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HER kinase inhibition in patients with HER2- and HER3-mutant cancers

David M. Hyman[1], Sarina A. Piha-Paul[2], Helen Won[1], Jordi Rodon[3], Cristina Saura[3], Geoffrey I. Shapiro[4], Dejan Juric[5], David I. Quinn[6], Victor Moreno[7], Bernard Doger[7], Ingrid A. Mayer[8], Valentina Boni[9], Emiliano Calvo[9], Sherene Loi[10], Albert C. Lockhart[11], Joseph P. Erinjeri[1], Maurizio Scaltriti[1], Gary A. Ulaner[1], Juber Patel[1], Jiabin Tang[1], Hannah Beer[1], S. Duygu Selcuklu[1], Aphrothiti J. Hanrahan[1], Nancy Bouvier[1], Myra Melcer[1], Rajmohan Murali[1], Alison M. Schram[1], Lillian M. Smyth[1], Komal Jhaveri[1], Bob T. Li[1], Alexander Drilon[1], James J. Harding[1], Gopa Iyer[1], Barry S. Taylor[1], Michael F. Berger[1], Richard E. Cutler Jr[12], Feng Xu[12], Anna Butturini[12], Lisa D. Eli[12], Grace Mann[12], Cynthia Farrell[12], Alshad S. Lalani[12], Richard P. Bryce[12], Carlos L. Arteaga[8], Funda Meric-Bernstam[2], José Baselga[1] & David B. Solit[1]

Somatic mutations of *ERBB2* and *ERBB3* (which encode HER2 and HER3, respectively) are found in a wide range of cancers. Preclinical modelling suggests that a subset of these mutations lead to constitutive HER2 activation, but most remain biologically uncharacterized. Here we define the biological and therapeutic importance of known oncogenic HER2 and HER3 mutations and variants of unknown biological importance by conducting a multi-histology, genomically selected, 'basket' trial using the pan-HER kinase inhibitor neratinib (SUMMIT; clinicaltrials.gov identifier NCT01953926). Efficacy in HER2-mutant cancers varied as a function of both tumour type and mutant allele to a degree not predicted by preclinical models, with the greatest activity seen in breast, cervical and biliary cancers and with tumours that contain kinase domain missense mutations. This study demonstrates how a molecularly driven clinical trial can be used to refine our biological understanding of both characterized and new genomic alterations with potential broad applicability for advancing the paradigm of genome-driven oncology.

Genomic profiling of human cancers has identified recurrent somatic mutations of HER2 (encoded by *ERBB2*) and HER3 (*ERBB3*), typically occurring in the absence of gene amplification[1–3]. Mutations in HER2 are clustered in the extracellular, transmembrane and kinase domains. Unlike other mutant oncogenes, such as *BRAF* or *KRAS*, no single mutant allele predominates and the precise distribution of mutations varies by tumour type[4]. By contrast, HER3 mutations cluster primarily in the extracellular domain and to a lesser extent in the kinase domain. Although HER2 and HER3 mutations are found in a wide variety of cancers, their overall prevalence does not exceed 10% in any individual tumour type, and the rate is more typically less than 5% for HER2 and less than 1% for HER3.

Biological modelling has yielded conflicting findings as to the functional consequences of HER2 and HER3 mutations. Substantial data suggest that a subset of these mutations induce ligand-independent constitutive HER2 receptor signalling and promote oncogenesis[5–7]. The mechanism of these oncogenic effects seems to differ by variant, with some causing enhanced HER2 kinase activity and others causing receptor dimerization[5,8]. Mutations in HER3, which in its wild-type configuration has impaired kinase function, seem to rely on wild-type HER2 to exert its oncogenic effects[7]. Most preclinical data that explore the functional consequences of HER2 and HER3 mutations have been generated using engineered models that overexpress the mutation, and thus the results may be confounded by the known oncogenic effects of HER2 overexpression. Further enforcing the potential importance of this confounding variable, models of HER2 mutation generated by gene-editing techniques have failed to demonstrate a malignant phenotype in the absence of mutations in other oncogenes such as *PIK3CA*[9].

Given the considerable diversity of HER2 and HER3 mutations, as well as the challenge of generating preclinical models that recreate their true biology in human cancers, we sought to define the therapeutic importance of HER2 and HER3 mutations by conducting SUMMIT—a global, multicentre, multi-histology basket trial in patients with tumours that contain these mutations (Extended Data Fig. 1). Patients were treated with neratinib, an irreversible pan-HER tyrosine kinase inhibitor, which potently inhibits the growth of HER2-mutant tumours in preclinical models[5]. Tumour tissue and plasma were collected to facilitate the detailed genomic characterization of patients. Here we present the results of this study, with a focus on the insights it provides into the biological and therapeutic importance of HER2 and HER3 mutations in patients with cancer.

Patient and mutation characteristics

Baseline patient demographics are shown in Table 1 and Extended Data Table 1. In total, 141 patients (125 with HER2-mutant tumours, 16 with HER3-mutant tumours) received neratinib treatment. These patients were diagnosed with 1 out of 21 unique cancer types, the most common being breast, lung, bladder and colorectal cancer (61% of patients treated). As has been seen in other basket studies[10,11], we identified and enrolled several orphan tumour types including cancers of the biliary tract, salivary gland, small bowel and vagina, as well as extramammary Paget's disease (in aggregate, 13% of all patients). Patients tended to be heavily pretreated with approximately half having received at least three previous lines of systemic therapy.

Enrolled patients had 31 unique HER2 and 11 unique HER3 mutations (Extended Data Fig. 2). The most frequent HER2 mutations

[1]Memorial Sloan Kettering Cancer Center, New York, New York, USA. [2]University of Texas, MD Anderson Cancer Center, Houston, Texas, USA. [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [4]Dana-Faber Cancer Institute, Boston, Massachusetts, USA. [5]Massachusetts Hospital Cancer Center, Boston, Massachusetts, USA. [6]USC Norris Comprehensive Cancer Center, Los Angeles, California, USA. [7]START Madrid Fundación Jímenez Díaz, Madrid, Spain. [8]Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, USA. [9]START Madrid, Centro Integral Oncológico Clara Campal (CIOCC), Madrid, Spain. [10]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia. [11]Washington University in St. Louis School of Medicine, St Louis, Missouri, USA. [12]Puma Biotechnology Inc., Los Angeles, California, USA.

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Table 1 | Patient demographics

Patient characteristic	HER2 mutant ($n=125$)	HER3 mutant ($n=16$)	Total ($n=141$)
Age, years			
Median (range)	61 (30–83)	66 (39–82)	61 (30–83)
<65 years, *n* (%)	81 (64.8)	7 (43.8)	88 (62.4)
≥65 years, *n* (%)	44 (35.2)	9 (56.3)	53 (37.6)
Sex, *n* (%)			
Female	80 (64.0)	12 (75.0)	92 (65.2)
Male	45 (36.0)	4 (25.0)	49 (34.8)
ECOG performance status, *n* (%)			
0	37 (29.6)	1 (6.3)	38 (27.0)
1	83 (66.4)	12 (75.0)	95 (67.4)
2	5 (4.0)	3 (18.8)	8 (5.7)
Previous systemic treatment lines, *n* (%)			
Any	121 (96.8)	16 (100)	137 (97.2)
1	33 (26.4)	1 (6.3)	34 (24.1)
2	30 (24.0)	11 (68.8)	41 (29.1)
≥3	58 (46.4)	4 (25.0)	62 (44.0)
Median time from metastasis to enrolment, years (range)	1.02 (0.0–15.0)	1.13 (0.3–4.5)	1.03 (0.0–15.0)
Tumour type, *n* (%)			
Lung	26 (20.8)	0 (0)	26 (18.4)
Breast	25 (20.0)	0 (0)	25 (17.7)
Bladder	16 (12.8)	2 (12.5)	18 (12.8)
Colorectal	12 (9.6)	5 (31.3)	17 (12.1)
Biliary tract	9 (7.2)	2 (12.5)	11 (7.8)
Endometrial	7 (5.6)	1 (6.3)	8 (5.7)
Cervical	5 (4.0)	0 (0)	5 (3.5)
Gastroesophageal	5 (4.0)	2 (12.5)	7 (5.0)
Ovarian	4 (3.2)	1 (6.3)	5 (3.5)
Other	16 (12.8)	3 (18.8)	19 (13.5)

were S310, L755, Y772_A775dup and V777 alleles. The HER2 kinase domain was most commonly mutated (66%), followed by the extracellular (26%) and transmembrane/juxtamembrane (8%) domains. The anticipated relationships between the mutated HER2 domain and tumour type were observed, with extracellular domain mutations predominant in bladder cancer, kinase domain missense mutations in breast and colon cancer, and kinase domain insertions in lung cancer[4]. Missense mutations were the most common class of genomic alteration (74%), followed by in-frame insertions (22%), the latter exclusively affecting the kinase domain. Two tumours contained HER2 insertions/deletions and one an in-frame kinase domain-retaining fusion (*GRB7-ERBB2*)[12,13]. HER3 mutations were all missense variants and clustered in the extracellular furin-like and receptor domains. In total, 87% (109 out of 125) of HER2 and 75% (12 out of 16) of HER3 mutations were at positions now known to be mutational hotspots[4]. This pattern of HER2 and HER3 mutations was comparable to the spectrum of non-truncating HER2 and HER3 mutations observed in previously published genomic landscape studies, including The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC)[4], although HER2 V777L and Y772_A755dup were more common in our study cohort (13.6% versus 5.3% and 12.0% versus 2.7%, respectively; Extended Data Fig. 3).

