CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Trastuzumab and Pertuzumab in patients with non-breast/ gastroesophageal HER2 amplified tumors: Results from the NCI–MATCH ECOG–ACRIN Trial (EAY131) Subprotocol J
Authors	Connolly, Roisin M.;Wang, Victoria;Hyman, David M.;Grivas, Petros;Mitchell, Edith P.;Wright, John J.;Sharon, Elad;Gray, Robert J.;McShane, Lisa M.;Rubinstein, Larry V.;Patton, David R.;Williams, P. Mickey;Hamilton, Stanley R.;Wang, Jue;Wisinski, Kari B.;Tricoli, James V.;Conley, Barbara A.;Harris, Lyndsay N.;Arteaga, Carlos L.;O'Dwyer, Peter J.;Chen, Alice P.;Flaherty, Keith T.
Publication date	2024-04-01
Original Citation	Connolly, R. M., Wang, V., Hyman, D. M., Grivas, P., Mitchell, E. P., Wright, J. J., Sharon, E., Gray, R. J., McShane, L. M., Rubinstein, L. V., Patton, D. R., Williams, P. M., Hamilton, S. R., Wang, J., Wisinski, K. B., Tricoli, J. V., Conley, B. A., Harris, L. N., Arteaga, C. L., O'Dwyer, P. J., Chen, A. P. and Flaherty, K. T. (2024) 'Trastuzumab and Pertuzumab in patients with non-breast/gastroesophageal HER2 amplified tumors: Results from the NCI–MATCH ECOG–ACRIN Trial (EAY131) Subprotocol J', Clinical Cancer Research, 30(7), pp.1273-1280. https://doi.org/10.1158/1078-0432.CCR-23-0633
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1158/1078-0432.CCR-23-0633
Rights	© 2024, American Association for Cancer Research.
Download date	2026-11-15 15:55:26
Item downloaded from	https://hdl.handle.net/10468/16796



University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Clin Cancer Res. 2024 April 01; 30(7): 1273–1280. doi:10.1158/1078-0432.CCR-23-0633.

Trastuzumab and Pertuzumab in Patients with non-Breast/ Gastroesophageal *HER2*-amplified Tumors: Results from the NCI-MATCH ECOG-ACRIN Trial (EAY131) Sub-protocol J

Roisin M Connolly[1,2], **Victoria Wang**[3], **David M Hyman**[4], **Petros Grivas**[5], **Edith P Mitchell**[6], **John J Wright**[7], **Elad Sharon**[8], **Robert J Gray**[3], **Lisa M McShane**[9], **Larry V Rubinstein**[9], **David R Patton**[10], **P Mickey Williams**[11], **Stanley R Hamilton**[12], **Jue Wang**[13], **Kari B Wisinski**[14], **James V Tricoli**[15], **Barbara A Conley**[16], **Lyndsay N Harris**[16], **Carlos L Arteaga**[13], **Peter J O'Dwyer**[17], **Alice P Chen**[15], **Keith T Flaherty**[18]

[1.] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland.

[2.] Cancer Research @UCC, College of Medicine and Health, University College Cork, Ireland.

[3.] Dana Farber Cancer Institute, ECOG-ACRIN Biostatistics Center, Boston, Massachusetts.

[4.] Memorial Sloan Kettering Cancer Center, New York, New York.*

[5.] University of Washington, Fred Hutchinson Cancer Center, Seattle, Washington.

[6.] Sidney Kimmel Cancer Center at Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

[7.] Investigational Drug Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland.

[8.] Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland.

[9.] Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland.

[10.] Center for Biomedical Informatics & Information Technology, National Cancer Institute, Bethesda, Maryland.

[11.] Frederick National Laboratory for Cancer Research, Frederick, Maryland.

[12.] City of Hope National Medical Center, Duarte, California.

[13.] UT Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas

[14.] University of Wisconsin Carbone Cancer Center, Madison, Wisconsin.

Correspondence to: Roisin M. Connolly, MB, BCh, MD, Cancer Research @ UCC, College of Medicine and Health, University College Cork, Western Gateway Building, 4.110, Western Road, Cork, Ireland, Phone: +353 21 4205708, roisin.connolly@ucc.ie.
*Current Affiliation: Loxo Oncology, Stamford, Connecticut.

Disclosures Corresponding Author: RC has received an unrestricted educational grant from Pfizer, and research funding for clinical trials from MSD Ireland, Pfizer, Daichii Sankyo, and Astra Zeneca; all to her institution. RC has consulted for Astra Zeneca/Daichii, Gilead and Seagen. She has received travel support from Novartis.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[15.] Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland.

[16.] Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland.

[17.] University of Pennsylvania, Philadelphia, Pennsylvania.

[18.] Massachusetts General Hospital Cancer Center, Boston, Massachusetts.

Abstract

Purpose: NCI-MATCH assigned patients with advanced cancer and progression on prior treatment, based on genomic alterations in pre-treatment tumor tissue. Arm J (EAY131-J) evaluated the combination of trastuzumab/pertuzumab (HP) across *HER2*-amplified tumors.

