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LCCC 1025: a phase II study of everolimus, trastuzumab, and vinorelbine to treat progressive HER2-positive breast cancer brain metastases

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Data Availability The datasets generated during and/or analyzed during the current study will be made available in the dbGAP repository.

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Compliance with Ethical Standards

Conflict of interest Carey K. Anders is an uncompensated consultant/advisory board member for Novartis, Sanofi, toBBB, Angiochem, Merrimack, Lily, Genentech, Nektar, and Kadmon, receives unrelated research funding from Novartis, Sanofi, toBBB, Angiochem, Merrimack, PUMA, Lily, Merck, Oncothyreon, Cascadian, Nektar, and Tesaro, and receives honoraria for UptoDate and Jones and Bartlett Publishing. Rita Nanda is a consultant/advisory board member for AstraZeneca, Celgene, Genentech, Merck, Pfizer, Puma, and Syndax. Nikita Shah is a consultant for Novartis. The other authors declare they have no conflicts of interest.

Ethical approval This manuscript complies with all current laws of the country in which they were performed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained by all individual participants included in the study.

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Abstract

Purpose—HER2 + breast cancer (BC) is an aggressive subtype with high rates of brain metastases (BCBM). Two-thirds of HER2 + BCBM demonstrate activation of the PI3K/mTOR pathway driving resistance to anti-HER2 therapy. This phase II study evaluated everolimus (E), a brain-permeable mTOR inhibitor, trastuzumab (T), and vinorelbine (V) in patients with HER2 + BCBM.

Patients and methods—Eligible patients had progressive HER2 + BCBM. The primary endpoint was intracranial response rate (RR); secondary objectives were CNS clinical benefit rate (CBR), extracranial RR, time to progression (TTP), overall survival (OS), and targeted sequencing of tumors from enrolled patients. A two-stage design distinguished intracranial RR of 5% versus 20%.

Results—32 patients were evaluable for toxicity, 26 for efficacy. Intracranial RR was 4% (1 PR). CNS CBR at 6 mos was 27%; at 3 mos 65%. Median intracranial TTP was 3.9 mos (95% CI 2.2–5). OS was 12.2 mos (95% CI 0.6–20.2). Grade 3–4 toxicities included neutropenia (41%), anemia (16%), and stomatitis (16%). Mutations in *TP53* and *PIK3CA* were common in BCBM. Mutations in the PI3K/mTOR pathway were not associated with response. *ERBB2* amplification was higher in BCBM compared to primary BC; ERBB2 amplification in the primary BC trended toward worse OS.

Conclusion—While intracranial RR to ETV was low in HER2 + BCBM patients, one-third achieved CNS CBR; TTP/OS was similar to historical control. No new toxicity signals were observed. Further analysis of the genomic underpinnings of BCBM to identify tractable prognostic and/or predictive biomarkers is warranted.

Clinical Trial: ().

Keywords

Breast cancer; Brain metastases; Metastases; PI3K, MEK; Targeted therapy

Introduction

HER2 + breast cancer (BC) is characterized by protein overexpression or gene amplification of human epidermal growth factor receptor 2 (HER2, *ERBB2*) [1]. Up to 30% of patients with advanced HER2 + breast cancer experience intracranial recurrence [2]. The precise reason for this increased incidence is unclear, but likely related to reduced ability of HER2-directed, monoclonal antibodies, trastu-zumab or pertuzumab, to cross the blood brain barrier and inherent genomic changes causing an increased propensity for HER2 + cells to seed the central nervous system (CNS) [3, 4]. While the advent of HER2-targeted therapies has improved the survival of patients with HER2 + BC brain metastases (BM), survival remains less than 2 years [5–7]. Novel, brain-permeable therapies targeting HER2 and inherent resistance pathways to more optimally treat HER2 + BCBM are needed.

Radiation therapy remains a mainstay to treat BCBM; neurosurgical resection is generally reserved for solitary lesions or for large, space-occupying lesions [8]. Current systemic treatment options for patients with progressive HER2 + BCBM include the HER1/2-targeting, small molecule inhibitor lapatinib, with or without capecitabine [9]. The LANDSCAPE study, evaluating lapatinib/capecitabine in radiation therapy-naïve patients, showed an intracranial response rate (RR) of 67% by volumetrics and progression-free survival (PFS) of 5.5 months [10]. The irreversible HER1/2 tyrosine kinase inhibitor, neratinib, plus capecitabine yielded intracranial RR of 49% by volumetrics and a similar PFS of 5.5 months. Treatment with neratinib/capecitabine results in notable toxicity, with grade 3 diarrhea in 32% of patients. Several case reports further illustrated durable intracranial responses to trastuzumab emtansine [11, 12].