Treatment outcomes

When stratified by tumour type, we observed responses to neratinib in patients with HER2-mutant breast, non-small-cell lung, cervical, biliary and salivary cancers, which led to expanded enrolment in several of these tumour types (Fig. 1a, Extended Data Table 1). Neratinib exhibited the greatest degree of activity in patients with breast cancer ($n=25$ total, objective response rate at week 8 (ORR_8) 32%, 95% confidence interval 15–54%), with responses observed in patients with missense mutations involving the extracellular and kinase domains, as well as insertions in the kinase domain. All patients with breast cancer were classified as HER2-negative (non-amplified) at the time of enrolment as per established guidelines[14]. Responses were observed in both oestrogen receptor-positive (30%, 6 out of 20) and -negative (40%, 2 out of 5) tumours. Overall, these breast cancer data are generally consistent with a previous report[15]. In patients with lung cancer ($n=26$), in which insertions in exon 20 predominate, we observed only one objective response. Of note, HER2 exon 20 insertions are paralogous of EGFR exon 20 insertions, which are resistant to first- and second-generation EGFR tyrosine kinase inhibitors[16]. Notably, the only patient with lung cancer to achieve a response evaluation criteria in solid tumours (RECIST) response had a kinase domain missense mutation (L755S). Despite the low response rate, the median progression-free survival in recurrent lung cancer was 5.5 months, with 6 patients remaining on therapy for more than 1 year, which compares favourably to second-line chemotherapy and immune checkpoint inhibitors[17], suggesting that neratinib may have a positive effect on the natural history of this disease. Responses were also observed in biliary and cervical cancers, and enrolment is ongoing in these cohorts to define this activity better. No responses were observed in bladder cancer ($n=16$) or colorectal cancer ($n=12$), suggesting lineage-dependent resistance to single-agent pan-HER kinase inhibition in these tumour types. In summary, among the HER2-mutant cohorts, breast cancer met the primary endpoint for efficacy, whereas lung, colorectal and bladder cancers did not. For the remaining tumour-specific cohorts, enrolment is continuing and they have therefore not undergone final efficacy analysis. Despite preclinical data to suggest that HER3 mutations can be oncogenic drivers, no responses to neratinib were observed in patients with HER3-mutant tumours.

When stratified by mutant allele, responses were observed in patients with tumours containing HER2 S310, L755, V777, G778_P780dup and Y772_A775dup mutations (Fig. 1b). Among patients with HER2 kinase domain hotspot missense mutations ($n=42$), responses were noted in four unique tumour types (breast, biliary, lung and salivary gland). By allele, we observed responses in several kinase domain mutants including L755S ($n=4$), V777L ($n=4$) and L869R ($n=1$). In patients with HER2 hotspot extracellular domain mutations (S310, $n=30$), responses were observed in breast, cervical and biliary cancers ($n=1$ for each), but not in bladder cancer, the cancer type in which these mutations predominate. Similarly, in patients with HER2 exon 20 insertions ($n=28$), responses were observed in two patients with breast cancer, but none were seen in patients with lung cancer, in which this class of alteration is most common. In exon 20 insertions, preservation of glycine at the 770 position, which seems to facilitate binding of covalent HER kinase inhibitors such as neratinib, did not predict for response as previously suggested by preclinical modelling[18] (Extended Data Fig. 4). Similarly, the number of amino acids involved in the insertion did not seem to predict outcome, with responses observed in patients with both 3 (G788_P780dup) and 4 (Y722_A755dup) amino acid insertions. Finally, among the 15 patients with HER2 mutations not known to be hotspots, only one responded to neratinib. Notably, this response occurred in a patient with breast cancer and a complex insertion/substitution (L755_E757delinsS), which, to our knowledge, has not been observed previously. Although this case illustrates that the tumours of some patients may be addicted to truly private oncogenic drivers (those arising in only a single patient), it is also noteworthy that this insertion occurs in a domain that is the target of recurrent insertions. The absence of clinical activity in the remaining 14 patients with cancers with non-hotspot mutations suggests that, although the recurrence of a mutation in HER2 is insufficient to define it as sensitizing to a HER2 kinase inhibitor, the absence of recurrence (that is, mutations that do not occur at hotspot positions) provides circumstantial evidence that the alteration is unlikely to be a driver.

Although the overall numbers of patients in each subgroup preclude formal statistical comparison, integrating efficacy, mutational and lineage data, we observed that clinical benefit from neratinib therapy appeared to vary as a function of both mutational and disease context

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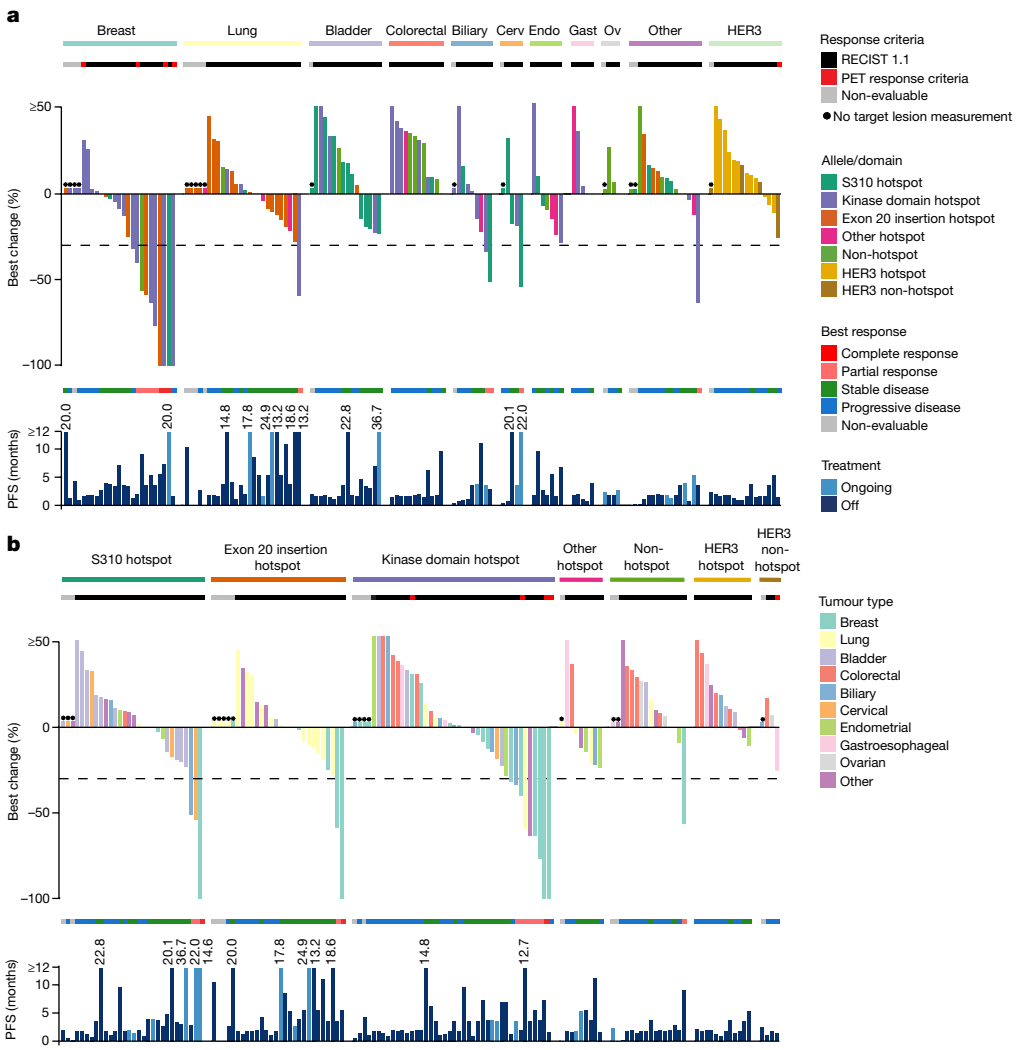

Figure 1 | Individual treatment outcome and response for 141 patients grouped by tumour cohort and mutant allele/domain. a, **b**, Top, percentage best change from baseline in the target lesion assessed by the appropriate response criteria (RECIST version 1.1 or PET). Each bar is colour coded according to its mutation allele/domain, for patients grouped by tumour cohort (**a**), or tumour type, for patients grouped by mutant allele/domain (**b**). Middle, best overall response. Bottom, progression-free survival (PFS), colour-coded by treatment status. *Non-evaluable. Cerv, cervical; endo, endometrial; gastro, gastroesophageal; ov, ovarian; PET, positron-emission tomography.

(Fig. 2). In tumour types sensitive to neratinib therapy, such as breast, biliary and cervical cancers, responses were collectively observed across all types and classes of HER2 mutations. By contrast, in lung cancer, a tumour type that exhibits modest sensitivity to neratinib, response was limited to a patient with a HER2 kinase domain missense mutation—a class of mutation with greater *in vitro* sensitivity to neratinib[5]. Finally, in tumour types with intrinsic lineage-based resistance to neratinib, such as bladder and colorectal cancers, responses were not observed regardless of the HER2 mutation, type or class.

Safety

All patients received neratinib with mandatory anti-diarrhoeal prophylaxis. With this regimen, the rate of grade 3 diarrhoea was 22% (Extended Data Table 2), consistent with previous experience[19]. Among patients who developed grade 3 diarrhoea, the median time to onset was 10 days and the median duration of the diarrhoea episode was 2 days. Patients were typically managed with dose interruption and reduction, with only 2.8% permanently discontinuing therapy owing to diarrhoea. The remainder of adverse events were predominantly low-grade.

Central confirmation of HER2 and HER3 mutations

There is active debate within the cancer research community as to whether central confirmation of mutational status before study entry is optimal for determining trial eligibility for precision medicine studies. To define the reproducibility of local mutational testing, DNA from archival formalin-fixed paraffin-embedded tumour and plasma samples were re-sequenced (see Methods). A total of 33 patients (26 HER2-mutant, 7 HER3-mutant) were excluded from this concordance analysis because the local test used was the same as the central tumour assay being evaluated. Of the remaining 99 patients with HER2 mutations, adequate material for tumour genomic testing was unobtainable for 26 patients. Overall, concordance in the remaining patients based on central tumour and/or plasma sequencing was 95% (69 out of 73), with 38 patients assessed by tissue and plasma, 14 by tissue alone, and 21 by plasma alone. Central testing identified one locally reported mutation (V773M) as a germline polymorphism and this patient, with renal cell carcinoma, had progressive disease at first scan. Central testing in the four cases in which the HER2 mutation could not be confirmed passed all quality-control metrics, but in two patients the testing was performed on material collected at least three years after the tissue used for local testing, raising the possibility that tumour heterogeneity was involved in the discordance. None of the patients with discordant HER2 results responded to neratinib, and their median progression-free survival was only 43 days (range: 5–58 days). Among the 9 patients eligible for concordance testing with HER3 mutations, tumour tissue was available for central sequencing in 8 patients, and overall concordance was 75% (6 out of 8).