Patients and Methods: Eligible patients had high levels of *HER2* amplification (copy number [CN] ≥7) detected by central next generation sequencing (NGS) or through NCI designated laboratories. Patients with breast/gastroesophageal adenocarcinoma, and those who received prior *HER2*-directed therapy were excluded. Enrollment of patients with colorectal cancer was capped at 4 based on emerging data. Patients received HP IV Q3 weeks until progression or unacceptable toxicity. Primary endpoint was objective response rate (ORR); secondary endpoints included progression-free survival (PFS) and overall survival (OS).

Results: Thirty-five patients were enrolled, with 25 included in the primary efficacy analysis (CN ≥7 confirmed by central lab, median CN=28). Median age was 66 (range 31–80), and half of all patients had ≥3 prior therapies (range 1– 11). The confirmed ORR was 12% (3/25 partial responses [colorectal, cholangiocarcinoma, urothelial cancers], 90% CI 3.4–28.2%). There was one additional partial response (urothelial cancer) in a patient with unconfirmed ERBB2 copy number. Median PFS was 3.3 months (90% CI 2.0–4.1) and median OS 9.4 months (90% CI 5.0–18.9). Treatment-emergent adverse events were consistent with prior studies. There was no association between *HER2* CN and response.

Conclusion: HP was active in a selection of *HER2*-amplified tumors (non-breast/gastroesophageal) but did not meet the predefined efficacy benchmark. Additional strategies targeting *HER2* and potential resistance pathways are warranted, especially in rare tumors.

Translational Relevance (128/150)

High level amplification of the human epidermal growth factor receptor 2 (HER2) receptor across tumor types may indicate a heavier biological dependence on this receptor and pathway than in tumors without such amplification. Trastuzumab and pertuzumab (HP) has an established role in *HER2*-amplified breast cancer. We hypothesized that HP would be active across *HER2*- amplified tumors, other than breast and gastroesophageal adenocarcinoma, and conducted a single-arm phase II trial to characterize the efficacy and safety in this selected patient population. HP was active in a selection of rare tumors (confirmed overall response rate 12%, 90% CI 3.4–28.2%) and did not meet the predefined efficacy benchmark; there were no new safety signals. Translational biomarker exploration, as well as additional strategies targeting *HER2* and potential resistance pathways, are warranted.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Keywords

Advanced malignancy; HER2; Trastuzumab; Pertuzumab

Introduction

Human epidermal growth factor receptor 2 (*HER2*)-directed therapies are approved for the treatment of patients with *HER2*-overexpressing breast and gastroesophageal adenocarcinoma, with associated survival advantages.(1,2) A variety of other tumor types also demonstrate amplification of the *HER2* receptor, which may indicate a putative driving role and heavier biological dependence of these tumors on this pathway compared with those tumors without such amplification.(3) Resistance to trastuzumab, the first *HER2*-directed therapy approved for clinical use, is a common clinical challenge; with dysregulation of downstream signaling pathways, alternative receptor tyrosine kinase signaling and accumulation of the truncated active kinase *p95-HER2* all being implicated.(4)

Based on extensive preclinical and clinical development, additional *HER2*-targeted therapies are now available and include the HER2/HER3 dimerization inhibitor pertuzumab.(5) Dual *HER2*-blockade with trastuzumab and pertuzumab (HP) has been shown to be more efficacious than trastuzumab alone in both early and late-stage breast cancer.(6–8) High tumor response rates (30–35%) have also been observed with HP in *HER2*-amplified colorectal cancer.(9) We thus hypothesized that HP would result in meaningful clinical benefit in patients with *HER2*-overexpressing advanced cancers where regulatory approval was not already obtained.

The ‘National Cancer Institute - Molecular Analysis for Therapy Choice’ (NCI-MATCH) trial is a signal-finding precision medicine study that incorporates genomic tumor testing to direct patients with refractory cancer to molecularly targeted treatments (NCT02465060). (10,11) Subprotocol Arm J evaluated the concurrent combination of HP across *HER2*-amplified tumors (copy number, CN ≥7), other than breast and gastric/GEJ adenocarcinoma. (12) A cutoff of 7 was chosen based on the fact that the use of next generation sequencing (NGS) to determine copy number variation was fairly new at the time the study began, and this was a conservative estimate.

Patients and Methods

Study Design and Patient Population

The NCI-MATCH master protocol is a multi-arm, molecular profile–driven, non-randomized phase II trial (EAY131, Supplementary Figure 1), developed by the ECOG-ACRIN Cancer Research Group and the NCI.(11) Progression following at least one line of standard systemic therapy and no other standard therapy available that has been shown to prolong overall survival (OS) ***OR*** where no standard treatment exists that has been shown to prolong OS was required for eligibility to the screening phase of the master protocol (Supplementary Methods). Consenting patients had their tumors molecularly characterized by NGS performed centrally or through NCI designated laboratories. Patients were required to have

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

either a core biopsy or available archived tumor tissue obtained within the last 6 months for assessment. Targeted NGS was performed using the Ion Torrent Oncomine AmpliSeqTM panel of 143 genes and was supplemented with Phosphatase and tensin homolog (PTEN), MutS homolog (MSH) and MutL homolog (MLH) immunohistochemistry (IHC).(10) Patients in a particular molecularly-defined subgroup received treatment matched to that tumor tissue alteration and proceeded to the treatment phase (subprotocol arms).