While HER2 + BCBM have illustrated respectable response to HER2-directed therapy, responses are not durable, and patients from the aforementioned studies progressed within 6 months. The phosphoinositide-3-kinase/ mammalian target of rapamycin (PI3K/mTOR) pathway has been implicated as a driver of metastasis in HER2 + BC and resistance to HER2-directed therapies [13, 14]. Hyperactivation of PI3K/mTOR after trastuzumab treatment [15] correlates with poor OS and increased metastasis to the brain [15]. BCBM have enrichment of PTEN loss and increased PI3K signaling [16–19]. Thus, inhibition of the PI3K/mTOR pathway, combined with HER2-directed therapy, may yield more sustained responses for patients with advanced HER2 + BCBM.

Everolimus is a brain-permeable, small molecule inhibitor of mTOR complex 1 (mTORC1). Everolimus was approved in the United States in 2012 for the treatment of refractory sub-ependymal giant cell astrocytomas, intracranial neoplasms in patients with mutations in *TSC1* or *TSC2* resulting in activation of mTOR [20]. The addition of everolimus to vinorelbine and trastuzumab for patients with metastatic HER2 + BC without BM yielded modest, yet significant, improvements in progression-free survival favoring the everolimus arm (7 versus 5.78 months, Hazard Ratio (HR) 0.78, $p = 0.0067$) [14]. To this end, we designed a phase II, open-label, single-arm study evaluating the efficacy and safety of everolimus plus vinorelbine and trastuzumab among patients with progressive HER2 + BCBM, with correlative DNA sequencing of primary and metastatic tumors.

Patients and methods

Patient population

Eligible patients, enrolled 9/9/2011–5/11/2016, had histologically confirmed HER2+ (3 + or amplified by fluorescence in-situ hybridization) breast adenocarcinoma with progressive and/or new BCBM ≥ 5 mm by gadolinium-enhanced magnetic resonance imaging (MRI). Receipt of prior intracranial radiation therapy was allowed, but not required. Additional inclusion criteria included age > 21 years, ECOG performance status of 0–2, life expectancy > 12 weeks, and adequate organ function. Concurrent dexamethasone was allowed if stable or decreasing dose ≥ 7 days.

Exclusion criteria included prior mTOR inhibition, intracranial hemorrhage, impending herniation, leptomeningeal disease, cardiac disease/dysfunction, or pregnancy/

breastfeeding, or HIV-positivity. Hepatitis B and C testing was required of high-risk patients. If sero-positive for hepatitis B, lamivudine prophylaxis was initiated 12 weeks prior to everolimus. If hepatitis C positive, close monitoring of liver function was required. All patients provided written informed consent, and the study was institutional review board approved (No. (NCT01305941).

Study design

This was an open-label, single-arm, phase II study (Fig. 1). The primary endpoint was intracranial response rate (RR) as defined via modified response evaluation criteria in solid tumors (RECIST) criteria [21]. Secondary objectives included intracranial RR by MacDonald criteria [22], time to progression (TTP), extracranial RR, progression-free survival (PFS), overall survival (OS), safety/tolerability as per NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [23], and targeted DNA sequencing [24].

Study treatment

Eligible patients received everolimus 5 mg PO daily as two 2.5-mg tablets, weekly vinorelbine 25 mg/m^2 intravenously (IV) (days 1, 8), and trastuzumab 2 mg/kg IV (days 1, 15) on a 21-day cycle. Vinorelbine was initially dosed on days 1, 8, and 15, but day 15 was removed due to neutropenia following accrual of 13 subjects (October 14, 2013).

Safety assessments

Adverse events were assessed every 3 weeks and graded according to the NCI CTCAE Version 4.0 [23].

Efficacy assessments

Response assessment was obtained every 9 weeks. Intracranial response rate (RR) was evaluated using modified RECIST criteria with brain MRI [21]. An intracranial response was defined as either a complete response (CR) or a partial response (PR) (30% decrease in the sum of the longest diameter (LD) of target lesions AND an absolute decrease of 5 mm in at least one target lesion). Clinical Benefit was defined as a CR, PR, or stable intracranial disease, reported as sustained for ≥ 3 months with no evidence of extracranial PD [9, 25]. Progressive disease (PD) intracranially was defined as a 20% increase in the sum LD of target lesions AND an absolute increase of 5 mm in at least one target lesion OR the appearance of one or more new lesions of at least 6 mm in size. Stable disease (SD) in the CNS did not meet criteria for either PR or PD.

Extracranial disease was assessed via a serial computed tomography of the chest/abdomen/pelvis and a nuclear bone scan (if bone metastases on baseline imaging). Extracranial disease status was determined using RECIST 1.1 criteria [25].