Genomic modifiers of response

Given the variability of treatment response, even among patients with the same tumour lineage and HER2-mutant allele, we sought to identify other genomic modifiers of response through broader genomic characterization of tumour-derived DNA (see Methods). First, we

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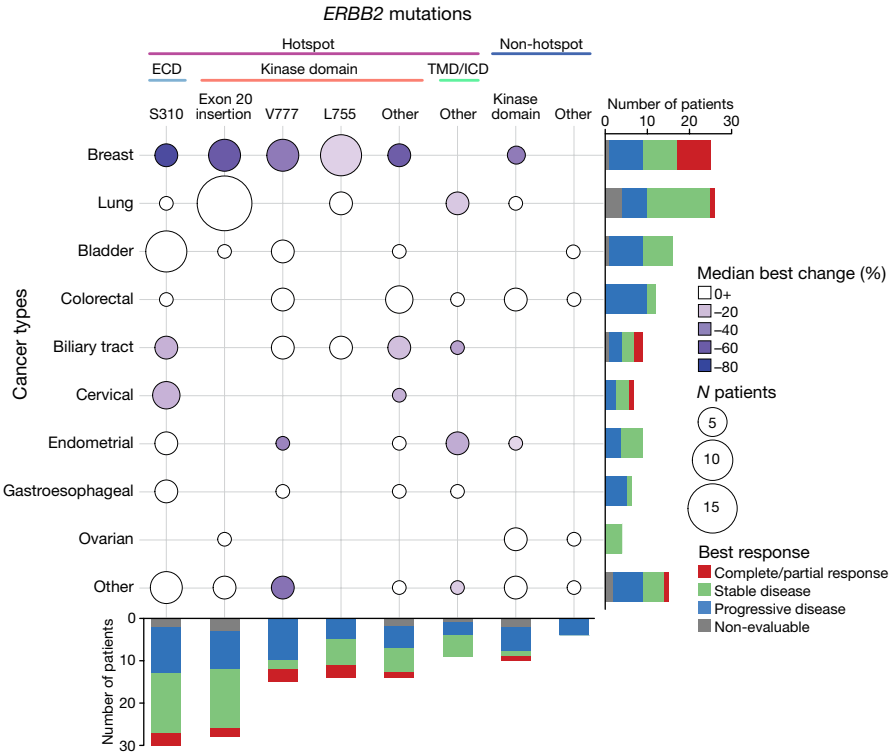

Figure 2 | Integrated efficacy by tumour type and HER2 allele/domain. The *y* axis represents the tumour types, and the *x* axis represents the mutated allele/domain and hotspot status. The hotspot mutations are further broken down into the various domains. The size of the circle is proportional to the count of the tumour type and allele/domain; the colour of the circle reflects the median percentage best change in the target lesions (any zero or positive median change is indicated in white). The stacked bars represent the best overall response for the tumour type or domain/allele, as indicated in the key. ECD, extracellular domain; ICD, intracellular domain; TMD, transmembrane domain.

explored the relationship between *ERBB2* amplification and outcome, as this is a well-established predictor of response to HER2-targeted therapies in patients lacking HER2 mutations. In total, 17% of patients (15 out of 86) had concurrent HER2 mutations and gene amplification. Amplifications preferentially targeted the mutant allele locus (86%, 12 out of 14 evaluable). Using a dichotomous definition of clinical benefit (stable disease or partial response lasting at least 24 weeks), *ERBB2* amplification did not correlate with outcome ($P = 0.50$; Fig. 3), suggesting that in the presence of HER2 mutations, amplification may not confer additional sensitivity to irreversible HER kinase inhibitors. We also explored the relationship of *ERBB2* mutation clonality on outcomes. In the 74 patients with adequate material to allow definitive assessment of *ERBB2* mutant clonality, the mutation was clonal in 95% (70 out of 74; Extended Data Fig. 5a). None of four patients with a subclonal *ERBB2* mutation achieved clinical benefit.

Hypothesizing that tumours with an increased tumour mutational burden (TMB) might be more likely to acquire HER2 mutations without developing oncogenic dependence (that is, passenger mutations), we evaluated whether overall TMB status affected outcome. Using a previously validated cut-off ($\geq$13.8 non-synonymous mutations per megabase of DNA[2]), 20% of patients (17 out of 86) met criteria for a high TMB. In total, 24% of patients (16 out of 66) without clinical benefit versus 5% of patients (1 out of 20) with benefit met criteria for a high TMB, a trend that did not reach statistical significance ($P = 0.10$).

Next, we evaluated whether the pattern of co-mutations affected clinical benefit in the subset of patients where broader profiling was available ($n = 86$). In patients with HER2-mutant disease, coincident mutations in TP53 and HER3 were enriched in patients with no clinical benefit (nominal $P = 0.018$ and $P = 0.064$, respectively; Fig. 3). Although not significant after correcting for multiple hypothesis testing, potentially owing to the relatively small sample size, it is noteworthy that no patients with clinical benefit possessed co-mutation of HER2 and HER3. Concurrent mutation of these genes was observed in multiple cancer types (breast $n = 3$, bladder $n = 2$, gastroesophageal $n = 2$, colorectal $n = 1$ and pancreatic $n = 1$) and involved a variety of unique HER2 and HER3 mutations ($n = 8$ and $n = 9$, respectively). Expanding our analysis to genomic activation at the pathway level, we identified somatic mutations of known oncogenic potential and grouped them by those involving the receptor tyrosine kinase (RTK)/RAS/RAF and PIK3CA/AKT/mTOR pathways, and cell cycle checkpoints (Extended Data Fig. 5b). In this analysis, concurrent aberrations in cell cycle checkpoints were associated with lack of clinical benefit ($P = 0.043$), and activation of RTK/RAS/RAF also trended towards a worse outcome ($P = 0.060$). The association between the cell-cycle pathway and lack of clinical benefit seems to be primarily driven by TP53 mutations, losing significance upon removal of TP53 mutations ($P = 0.769$). Interestingly, activation of the PI3K/AKT/mTOR pathway, an established negative predictor of response to HER2-targeted therapy in HER2-amplified breast cancer[20–22], did not adversely affect the likelihood of clinical benefit ($P = 0.753$). It is possible that the clinical impact of concurrent gene/pathway activation may vary by tumour type, and future disease-specific studies are needed to define these associations better. Although these were exploratory analyses that will require confirmation, our results suggest that concurrent activation of specific genes as well as pathways may act as an additional modifier of response beyond cancer type and specific HER2 mutant allele.

Discussion

The ability to profile cancer comprehensively at the point of care has made possible the opportunity to personalize therapy for each patient based on the compendium of genomic alterations identified[23]. Despite the promise of this approach, implementing this paradigm in clinical practice has been hampered by considerable gaps in knowledge about the biological and clinical importance of most genomic variants identified[24]. This challenge is exemplified by the marked diversity and wide distribution of HER2 and HER3 mutations in human cancers,

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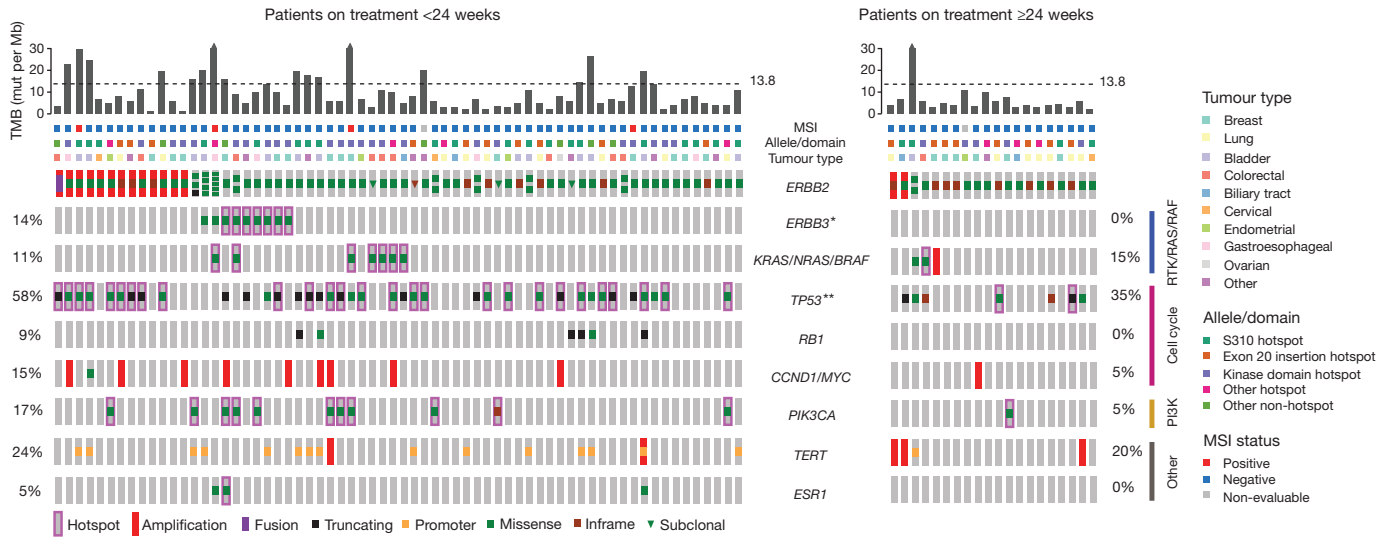

Figure 3 | Genomic modifiers of response and outcome by treatment duration. Comprehensive OncoPrint of the dichotomous clinical benefit groups for 86 patients with broad profiling data (left: no benefit ($n = 66$, biologically independent samples), right: clinical benefit ($n = 20$, biologically independent samples)). From top to bottom: TMB with the dotted line indicating the threshold for high TMB at 13.8 mutations (mut) per megabase; microsatellite (MSI) status; allele/domain; tumour type; HER2 (*ERBB2*) status showing amplification; clonality and the presence of a single or multiple mutations; and co-alterations in genes associated with key pathways. *$P = 0.064$, **$P = 0.018$, Fisher's exact test. Statistical significance is lost when corrected for multiple hypothesis testing.

as well as by the difficulty of generating preclinical models of these mutations that correctly recreate their biology in patients. To our knowledge, SUMMIT provides the first comprehensive dataset on the clinical actionability of HER2 and HER3 mutations. We found that HER2 mutations are associated with HER2-dependence in a subset of patients with HER2-mutant tumours, but that response to HER kinase inhibition varies a function of the individual mutant variant, the tumour type as well as the pattern of co-mutations present.

