanism of action that makes it particularly efficacious in disease in which resistance has developed.**

43. Wong KK, Fracasso PM, Bukowski RM *et al.* A Phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. *Clin. Cancer Res.* 15(7), 2552–2558 (2009).

44. Burstein HJ, Sun Y, Dirix LY *et al.* Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J. Clin. Oncol.* 28(8), 1301–1307 (2010).

45. Cobleigh MA, Vogel CL, Tripathy D *et al.* Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J. Clin. Oncol.* 17(9), 2639–2648 (1999).

46. Pegram MD, Lipton A, Hayes DF *et al.* Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. *J. Clin. Oncol.* 16(8), 2659–2671 (1998).

47. Freedman RA, Gelman RS, Wefel JS *et al.* Translational Breast Cancer Research Consortium (TBCRC) 022: a Phase II trial of neratinib for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J. Clin. Oncol.* 34(9), 945–952 (2016).

48. Martin M, Bonneterre J, Geyer CE Jr. *et al.* A phase two randomised trial of neratinib monotherapy versus lapatinib plus capecitabine combination therapy in patients with HER2+ advanced breast cancer. *Eur. J. Cancer* 49(18), 3763–3772 (2013).

49. Awada A, Colomer R, Inoue K *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.* 2(12), 1557–1564 (2016).

50. Saura C, Garcia-Saenz JA, Xu B *et al.* Safety and efficacy of neratinib in combination with capecitabine in patients with metastatic human epidermal growth factor receptor 2-positive breast cancer. *J. Clin. Oncol.* 32(32), 3626–3633 (2014).

51. Freedman RA, Gelman RS, Anders CK *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.* 37(13), 1081–1089 (2019).

52. Saura C, Oliveira M, Feng Y, Dai M, Hurvitz SA. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥2 HER2-directed regimens: findings from the multinational, randomized, Phase III NALA trial. *J. Clin. Oncol.* 37, 1002–1002 (2019).

•• **Final analysis of NALA reports a delay in time to intervention of CNS metastasis.**

53. Modi S, Saura C, Yamashita T *et al.* Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N. Engl. J. Med.* 382(7), 610– 621 (2019).

•• **This Phase II trial reports impressive response rates with DS-8201 in heavily pretreated patients with HER2-positive metastatic breast cancer.**

54. Murthy RK, Loi S, Okines A *et al.* Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N. Engl. J. Med.* 382(7), 597– 607(2019).

•• **The addition of tucatinib to trastuzumab and capecitabine demonstrates significant improvements in outcomes in patients with HER2 positive metastatic breast cancer with brain metastasis.**

55. Borges VF, Ferrario C, Aucoin N *et al.* Tucatinib combined with ado-trastuzumab emtansine in advanced ERBB2/HER2-positive metastatic breast cancer: a Phase 1b clinical trial. *JAMA Oncol.* 4(9), 1214–1220 (2018).