Health-related quality of life

Participants' health-related quality of life (HRQL) was assessed using the Functional Assessment of Cancer Therapy, General (FACT-G) along with the Brain Tumor and Breast Cancer Additional Concerns Subscales (www.facit.org) [26–28]. HRQL questionnaires were

administered during the pre-study evaluation, every 9 weeks during treatment, at the time of progression, and at 60-day follow-up.

DNA sequencing

Formal-fixed, paraffin-embedded primary and/or metastatic tumors from enrolled patients were collected. A hematoxylin and eosin (H&E) slide from each case was reviewed by the study pathologist (NP, CRM) to map tumor content and location. DNA sequencing was performed according to the UNCSeq protocol [24]. Briefly, 750 ng DNA library was target-captured with 250–800 genes from UNCSeq V7, V7.1, or V8 (eTable 1). Quality libraries were sequenced on the Illumina NextSeq500 (3/pool, NextSeq v2 300 cycle, v2 High-Output Flowcells, 2 × 100 paired-end).

DNA sequencing mapping

Sequencing reads were mapped to the reference genome hs37d5 with added viral contigs by BWA 0.7.9a [29] and samtools 0.1.19–44428 cd [30], sorted with biobambam 2.0.33 [31], filtered and quality controlled with BEDTools 2.0.15 [32], realigned with ABRA 0.96 [33], and analyzed for further quality metrics with PicardTools 1.92 [34]. Germline calls were made with Freebayes v0.9.15–1-g076a2a2 [35] and ISAAC 1.0.4 [36]. For tumors with a matched normal, somatic calls were made with STRELKA [37] by comparing the matched tumor and normal. If matched normal was unavailable, 20 normal samples from the same targeted capture version of UNCSeq were used to compare for somatic variance calling. Somatic variants were filtered and annotated with SNPSift 1.3.4 [38], SNPEff [39], COSMIC v10250210 [40], dbSNP 132 [41], ExAC 0.3 [42], and Oncotator 1.9.0 [43]. All sequenced patient samples are including in the 1025 dataset in dbGaP.

DNA mutation and copy number analyses

Mutations previously reported in COSMIC ≥ 10 times or with an ExAC population frequency $< 1 \times 10^{-5}$ were kept for further analyses; mutations with more frequent prevalence in the population, but not reported in COSMIC, were discarded. All mutations in HLA genes were removed due tothe high degree of genetic diversity in the population. Mutation plotting was performed with GenVisR [44]. SynthEx [45] was applied to the mapped DNA sequencing data using KNN=4 using previously sequenced UNCSeq [24] normals. Pearson correlation was calculated with R v.3.3.2.

Statistical analyses

A two-stage design [46] was planned to test the null hypothesis response rate of 5% against a one-sided alternative. After evaluating 11 patients for response in the first stage, the trial would be terminated if no patient had a CR, PR, or Clinical Benefit (CR+PR + SD ≥ 3) [9, 21]. If at least one patient met these criteria, an additional 17 patients would be enrolled during the second stage for a total of 28. At the end of the trial, if the total number of responses (CR+PR) is 4 or more, the combination would be considered promising. This trial design yielded a type-I error rate of at most 0.05. The power was at least 80% if the true response rate (response = CR+PR) was equal to 0.2 and for any value of Clinical Benefit Rate (CBR). Fisher's Exact test was used to compare intracranial RR by HR status. The

Kaplan Meier method estimated time to intracranial progression (TTP) and overall survival (OS), with both measurements starting at time of treatment initiation. The association of changes in QOL measures from baseline to 9 weeks with clinical benefit at 12 weeks was evaluated using Wilcoxon Rank Sum tests.

Results

Patient characteristics

Forty-one patients were enrolled, of which 9 were consented and not treated (7 were deemed ineligible, 1 non-compliant with screening, and 1 withdrew consent prior to treatment). Thirty-two patients were evaluable for toxicity; 26 patients were evaluable for efficacy. Enrollment was halted at 26 evaluable patients as there was only 1 PR (in stage I); 4 responses were needed to reject the null hypothesis which was unattainable.

Patient demographics and prior treatments are outlined in Table 1. Median age was 53 years (28–70). Most patients (84%) were white; 16% black. 41% of patients were diagnosed with stage IV BC de novo; median time since diagnosis of BCBM prior to study enrollment was 1.12 years (0.4–6.5).

Most patients received systemic therapy in the metastatic setting; median prior lines of therapy was 2 (0–7). Prior anti-HER2 therapies included 97% trastuzumab, 73% lapatinib, 40% pertuzumab, and 27% trastuzumab emtansine. Local therapy directly to the CNS included neurosurgery (32%), whole brain radiation therapy (69%), and stereotactic radiosurgery (53%). One patient had not received local therapy to the brain and was neurologically stable.