Although we identified promising preliminary activity for neratinib in breast, biliary and cervical cancers, the response rate in these tumours was still lower than with approved therapies that target oncogenic alterations in *EGFR*, *ALK*, *ROS1* and *BRAF*. The low response rate in lung cancer, in which HER2 mutations exhibit mutually exclusivity with other known drivers[25], is also notable and may in part reflect a lower potency of neratinib inhibition in Y772_A775dup compared to other insertions or missense mutants[18]. Successfully targeting HER2 activation in other contexts has historically necessitated drug combinations. For example, single-agent trastuzumab has a response rate of only approximately 20% in *ERBB2*-amplified breast cancer[26,27]. By contrast, the overall survival in *ERBB2*-amplified breast and gastroesophageal cancers is markedly improved by adding trastuzumab to chemotherapy[28,29]. More recently, the intensification of HER2 inhibition through the combination of two HER2-targeted agents has been shown to result in synergistic efficacy in patients with *ERBB2*-amplified breast[30–32] or colorectal[33,34] cancers, as well as in HER2-mutant colorectal cancer xenografts[6]. Cumulatively, these data suggest that combining neratinib with another HER2-targeted therapy is a rational next step, and SUMMIT has been amended to evaluate this approach in multiple HER2-mutant tumour types.

SUMMIT represents a continued evolution in the design of basket studies, which enrol patients on the basis of qualifying mutations rather than tumour type. The initial generation of these studies focused on evaluating individual somatic mutations that were already clinically validated in one cancer (such as BRAF V600 in melanoma) in other tumour types[10,35]. More recently, basket studies have been used to generate initial or even practice-changing clinical data of truly novel genomic biomarkers, especially when these genomic alterations occur at low frequency across a wide distribution of cancer types[11,36,37]. SUMMIT extends this concept one step further by demonstrating for the first time how a single study can be used to simultaneously evaluate a range of individual variants in HER2 and HER3, each with varying degrees of prior biologic characterization. This permissive enrolment strategy allowed us to treat patients harbouring mutations that, at the time of enrolment, had not been characterized preclinically as gain-of-function but were either recurrent or paralogous to known activating mutations in homologous genes. For example, patients with previously uncharacterized HER2 variants, such as V697L, D769N/H/Y and L869R, were included in this manner and responded to treatment, thus providing initial clinical proof-of-concept that these mutations confer a gain-of-function phenotype even before formal biologic characterization. The approach of pairing a permissive enrolment strategy with allele prioritization based on recurrence, paralogy and other readily computable features has potentially broad applicability to implementing genomic-driven oncology[24]. This strategy will take on even greater importance as clinical testing moves from targeted sequencing to whole exome or even whole genome sequencing, techniques that will allow for evaluation of an even greater number of therapeutic hypothesis but will also exponentially expand the number of uncharacterized alleles we routinely identify.

SUMMIT provides additional insights into the conduct of molecularly driven oncology studies. Our ability to understand the complex interactions between tumour lineage, individual HER2 variant and response to neratinib was only possible because of the relatively large size of this study ($n = 141$). By comparison, many of the 'master/umbrella' protocols that are currently underway are designed to enrol a maximum of 30–40 patients into each genomically defined treatment arm. Our experience suggests that many studies of this size may be inadequately powered to identify the subgroups with true efficacy, assuming that most genomic alterations will not predict for tumour-type agnostic efficacy. SUMMIT also demonstrates the feasibility of enrolling patients based on local testing, with patients treated on the basis of 30 unique sequencing assays performed in 25 different laboratories. Despite this, concordance on retrospective central review was extremely high (96%).

An important impediment to progress in oncology has been the limited availability of preclinical model systems that accurately recreate the complex biology of human cancer. Although important strides have been made, the wide-scale profiling of cancer in the clinic provides the potentially transformative opportunity to interrogate cancer biology at the bedside in a manner previously only possible at the bench. Here,

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we demonstrate how this opportunity can be leveraged to probe the biology of a diverse set of HER2 and HER3 mutations across a variety of solid tumours through pharmacological HER kinase inhibition in patients. In doing so, we found that response to pharmacological inhibition was based on the characteristics of both tumour type and genomic variant to a degree that was not predicted by established preclinical models. In summary, SUMMIT demonstrates how the clinical trial can become an important tool in refining our understanding of the biological dependencies in human cancers.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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METHODS

Patients. Eligible patients had histologically confirmed advanced solid tumours harbouring HER2 or HER3 mutations, an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2 and an unlimited number of previous therapies. Patients with previous exposure to HER kinase inhibitors and unstable brain metastases were excluded. HER2 and HER3 mutations were determined by local tumour testing as routinely performed or ordered by each participating site. In total, 85% (120 out of 141) of enrolled patients were identified by next-generation sequencing assays. In 81% of cases (97 out of 120), the next-generation sequencing assay included full exon coverage for *ERBB2* or *ERBB3*, whereas in 19% (23 out of 120) of cases, only select exons or hotspots were included in the assay design. The remaining 15% (21 out of 141) of patients were enrolled via RT–PCR, Sanger, pyrosequencing, or mass spectrometry-based sequencing methods. The study was approved by the institutional review board or independent ethics committee at each site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. Written informed consent was obtained from all participants.

Study design, treatment and endpoints. This was a multi-cohort basket study of patients with solid tumours harbouring HER2 and HER3 mutations. Patients with HER2-mutant tumours were enrolled into one of several disease-specific cohorts or an 'other' cohort for tumour types not otherwise specified; all patients with HER3-mutant tumours were enrolled to one cohort. Patients known to contain both HER2 and HER3 mutations at the time of enrolment were assigned to the HER2-mutant cohort. Patients were treated with neratinib 240 mg daily on a continuous basis with mandatory loperamide prophylaxis during cycle 1. The primary endpoint was ORR_8, as assessed by investigators according to RECIST (version 1.1). Secondary endpoints included best overall response, progression-free survival, overall survival and safety. Patients who were not evaluable by RECIST were permitted to enrol and were evaluated for response by ^{18}F-fluorodeoxyglucose PET according to a modified version of the original PET Response Criteria in Solid Tumours (PERCIST; version 1.0)[38], referred to here as PET Response Criteria (PRC, Extended Data Table 3).

Assessments. Disease assessments with computed tomography, magnetic resonance imaging or combined positron emission tomography–computed tomography (for those evaluated by PRC) were performed at baseline and then every 8 weeks until disease progression, death or withdrawal. Adverse events were graded by the investigator according to the Common Terminology Criteria for Adverse Events (version 4.0) until day 28 after discontinuation of study treatment.

Genomic biomarker studies. All samples were assigned anonymized identifiers by the study sponsor based on the order of study enrolment. Both tumour DNA and tumour-derived cell-free DNA in plasma were collected with the goals of confirming locally reported HER2/3 mutations as well as evaluating how *ERBB2* and *ERBB3* copy number and clonality as well as co-mutational pattern affected outcome. Collection of archival tumour and plasma samples was mandatory for all patients. Next-generation sequencing was performed using targeted sequencing of pretreatment DNA from formalin-fixed paraffin-embedded tumour and matched blood specimens (preferentially) and cell-free DNA (if tumour was not available or was inadequate). A custom single-gene *ERBB2* capture next-generation sequencing test was also performed on pretreatment cell-free DNA in a subset of patients with HER2-mutant disease.

Central sequencing confirmation. For patients with adequate material, DNA from formalin-fixed paraffin-embedded ($n = 91$) or tumour-derived cell-free DNA from plasma ($n = 15$) and matched germline DNA ($n = 102$) underwent targeted next-generation sequencing assay using Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT)[2], producing an average of 738-fold coverage per tumour (range: 253–1,383). In brief, this assay uses a hybridization-based exon capture designed to capture all protein-coding exons and select introns of oncogenes, tumour-suppressor genes and key members of pathways that may be actionable by targeted therapies. In this study, either 341 ($n = 18$) or 410 ($n = 88$) key cancer-associated genes were analysed (Supplementary Information). Sequencing data were analysed as previously described to identify somatic single-nucleotide variants, small insertions and deletions, copy number alterations and structural arrangements[39]. In addition, hotspot alterations were identified using an adaptation of a previously described method[4] applied to a cohort of 24,592 sequenced human cancers[40]. For gene-level analysis, select genes within our targeted 341/410 MSK-IMPACT panel involved in the RTK/RAS/RAF, PIK3CA/AKT/mTOR, and cell cycle checkpoint pathways were selected using the KEGG pathway database[41]. For pathway level analysis, only potentially oncogenic alterations in the selected genes were included and determined to be oncogenic by OncoKB (version September 2017), a curated knowledge base of the oncogenic effects and treatment implications of mutations and cancer genes (http://www.oncokb.org[42]).

HER2 amplification and clonality analysis. For patients in the HER2-mutant arm with MSK-IMPACT sequencing data (with matched germline DNA, $n = 74$), the Fraction and Allele-Specific Copy Number Estimates from Tumour Sequencing (FACETS) algorithm (version 0.3.9) was used to estimate tumour purity and ploidy, and total and allele-specific copy number[43]. Tumour samples with purity less than 20% were excluded from this analysis. Focal HER2 amplifications for tumours with MSK-IMPACT and FACETS data were inferred using the following criteria: fold change ≥ 1.5 (MSK-IMPACT tumour:normal sequencing coverage ratio) and total HER2 copy number ≥ 4 copies (FACETS-derived total copy number). To infer clonality of each HER2 mutation, cancer cell fractions were estimated with 95% confidence intervals by integrating FACETS-derived joint segmentation and MSK-IMPACT mutation data as input into the ABSOLUTE algorithm[44] (version 1.0.6). Mutations were classified as either clonal or subclonal based on the following criteria: clonal if the estimated cancer cell fractions > 0.85, otherwise subclonal. For patients with HER2 amplification, the mutation copy number (mutation multiplicity) was calculated as previously described[45] to infer amplification of the mutant allele when the mutation multiplicity was greater than half of the total HER2 copy number.