Recursive partitioning analysis (RPA) scores [47], a prognostic model for patients with BCBM, were 1 (31%), 2 (65%), and 3 (3%). Approximately one-third of patients were on steroids and two-thirds had extracranial disease at time of enrollment.

Toxicity and dose intensity

Study design is outlined in Fig. 1. Everolimus plus vinorel-bine and trastuzumab was generally well tolerated with no new safety signals (Fig. 2a). The most common grade 1–2 toxicities included oral mucositis (50%), constipation (31%), fatigue (28%), anemia (16%), elevated ALT (19%), diarrhea (22%), anorexia (22%), elevated AST (19%), thrombocytopenia (19%), acneiform rash (16%), and peripheral neuropathy (16%).

The most common grade 3–4 toxicities included neutropenia (41%), leukopenia (31%), oral mucositis (16%), and anemia (16%). Of note, steroid mouth rinse was not mandated as the results of the SWISH study were not reported until 2016 [48].

Efficacy

Objective response rate

Among 26 patients evaluable for efficacy, the intracranial RR by modified RECIST was 4% (0 complete responses (CR); 1 partial response (PR); Table 2 and Fig. 2b). Seventeen

additional patients (65%) had stable disease (SD) as best response. Clinical benefit rate (CBR) for ≥ 6 months was 27% and for ≥ 3 months was 69%. Extracranial RR for 12 patients was 42% PR and 50% SD.

Intracranial RR were not significantly different by hormone receptor (HR) status ($p = 0.26$). For those with ER/ PR negative, HER2 + BC ($n = 15$), intracranial RR were PR 6.7%, SD for ≥ 6 months 27%, SD for 3–6 months 27%, and PD 40%. For those with ER and/or PR positive, HER2 + BC ($n = 11$), intracranial RR were PR 0%, SD for ≥ 6 months 18%Clinical benefit rat, SD for 3–6 months 64%, and PD 18%.

Intracranial RR was also evaluated by bi-dimensional MacDonald criteria: 0% CR, 8% with > 50% decrease, 54% with decrease ≤ 50% and < 25% increase, and 38% with > 25% increase in intracranial lesions, eFigure 1.

Time to intracranial progression

The median TTP was 3.93 months (95% CI 2.27–5.00; Fig. 2c). There was no difference in TTP by HR status: HR– 3.88 months versus HR + 4.01 months (95% CI 2.11–5.46 versus 95% CI 2.04–5.49, respectively; eFigure 2A). Only 4 patients had extracranial progression prior to intracranial progression; however, the estimate for median time to first (extra- or intra-) progression is the same (3.93 CI 2.27–4.34).

Overall survival

OS for evaluable patients was 1.01 years (95% CI 0.57–1.78; Fig. 2d). OS was numerically, but not significantly, longer for those with HR+ (1.78 years, 95% CI 0.55–2.69), compared to those with HR– BC (0.63 years, 95% CI 0.32–1.35, $p = 0.14$; eFigure 2B).

Health-related quality of life

Of the 32 patients evaluable for toxicity, 20 completed baseline QOL, and 11 completed both baseline and 9-week QOL assessment. On a scale of 0–108, median baseline FACT-G scores were 76 (range 54–105). Change from baseline to 9-week follow-up was – 10.5. Median baseline Brain Cancer subscale results (range 0–92) were 63 (range 46–88), with change from baseline to 9 weeks of – 1.0. Median Breast Cancer subscale results (range 0–40) were 27 (range 17–35), with change from baseline to 9 weeks of 1.0 (eTable 2).

Tumor sequencing and correlative endpoints

Hypothesis-generating targeted DNA sequencing was completed on 23 samples from 20 patients: 12 primaries, 11 metastases (6 BCBM, 3 lymph nodes (LN), 2 liver metastases), with 3 matched primary/metastasis pairs (2 primary/ brain, 1 primary/LN) (diagram, eFigure 3). The most commonly mutated gene was *TP53* (87%, 20/23), followed by *PI3KCA* (35%, 8/23, Fig. 3a), with 5/8 being the canonical His1074Arg *PIK3CA* mutation. Given that the mechanism of action of everolimus targets PI3K/mTOR signaling, we next examined alterations in the PI3K/mTOR pathway: 68% (15/23) of tumors had at least one alteration in the pathway, with 35% (8/23) of tumors having > 1 (Fig. 3B). PI3K/ mTOR mutations were not associated with clinical response, and globally these genes illustrated copy number loss (bottom row, Fig. 3b).

We next examined intracranial TTP in the context of BCBM copy number alterations. Interestingly, loss of chr11q23.2 was associated with shortened time to intracranial progression ($p = 0.051$, $R^2 = 0.805$, Fig. 3c). Genes at this copy number segment include some involved in neuronal processes and tumor progression: *KMT2A* [49, 50], *ARCN1* [51], *PHLDB1* [51, 52], *DDX6* [52, 53], *CXCR5* [54, 55], *ABCG4* [56–58], and *NLRX1* [59, 60].

Lastly, evaluation of *ERBB2* amplification across our dataset demonstrated considerable heterogeneity. 19/23 tumors had copy number gain, while one primary without *ERBB2* CN amplification contained a previously reported K755S Tyr-kinase domain mutation [40]. Interestingly, *ERBB2* amplification increased in BCBM compared to matched primaries (Fig. 3D, horizontal line). HER2 amplification in the primary (black dots) BC negatively trends with OS from original BC diagnosis (Fig. 3d, $p = 0.085$, $R^2 = -0.39$).

Discussion

This study investigated the efficacy of mTOR inhibition using brain-penetrant everolimus in combination with standard anti-HER2 therapy, vinorelbine and trastuzumab, in patients with progressive HER2 + breast cancer brain metastases (BCBM). While intracranial response rate (RR) to combination therapy was only 4%, intracranial clinical benefit was observed at 3 (69%) and 6 months (27%). Intracranial time to progression (TTP) was nearly 4 months for this heavily pretreated patient population. Median survival was > 1 year with average time from BCBM diagnosis to study participation also > 1 year. Thus, enrolled patients lived > 2 years with HER2 + BCBM, consistent with current literature [61–63]. Quality of life scores were not adversely impacted by treatment with this regimen; however, improvements in quality of life were not observed in the responding patients.

Clinically, everolimus has been evaluated across various BC subtypes. In HR+, HER2− metastatic BC, the addition of everolimus to aromatase inhibition yielded significant improvements in PFS that led to FDA approval [64]. Moreover, the addition of everolimus to standard adjuvant endocrine therapy is being examined in a large phase III clinical trial (NCT01674140). In HER2 + metastatic BC, the addition of everolimus to vinorelbine and trastuzumab yielded improvements in PFS (7 versus 5.78 months, $p = 0.0067$) [14]. Coupling the known brain-permeable property of everolimus with the high incidence of BCBM in HER2 + BC, our study and others are examining everolimus in the setting of CNS relapse. Results anticipated from the phase 1b/2 study of lapatinib, everolimus, and capecitabine in trastuzumab-pretreated HER2 + BCBM (NCT01783756) will continue to contextualize our findings.

Our exploratory correlative sequencing results in primary and metastatic HER2 + BC demonstrate frequent alterations in *TP53* and throughout the *PI3KCA* pathway. We identified *TP53* alterations in 83% of HER2-positive primaries and 100% of BCBM, similar to previous reports [65, 66]. Increased HER2-amplification in the BCBMs was observed, including a relative increase in the BCBM in two matched pairs, and is consistent with previous reports [67, 68]. Further characterization of chr11q23.2 with RNAseq is needed to understand dynamic gene expression localized to this segment of the genome, many of

which are involved in neuronal processes [49–60]. Overall, our data support prior findings of genetic heterogeneity in metastatic HER2 + BCBM amid a background of *TP53* mutations and *ERBB2* amplification.

The present study must be interpreted considering its limitations. The sample size is small, particularly for robust correlative findings, thus is exploratory and hypothesisgenerating. Future studies with larger patient populations, prospective sample collection, and parallel RNA and DNA sequencing could more efficiently identify potential correlations between genetic alterations, gene expression, and clinical outcomes, and better define the evolution of genetic changes within patients over the course of their disease.