TMB and MSI. TMB, defined as the number of non-synonymous mutations per megabase, was calculated for patients with MSK-IMPACT sequencing data ($n = 106$)[6]. MSI was assessed for patients with HER2-mutant tumours with matched germline DNA sequencing data ($n = 89$) using an orthogonal bioinformatics tool, MSIsensor[46]. Furthermore, mutations were decomposed into the 30 constituent mutational signatures as described previously[47]. In brief, MSIsensor scores <10 were classified as microsatellite stable and >10 were considered MSI-high using a previously validated cut-off score[48]. Those with a MSIsensor score of <10 but having evidence of a dominant mismatch repair mutational signature were also considered MSI[43,47].

Statistical analysis. For each HER2-mutant tumour type and the HER3-mutant cohort, a Simon optimal two-stage design with a true $ORR_8 \leq 10\%$ was considered unacceptable (null hypothesis), whereas a true $ORR_8 \geq 30\%$ (alternative hypothesis) merited further study. Efficacy in each cohort was analysed independently and the study was not designed to compare efficacy across cohorts formally. All patients who received at least one dose of neratinib were included in the safety and efficacy cohorts. All data reflect an interim data-cut taken on 10 March 2017 from patients enrolled up to 16 December 2016 (Extended Data Fig. 6). Most patients were off therapy at the time of data analysis (Extended Data Table 4). Progression-free survival was estimated using the Kaplan–Meier method. The study is registered at http://www.clinicaltrials.gov, under the identifier NCT01953926. Individual associations among genomic changes and response were assessed by either Fisher's exact or chi-squared tests (where appropriate) and corrected for multiple hypothesis testing using Benjamini–Hochberg correction.

Chi-squared or Fisher's exact tests were performed to compare gene-level and pathway-level associations between the dichotomous clinical benefit groups. *P* values were corrected for multiple hypothesis testing using Benjamini–Hochberg correction. HER2 and HER3 lollipop distribution plots were generated using ProteinPaint[49]. All other figures were generated using R software (http://www.R-project.org/).

This clinical trial was not randomized and investigators were not blinded to treatment allocation and outcome assessment.

Data availability. All datasets generated during and/or analysed during the current study, including patient-level clinical data as well as all sequencing data have been deposited and are publically available in the cBioPortal for Cancer Genomics under the accession code 'SUMMIT, Nature, 2018' (http://www.cbioportal.org/study?id=summit_2018).

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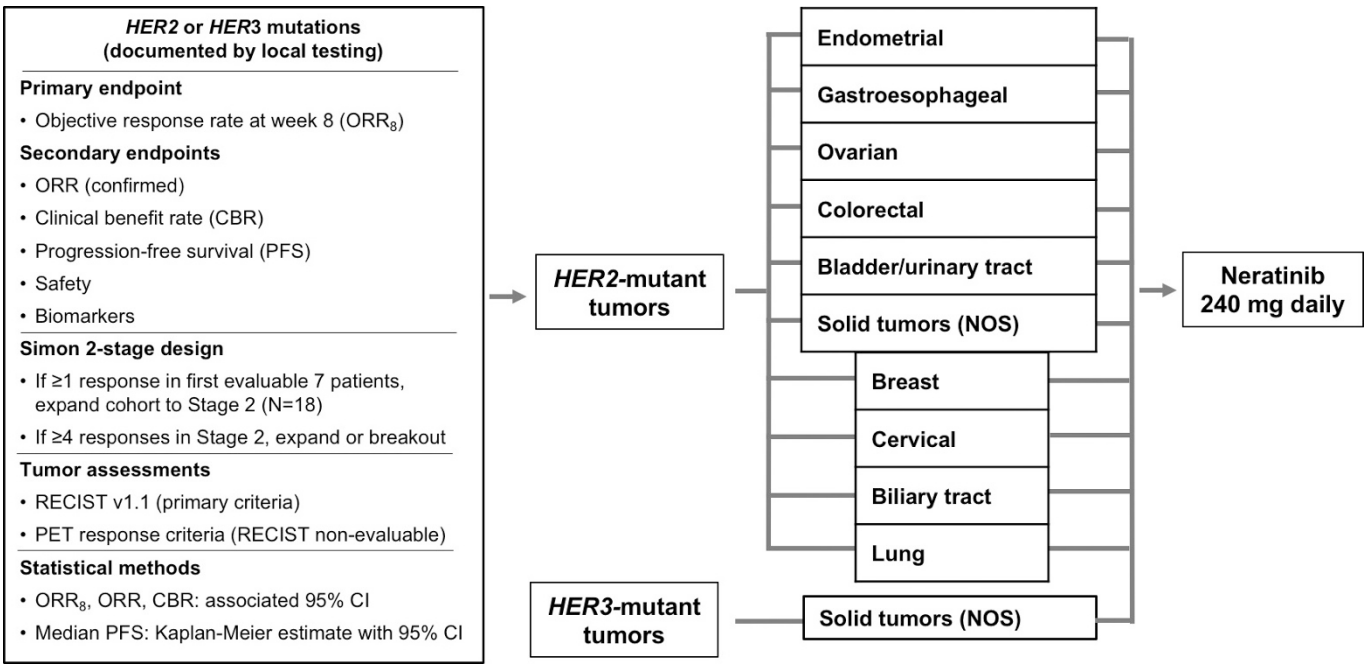

Extended Data Figure 1 | Design of SUMMIT study. Five tumour-specific HER2 (*ERBB2*)-mutant cohorts were pre-specified (endometrial, gastroesophageal, ovarian, colorectal and bladder/urinary tract). In addition, a sixth 'solid tumour (not otherwise specified, NOS)' HER2-mutant cohort allowed for the enrolment of patients with any other cancer types. A sufficient number of patients with breast, cervical, biliary and lung cancer were enrolled in the solid tumours (NOS) cohort to permit independent efficacy analysis using the same design as the pre-specified cohorts. Patients with HER3 (*ERBB3*)-mutant tumours were enrolled in a HER3-specific cohort regardless of tumour type. CBR, clinical benefit rate; cfDNA, cell-free (tumour) DNA; CI, confidence interval.

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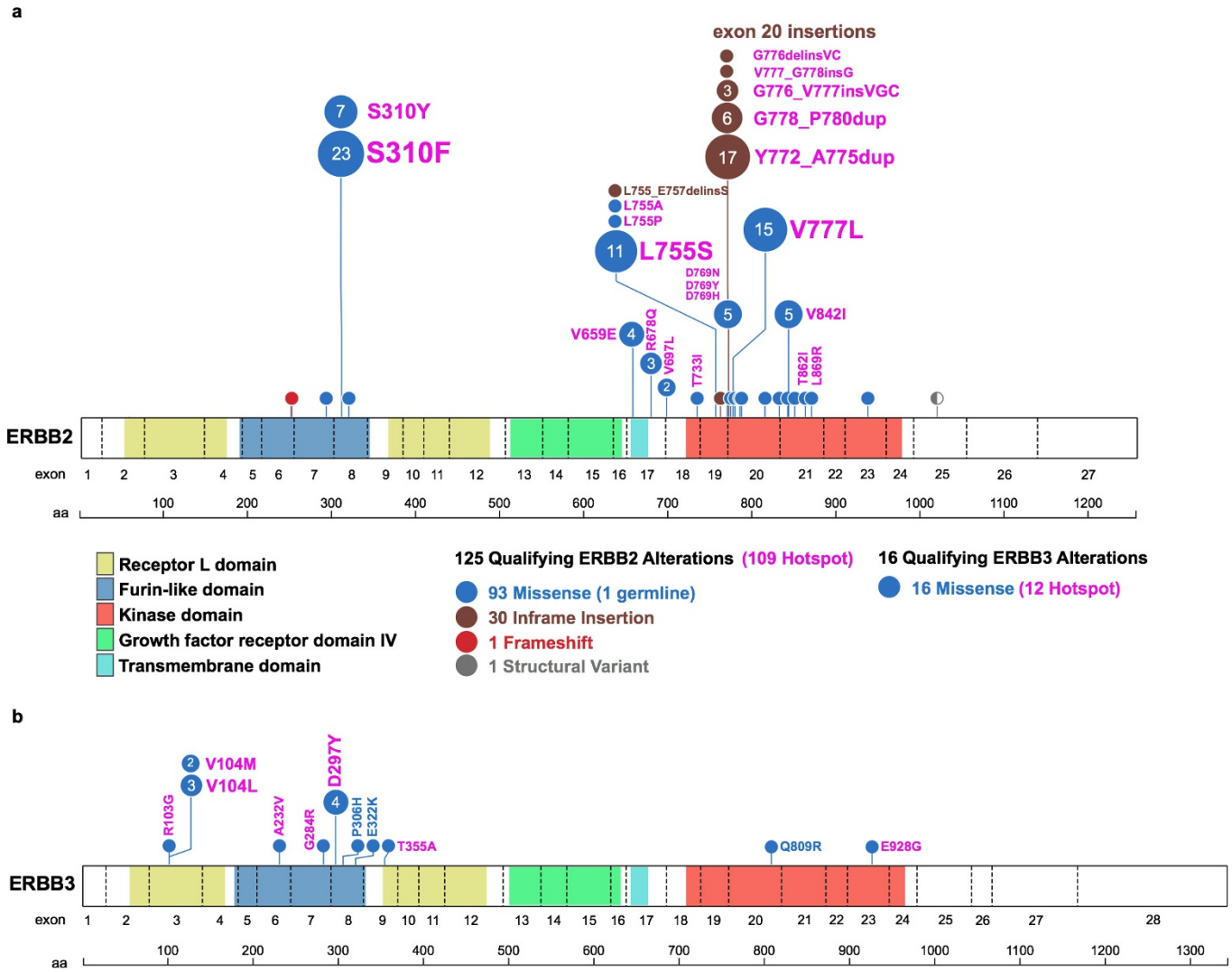

Extended Data Figure 2 | Distribution of HER2 and HER3 mutations positioned by their amino acid coordinates across the respective protein domains. a, **b**, HER2 (**a**) and HER3 (**b**) mutations (125 and 16 mutations, respectively). Each unique mutation is represented by a circle, with the circle size and number representing the frequency, and coloured to show the mutation class as indicated in the legend. The corresponding amino acid change and common hotspot mutations (shown in pink) are labelled next to the circles.

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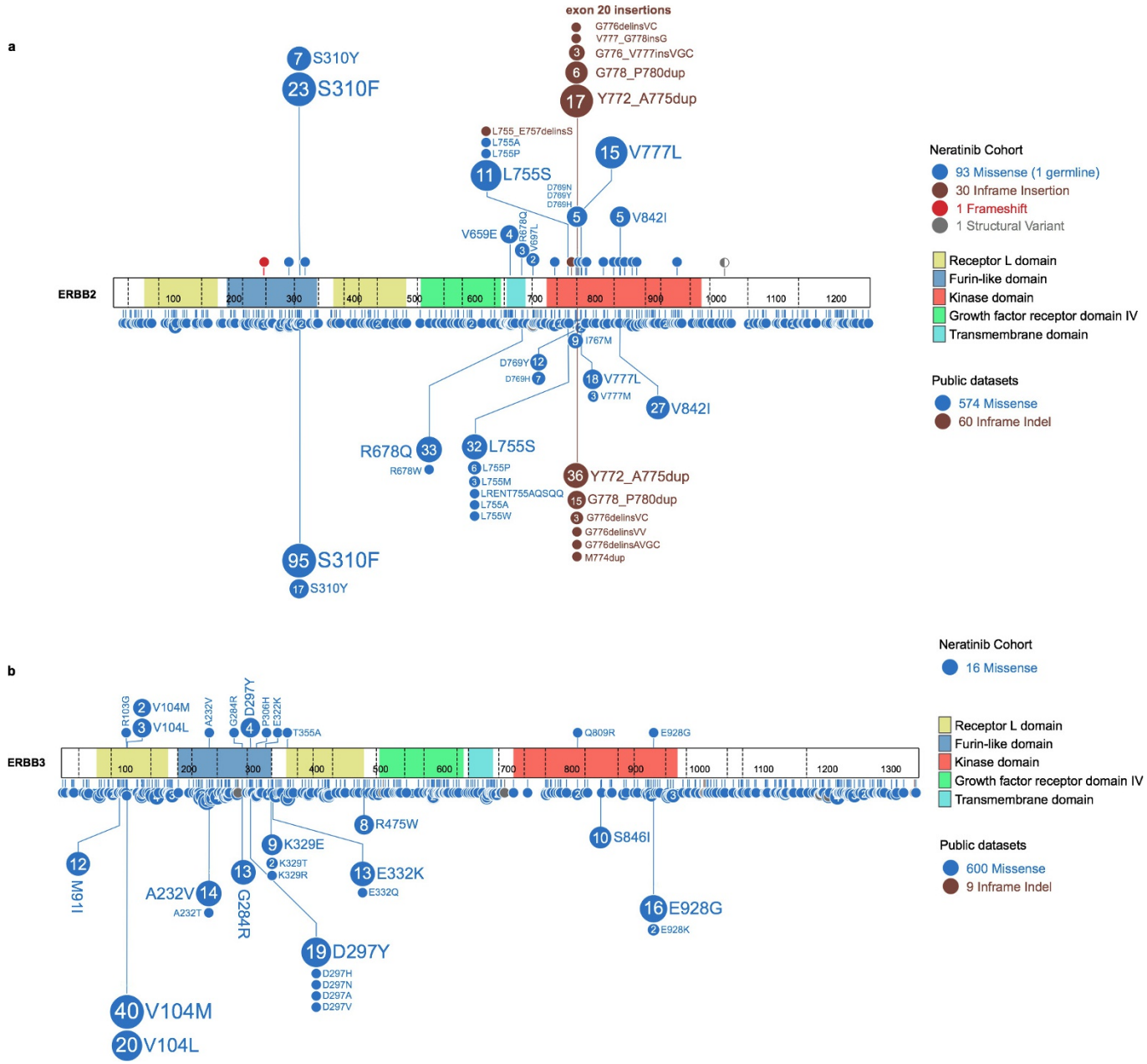

Extended Data Figure 3 | Spectrum of HER2 and HER3 mutations observed in the neratinib study versus TCGA, ICGC and other public datasets. a, **b**, Distribution of HER2 (**a**) and HER3 (**b**) mutations observed across our cohort in comparison to the spectrum of HER2 and HER3 mutations (reflected lollipop) from publically available datasets (TCGA, ICGC and other published studies).

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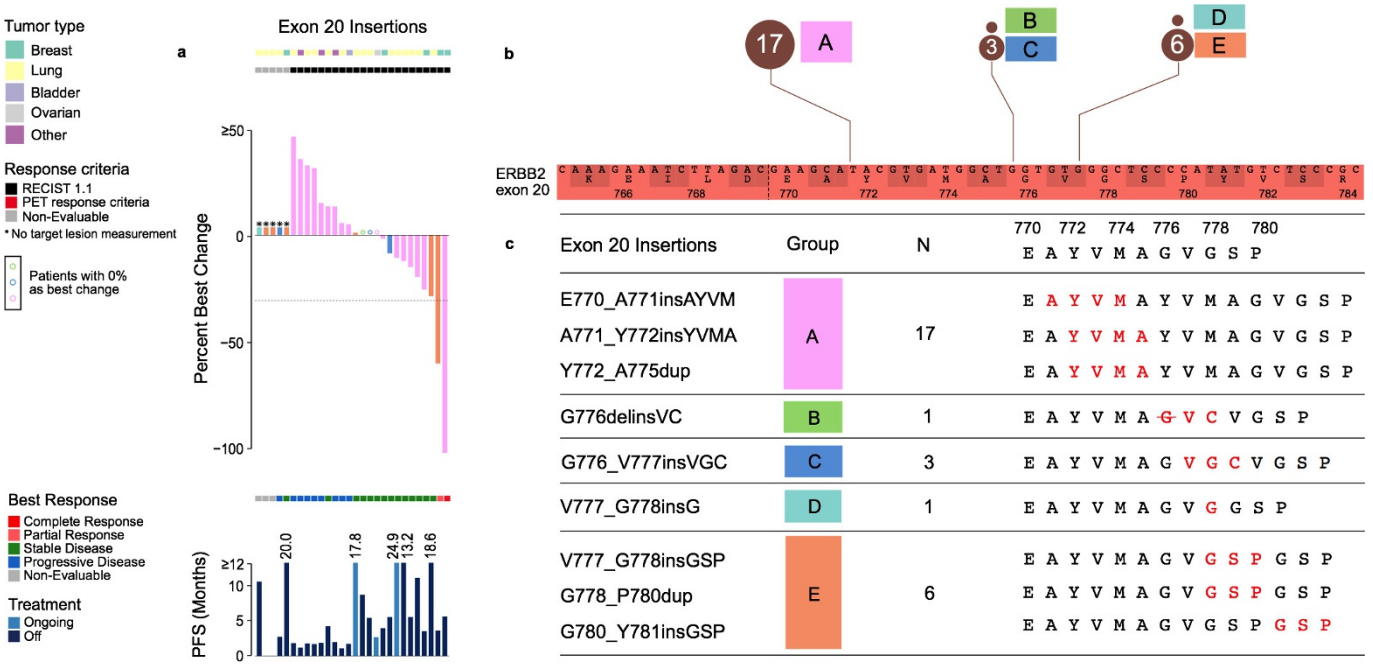

Extended Data Figure 4 | Distribution and outcome of 28 HER2 exon 20 insertions. a, Percentage best change and PFS plots corresponding to each type of exon 20 insertion (colour coded by synonymous amino acid change). Three cases with no change are indicated in colour-coded circles above the *x* axis. **b**, Zoomed-in schematic of all exon 20 insertions positioned by their amino acid coordinates and frequencies. **c**, Five unique types of exon 20 insertions observed in the study with the resulting full amino acid sequences (insertion indicated in red).

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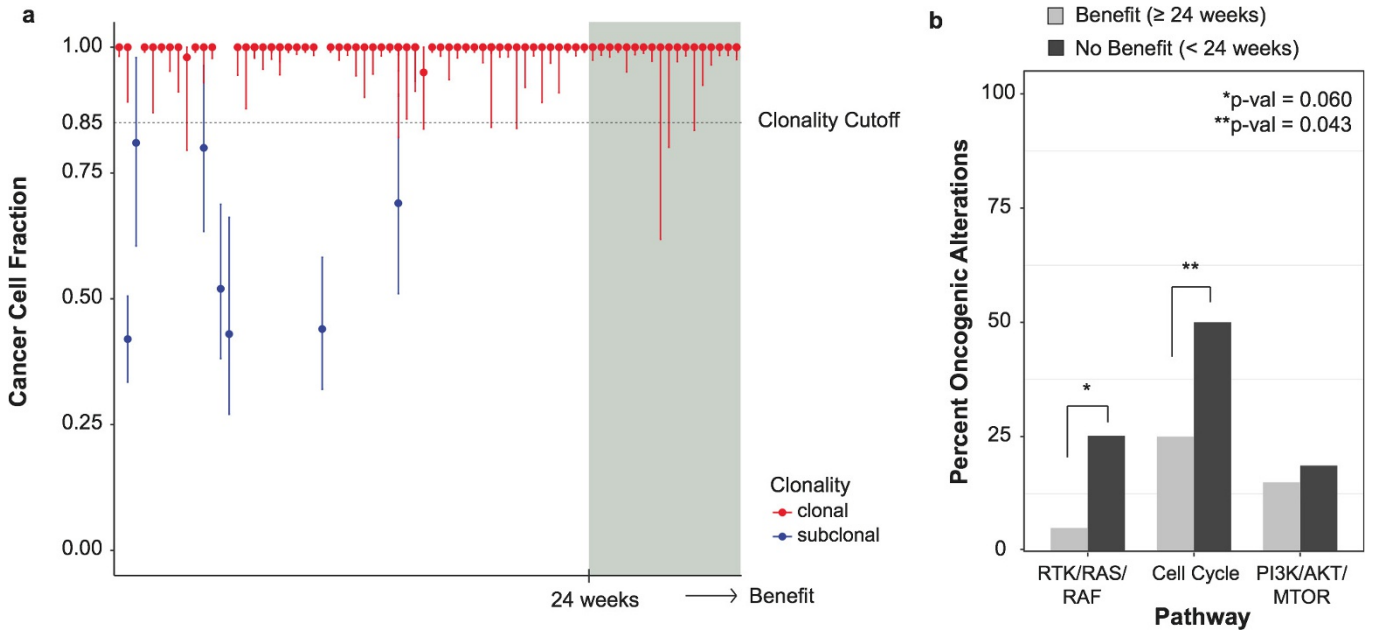

Extended Data Figure 5 | Genomic modifiers of response and outcome by treatment duration. a, Cancer cell fractions with 95% confidence intervals and clonality status of all HER2 mutations in 74 patients with sufficient sequencing data ordered by increasing clinical benefit (weeks on therapy). **b**, Comparison of the percentage activation of known oncogenic alterations in the three pathways between the patients of clinical benefit ($n = 20$, biologically independent samples) and no benefit ($n = 66$, biologically independent samples). Nominal Fisher's P values are shown.