In closing, while the combination of everolimus, vinorelbine, and trastuzumab did not meet our pre-specified intracranial response endpoint, TTP and OS were similar to prior studies in a heavily pretreated patient population with vanishingly few additional clinical options. Moreover, this combination showed an acceptable toxicity profile. Further evaluation of the molecular profile of primary and/or metastatic tumors from patients with HER2 + BCBM should be investigated to correlate genomic alterations with clinical response. If able to enrich for responders using a strategic biomarker approach, comparison of this combination to current standard of care in the setting of HER2 + BCBM is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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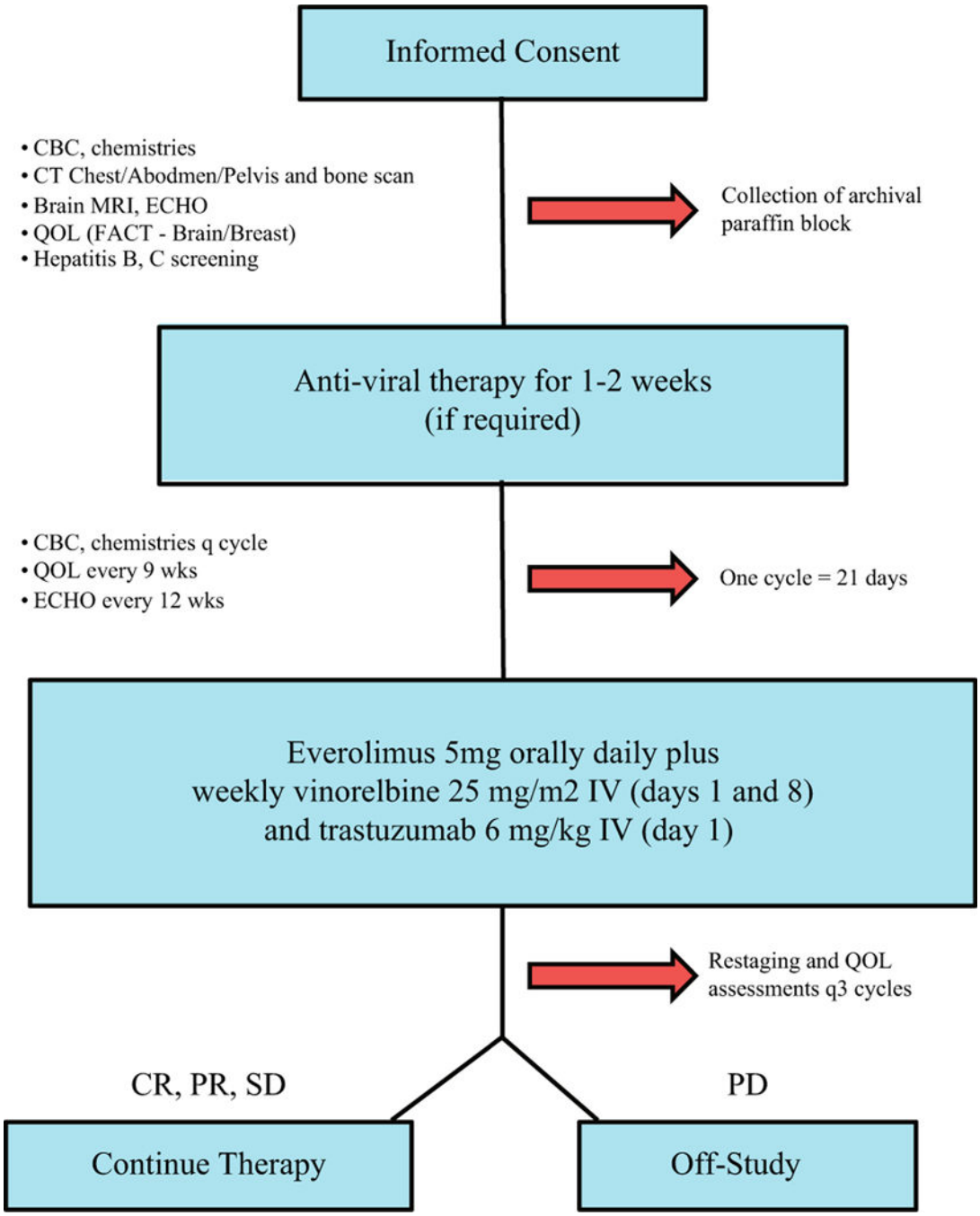

Fig. 1.

Consort diagram of LCCC 1025: vinorelbine, trastuzumab, and everolimus in HER2 + breast cancer brain metastases