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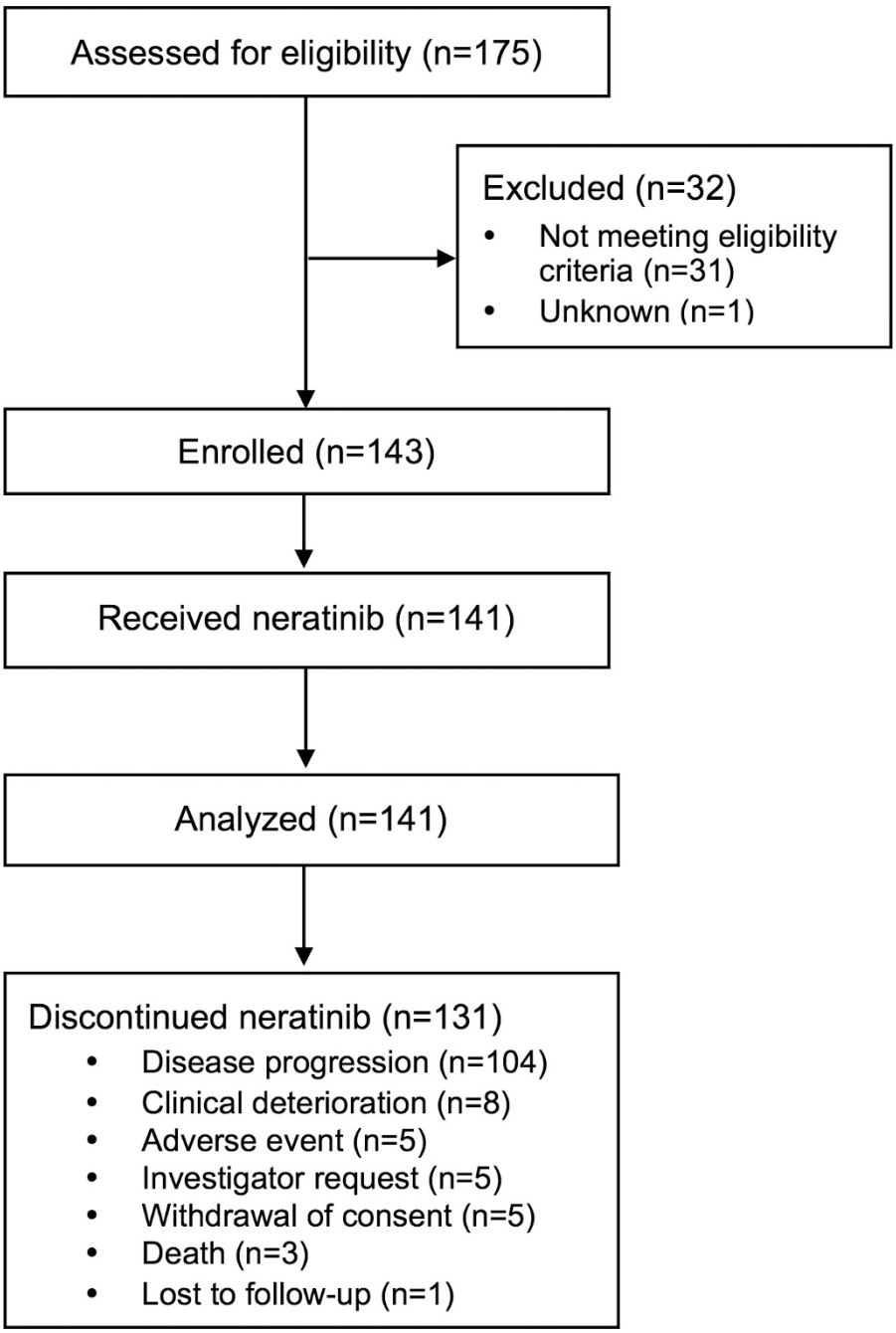

Extended Data Figure 6 | SUMMIT CONSORT diagram.

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Extended Data Table 1 | Patient demographics and efficacy by cohort

	HER2										HER3
Characteristic	Breast (n=25)	Lung (n=26)	Bladder (n=16)	Colorectal (n=12)	Biliary tract (n=9)	Cervical (n=5)	Endometrial (n=7)	Gastro-esophageal (n=5)	Ovarian (n=4)	NOS (n=16)	NOS (n=16)
Median (range), years	57.0 (37-80)	62.0 (46-74)	65.0 (48-83)	65.0 (30-81)	66.0 (57-78)	49.0 (42-56)	57.0 (54-74) 5	67.0 (36-70)	56.5 (38-58)	59.0 (32-80)	66.0 (39-82)
<65 years, n (%)	19 (76.0)	18 (69.2)	8 (50.0)	6 (50.0)	2 (22.2)	5 (100)	(71.4)	1 (20.0)	4 (100)	13 (81.3)	7 (43.8)
≥65 years, n (%)	6 (24.0)	8 (30.8)	8 (50.0)	6 (50.0)	7 (77.8)	0 (0)	2 (28.6)	4 (80.0)	0 (0)	3 (18.8)	9 (56.3)
Sex, n (%)											
Female	24 (96.0)	17 (65.4)	3 (18.8)	6 (50.0)	5 (55.6)	5 (100)	7 (100)	2 (40.0)	4 (100)	7 (43.8)	12 (75.0)
Male	1 (4.0)	9 (34.6)	13 (81.3)	6 (50.0)	4 (44.4)	0 (0)	0 (0)	3 (60.0)	0 (0)	9 (56.3)	4 (25.0)
ECOG PS, n (%)											
0	7 (28.0)	11 (42.3)	6 (37.5)	5 (41.7)	2 (22.2)	1 (20.0)	2 (28.6)	0 (0)	0 (0)	3 (18.8)	1 (6.3)
1	17 (68.0)	14 (53.8)	10 (62.5)	7 (58.3)	6 (66.7)	4 (80.0)	5 (71.4)	5 (100)	4 (100)	11 (68.8)	12 (75.0)
2	1 (4.0)	1 (3.8)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (12.5)	3 (18.8)
Prior systemic lines, n (%)	0 (0)	1 (3.8)	1 (6.3)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.3)	0 (0)
None	3 (12.0)	12 (46.2)	2 (12.5)	4 (33.3)	3 (33.3)	0 (0)	1 (14.3)	2 (40.0)	0 (0)	6 (37.5)	1 (6.3)
1	2 (8.0)	6 (23.1)	9 (56.3)	3 (25.0)	2 (22.2)	3 (60.0)	2 (28.6)	1 (20.0)	0 (0)	2 (12.5)	11 (68.8)
2	20 (80.0)	7 (26.9)	4 (25.0)	5 (41.7)	3 (33.3)	2 (40.0)	4 (57.1)	2 (40.0)	4 (100)	7 (43.8)	4 (25.0)
≥3											
Median time from metastasis to enrolment, years (range)	2.64 (0.1-15.0)	0.83 (0.1-3.1)	0.69 (0.2-2.3)	1.14 (0.0-2.7)	1.00 (0.0-2.8)	1.40 (0.3-4.5)	0.43 (0.2-4.4)	0.80 (0.4-4.3)	7.54 (1.1-7.7)	1.35 (0.0-5.4)	1.13 (0.3-4.5)

Outcome	HER2										HER3
	Breast (n=25)	Lung (n=26)	Bladder (n=16)	Colorectal (n=12)	Biliary tract (n=9)	Cervical (n=5)	Endometrial (n=7)	Gastroeso-phageal (n=5)	Ovarian (n=4)	NOS (n=16)	NOS (n=16)
ORR at week 8, n (%) [95% CI]	8 (32.0) [14.9–53.5]	1 (3.8) [0.1–19.6]	0 (0.0) [0.0–20.6]	0 (0.0) [0.0–26.5]	2 (22.2) [2.8–60.0]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–41.0]	0 (0.0) [0.0–52.2]	0 (0.0) [0.0–60.2]	1 (6.3) [0.2–30.2]	0 (0.0) [0.0–20.6]
ORR, n (%) [95% CI]	6 (24.0) [9.4–45.1]	1 (3.8) [0.1–19.6]	0 (0.0) [0.0–20.6]	0 (0.0) [0.0–26.5]	0 (0.0) [0.0–33.6]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–41.0]	0 (0.0) [0.0–52.2]	0 (0.0) [0.0–60.2]	0 (0.0) [0.0–20.6]	0 (0.0) [0.0–20.6]
Clinical benefit rate, n (%) [95% CI]	10 (40.0) [21.1–61.3]	11 (42.3) [23.4–63.1]	3 (18.8) [4.0–45.6]	1 (8.3) [0.2–38.5]	3 (33.3) [7.5–70.1]	3 (60.0) [14.7–94.7]	2 (28.6) [3.7–71.0]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–60.2]	3 (18.8) [4.0–45.6]	2 (12.5) [1.6–38.3]
Median PFS, months	3.5	5.5	1.8	1.8	2.8	20.1	2.6	1.7	2.1	1.9	1.7

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Extended Data Table 2 | Treatment-emergent adverse events (occurring in ≥ 10% of patients)

	Neratinib monotherapy (N=141)	
Adverse event, n (%)	**Any grade**	**Grade ≥3**
Diarrhoea	104 (73.8)	31 (22.0)*
Nausea	61 (43.3)	3 (2.1)
Vomiting	58 (41.1)	3 (2.1)
Constipation	49 (34.8)	2 (1.4)
Fatigue	45 (31.9)	5 (3.5)
Decreased appetite	40 (28.4)	1 (0.7)
Abdominal pain	33 (23.4)	7 (5.0)
Anaemia	22 (15.6)	10 (7.1)
Dyspnoea	18 (12.8)	5 (3.5)
Dehydration	17 (12.1)	8 (5.7)
Aspartate aminotransferase increased	15 (10.6)	5 (3.5)
Asthenia	15 (10.6)	1 (0.7)
Weight decreased	15 (10.6)	0
Characteristics of diarrhoea		
Action taken with neratinib, n (%)		
Permanent discontinuation	4 (2.8)	
Serious† diarrhoea, n (%)	15 (10.6)	
Median (range) number of grade 3 diarrhoea episodes per patient	1 (1–12)	
Median (range) duration of grade 3 diarrhoea episode, days	2 (1–8)	
Median (range) time to first grade 3 diarrhoea episode, days	10 (4–87)	

*All events of grade 3.
†Serious adverse event as defined per study protocol.

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Extended Data Table 3 | PET response criteria

Response category	Based on sum of SUV_{max} from 1 to 5 target lesions. Each target lesion with initial SUVmax of >1.5 × normal liver background SUVmax
Complete metabolic response (CMR)	• Reduction of SUVmax of all target lesions to less than normal liver background SUVmax (for non-brain lesions) or less than normal brain background SUVmax (for brain lesions) AND • The reduction of all other FDG-avid lesions consistent with disease to less than normal liver background SUVmax
Partial metabolic response (PMR)	• Sum of SUV_{max} of all target lesions is decreased by ≥30% compared to baseline sum of SUVmax of all target lesions AND • No new lesions
Stable metabolic disease (SMD)	Not satisfying the criteria for CMR, PMR, PMD, or NE
Progressive metabolic disease (PMD)	• Sum of SUV_{max} of all target lesions is increased by ≥30% OR • Appearance of one or more unequivocal new FDG-avid lesions
Not evaluable (NE)	• Missing FDG-PET series or incomplete anatomy at follow-up timepoint • A PET/CT scanner change from baseline • Variation in FDG uptake time ≥15 minutes compared to baseline • Change in reconstruction algorithm

CT, computed tomography; FDG-PET, ^{18}F-fluorodeoxyglucose positron-emission tomography; SUVmax, maximum standardized uptake value.

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Extended Data Table 4 | Patient disposition by cohort

	HER2										HER3
Characteristic	Breast (n=25)	Bladder (n=16)	Lung (n=26)	Colorectal (n=12)	Biliary tract (n=9)	Cervical (n=5)	Endometrial (n=7)	Gastro-esophageal (n=5)	Ovarian (n=4)	NOS (n=16)	NOS (n=16)
Patients continuing on treatment, n (%)	1 (4)	1 (6.2)	1 (3.8)	0 (0)	1 (11.1)	2 (40)	1 (14.3)	0 (0)	1 (25)	2 (12.5)	0 (0)
Treatment discontinuation, n (%)	24 (96.0)	15 (93.8)	25 (96.2)	12 (100)	8 (88.9)	3 (60.0)	6 (85.7)	5 (100)	3 (75.0)	14 (87.5)	16 (100)
Death	0 (0)	1 (6.3)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.3)
Disease progression	22 (88.0)	12 (75.0)	18 (69.2)	11 (91.7)	5 (55.6)	2 (40.0)	4 (57.1)	4 (80.0)	2 (50.0)	9 (56.3)	15 (93.8)
Clinical deterioration	0 (0)	0 (0)	3 (11.5)	0 (0)	1 (11.1)	0 (0)	0 (0)	1 (20.0)	1 (25.0)	2 (12.5)	0 (0)
Adverse Event	0 (0)	0 (0)	2 (7.7)	0 (0)	1 (11.1)	0 (0)	1 (14.3)	0 (0)	0 (0)	1 (6.3)	0 (0)
Investigator Request	0 (0)	1 (6.3)	0 (0)	1 (8.3)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	2 (12.5)	0 (0)
Withdrawal of consent	2 (8.0)	0 (0)	2 (7.7)	0 (0)	0 (0)	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lost to follow-up	0 (0)	1 (6.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subjects ended study, n (%)	15 (60.0)	14 (87.5)	16 (61.5)	9 (75.0)	6 (66.7)	1 (20.0)	6 (85.7)	5 (100)	3 (75.0)	7 (43.8)	14 (87.5)
Death	12 (48.0)	13 (81.3)	13 (50.0)	8 (66.7)	6 (66.7)	1 (20.0)	5 (71.4)	3 (60.0)	3 (75.0)	7 (43.8)	11 (68.8)
Withdrawal of consent	2 (8.0)	0 (0)	2 (7.7)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	2 (12.5)
Lost to follow-up	1 (4.0)	1 (6.3)	1 (3.8)	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (20.0)	0 (0)	0 (0)	1 (6.3)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20.0)	0 (0)	0 (0)	0 (0)

NOS, not otherwise specified.

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nature research

Corresponding author(s): David Hyman

☐ Initial submission ☐ Revised version ☒ Final submission

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Experimental design

1. Sample size

Describe how sample size was determined.

The sample size required depends on the objective response rates at 8 weeks (ORR8). For each cohort, using Simon's optimal 2-stage design (with significance level 10% and power of 80%), a true ORR8 of 10% or less will be considered unacceptable (null hypothesis) whereas a true ORR8 of minimally 30% (alternative hypothesis) will merit further study. In the first stage, enrollment will continue until 7 patients per the Simon 2-stage optimal design. If no responses are observed, enrollment in the second stage for the cohort may be discontinued. Otherwise, the second stage will open and 11 additional response evaluable patients will be assessed for a total of 18 patients in the cohort. The null hypothesis will be rejected (for each cohort separately) if at least 4 responses are observed in each cohort. Once the Simon 2-stage criteria are met for the ERBB2 mutant breast cohort, enrollment into this cohort may continue until approximately 50 patients.

2. Data exclusions

Describe any data exclusions.

The clinical data presented represent an intention to treat population with all patients who received at least one dose of neratinib included in analysis. The genomic data presented include all samples that underwent sequencing and passed routine QA/QC procedures as described and referenced.

3. Replication

Describe whether the experimental findings were reliably reproduced.

As this is a clinical trial, no replication was possible or performed.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

There was no randomization.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

This was an open label study with no blinding.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒	A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐	A statement indicating how many times each experiment was replicated
☐	☒	The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒	A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒	The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒	A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒	Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	SAS EG5.1 by SAS Institute Inc., ABSOLUTE v. 1.0.6, FACETS v. 0.3.9, R v. 3.3.1, MSIsensor v. 0.2

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	No unique materials were used

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	No antibodies were used

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	No eukaryotic cell lines were used
b. Describe the method of cell line authentication used.	No eukaryotic cell lines were used
c. Report whether the cell lines were tested for mycoplasma contamination.	No eukaryotic cell lines were used
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	No eukaryotic cell lines were used

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.	No animals were used

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.	A detailed summary of the demographics of the human research participants are included in Table 1 and Extended Data Table 1. In addition, patient level demographic data are provided in the cBioPortal project associated with this manuscript.

CORRECTION

https://doi.org/10.1038/s41586-019-0974-0

Author Correction: HER kinase inhibition in patients with HER2- and HER3-mutant cancers

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receipt of consulting and travel fees from Novartis and Eli Lilly; and serving as cofounder of Venthera. **J.B.** also reports serving as investigator on a patent licensed to Memorial Sloan Kettering for use of phosphoinositide-3-kinase (**PI3K)** inhibitors for treatment of vascular malformations and serving as investigator for patents pending assignment to Memorial Sloan Kettering for combination therapy using PDK1 and PI3K inhibitors and inhibition of KMT2D for the treatment of breast cancer. **S.A.P.-P.** receives research funding from AbbVie, Aminex Therapeutics, BioMarin Pharmaceutical, Bristol-Myers Squibb, Curis, Five Prime Therapeutics, Genmab, GlaxoSmithKline, Helix BioPharma, Incyte, Medivation, Merck Sharp & Dohme, Novartis, Pieris Pharmaceuticals, Pfizer, Puma Biotechnology, Taiho Oncology, Tesaro and TransThera Bio. **K.J.** reports receipt of personal fees from Novartis, Astra Zeneca, Spectrum Pharmaceuticals, ADC Therapeutics, Pfizer, Bristol-Myers Squibb, Taiho Oncology and Jounce Therapeutics, and institutional research funding from Novartis, Clovis Oncology, Genentech, Astra Zeneca, ADC Therapeutics, Novita Pharmaceuticals, Debio Pharmaceuticals, Pfizer and Eli Lilly. **J.J.H.** reports receipt of personal fees from Bristol-Myers Squibb and Eli Lilly, and research funding from Bristol-Myers Squibb. **J.R.** reports non-financial support and reasonable reimbursement for travel from the European Journal of Cancer, Vall d'Hebron Institut of Oncology, the Chinese University of Hong Kong, SOLTI, Elsevier and GlaxoSmithKline, and receipt of consulting and travel fees from Novartis, Eli Lilly, Orion Pharmaceuticals, Servier Pharmaceuticals, Peptomyc, Merck Sharp & Dohme, Kelun Pharmaceutical/Klus Pharma, Spectrum Pharmaceuticals, Pfizer, Roche Pharmaceuticals and Ellipses Pharma (including serving on the scientific advisory board 2015 to the present). **J.R.** also reports receipt of research funding from Bayer and Novartis, and serving as an investigator in clinical trials with Spectrum Pharmaceuticals, Tocagen, Symphogen, BioAtla, Pfizer, Genmab, CytomX, Kelun Biotech, Takeda-Millennium, GlaxoSmithKline and IPSEN. **C.S.** reports research funding to her institution (Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain) from AstraZeneca, Roche/Genentech and Puma, and served as a consultant, participated in advisory boards or received travel grants from AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Roche, Genomic Health, Novartis, Pfizer, Pierre Fabre, Puma and Synthon. **C.L.A.** served as a consultant for Genentech and Puma Biotechnology. **G.I.S.** reports support from PUMA to the Dana-Farber Cancer Institute for the conduct of the study. **G.I.S.** also reports (for work not directly related to this Article) receipt of grants and personal fees from Lilly, grants and personal fees from Merck/EMD Serono, grants and personal fees from Sierra Oncology, grants from Merck, grants and personal fees from Pfizer, grants from Array, personal fees

CORRECTIONS & AMENDMENTS

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