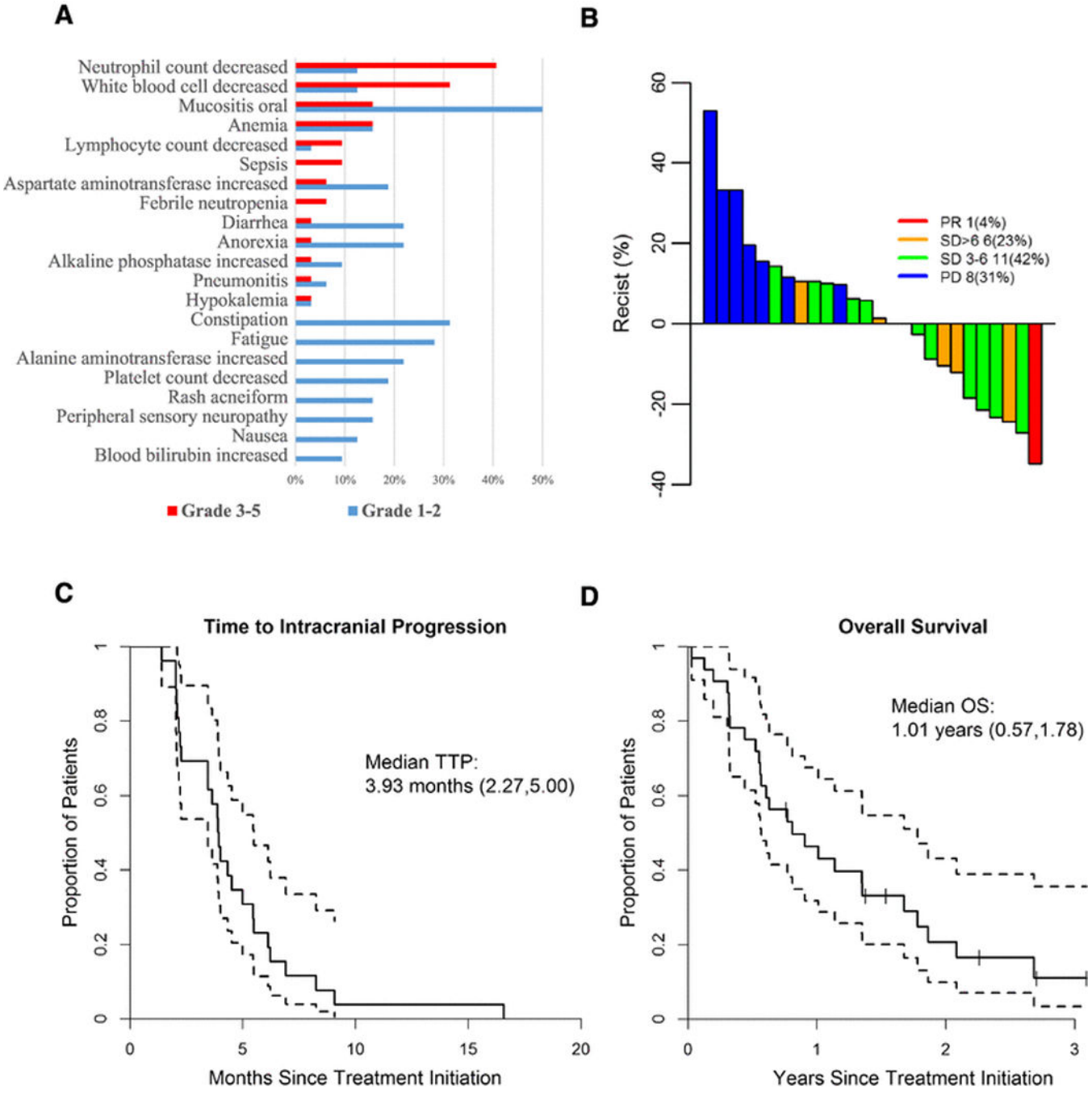

Fig. 2.

Clinical outcomes and survival. **a** Most prevalent toxicities (All grades) in response to everolimus, vinorelbine, trastuzumab therapy. Grade 1 and 2 toxicities are presented in blue; Grade 3–5 toxicities are presented in red. **b** Waterfall plot of intracranial objective response rates by modified RECIST criteria. **c** Median time toprogression (TTP) and **d** median overall survival (OS) in response to everolimus, vinorelbine, trastuzumab among patients with progressive or new brain metastases arising from HER2 positive breast cancer

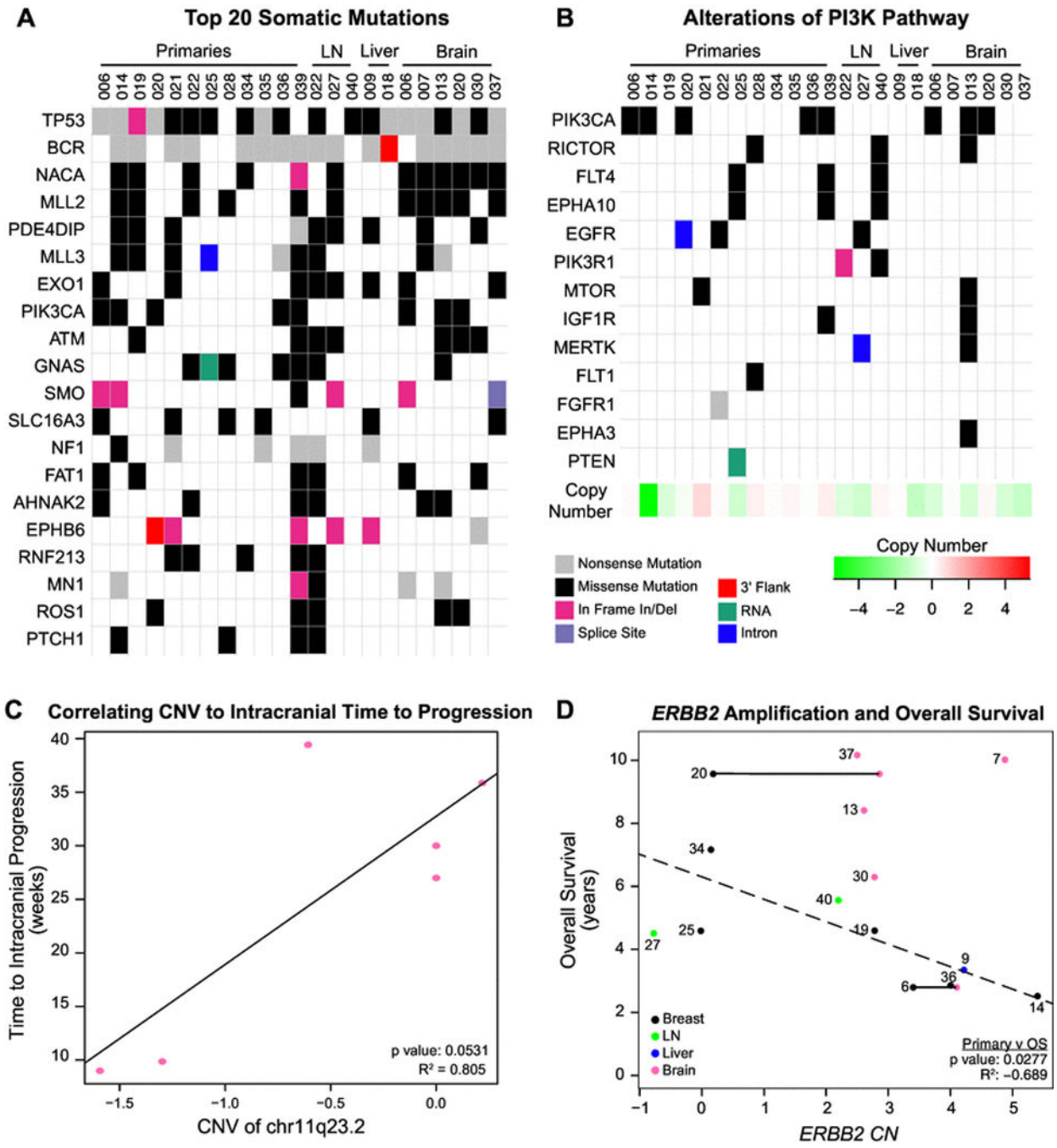

Fig. 3.

Targeted DNA sequencing mutations and copy number alterations. **a** Significantly mutated genes (SMGs) across all available tissues, **b** mutations in the PI3K/mTOR pathway, **c** HER2 Copy Number Variations (CNVs) versus Intracranial Time to Progression in brain metastases, **d** HER2 CNVs versus Overall Survival across all available tissues. Dotted line is the correlation based on the primary tumors only. Horizontal lines indicate tissues from matched pairs ($n = 2$)

Table 1

Patient demographics and prior treatment information

Demographics and clinical data	
Median age, years (range)	53 (28–70)
Race, White	26/31 (84%)
Black/other	5/31 (16%)
Stage at breast cancer diagnosis, 0–III	19 (59%)
IV	13 (41%)
Median Time since first brain metastases (years)	1.12 (0.4–6.5)
Prior systemic chemotherapy (metastatic)	30 (94%)
Prior metastatic lines, # (range)	2 (0–7)
Prior anti-HER2 (metastatic)	30 (94%)
Trastuzumab	29/30 (97%)
Lapatinib	22/30 (73%)
Pertuzumab	12/30 (40%)
TDM-1	8/30 (27%)
Prior CNS local therapy	
Surgery	10/31 (32%)
Any CNS RT	31/32 (97%)
WBRT	22/32 (69%)
SRS	17/32 (53%)
Median time since CNS RT (days) (n = 31)	237 (IQR 135–392) (range: 12–1911)
CNS RT within 12 weeks of starting treatment	2 (6%)
Recursive partitioning analysis score (1, 2, or 3)	10 (31%), 21 (65%), 3 (3%)
Steroid use at baseline	10 (31%)
Extracranial disease at enrollment	20 (63%)

Table 2

Summary of objective response rates (best response observed at any time)

Summary of objective response rates	**Intracranial (*n* = 26) *N* (%)**	**Extracranial (*n* = 12) *N* (%)**
Complete response	0 (0%)	0 (0%)
Partial response	1 (4%)	5 (42%)
Stable disease	17 (65%)	6 (50%)
Progressive disease	18 (69%)	1 (8%)
Clinical benefit rate (CR or PR + SD ≥ 6 months)	7 (27%)	–
Clinical benefit rate (CR or PR + SD ≥ 3 months)	8 (69%)	–