Participants who met eligibility requirements from the master protocol, and with *HER2* amplification as established in the analytical assay (CN ≥7)(10) detected by NGS, were considered for the Arm J subprotocol. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.(13), ECOG performance status 0–1, and left ventricular ejection fraction (LVEF) ≥ institutional lower limit normal were also required. Those with breast/gastroesophageal adenocarcinoma, and those who received prior *HER2*-directed therapy, were excluded. Enrollment of participants with colorectal cancer was capped at 4 based on emerging data.(9,14)

The study was performed in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The study (ClinicalTrials.gov identifier: NCT06136897) was approved by the NCI Central Institutional Review Board and by the institutional review board of record for all participating institutions. All patients signed a written informed consent prior to participation.

Treatment and evaluation

Patients were treated with the standard intravenous dosing of trastuzumab and pertuzumab every 3 weeks for a 21-day cycle, until progression or unacceptable toxicity. Pertuzumab was administered before trastuzumab each cycle; 840mg loading dose and 420 mg thereafter. Trastuzumab loading dose was 8mg/kg then 6mg/kg thereafter. Restaging scans were performed every three cycles for the first 33 cycles and every four cycles thereafter. Echocardiography was required at baseline and every 3 months thereafter.

Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) were used to grade treatment-related toxicity. Dose modifications of study agents were not permitted. Dose delays and discontinuation of study therapy were permitted as outlined in the study protocol (Supplementary Methods).

Statistical Considerations

The primary endpoint was objective response rate (ORR), defined as rate of complete or partial response per RECIST version 1.1. Allowing for a 10% ineligibility rate, the accrual goal was 35 patients for each subprotocol. The study design had the operating characteristics of at least 92% power to distinguish an ORR of 25% from a null of 5% with one-sided Type 1 error of 1.8%. If the ORR was ≥ 5/31 (16%), the study therapy would be deemed promising and worthy of further evaluation. Eligible and treated patients enrolled on basis of MATCH central NGS assay, *or* outside assays with molecular abnormalities confirmed by MATCH assay were included in the primary analyses. The null hypothesis is tested at one-sided significance level of 1.8% for arms with more than 31 patients in the primary analysis, and at 5% for arms with less than 31 patients in the primary analysis. Since there

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

are 25 patients in the primary analysis for Arm J, a minimum of 4 responders were needed to consider HP worthy of further evaluation in patients with *HER2* amplifications.

Secondary endpoints included progression-free survival (PFS), 6-month PFS rate, toxicity, and potential prognostic/predictive biomarkers. Exploratory endpoints included correlating response with *HER2* CN by NGS. Data cutoff was November 3, 2021. All statistical analyses were performed with R, version 4.1.0 (R Foundation for Statstical Computing).

Data Availability Statement

The data underlying this article is available from the authors upon request and will be made available for request from the NCTN/NCORP Data Archive (https://nctn-data-archive.nci.nih.gov/) upon completing a Data Request Form for data from NCT06136897.

Results

Patient Characteristics

From March 2017 to June 2019, thirty-five patients were enrolled in the study (Figure 1) with histopathologic tumor classification presented in Supplementary Table 3. All enrolled patients started protocol therapy, although three subjects were found to be ineligible due to low creatinine clearance (n=2) and presence of an intra-cardiac defibrillator (n=1). Of 32 analyzable patients (Supplementary Table 2), 25 had CN ≥7 confirmed by central lab (median CN=21, range 7.3 – 84.0) and were included in primary efficacy analysis of ORR per protocol (Primary Analysis Population, Table 1). Of these 25 patients, 11 were enrolled based on the central MATCH assay and 14 patients on the basis of results from NCI designated laboratories (outside assays). The MATCH assay case status is summarized in Supplementary Table 1.

In the primary analysis population, median age was 66 (range 31–80), 56% were female, and half of all patients had ≥3 prior therapies (range 1– 11) (Table 1). The most common tumor types included gynecologic (n=11) and gastrointestinal (n=11) cancers (Supplementary Table 3b). Gynecologic malignancies by histopathologic tumor classification were heterogeneous as presented in Supplementary Table 3b, and gastrointestinal cancers included colorectal adenocarcinoma (n=4) and cholangiocarcinoma (n=3).

Treatment & Safety

The median number of treatment cycles received was 4 (range 1–39) for the 25 patients in the primary analysis. At the data cutoff date (November 2021), one patient was still on treatment. The main reason for discontinuation of protocol therapy was disease progression (24/32, 75%), with only 2 patients discontinuing due to AEs. AE analysis included all treated patients. Tables 2 and A4 summarize the treatment-emergent adverse events, which were consistent with prior HP studies. There were two reported instances of Grade 3 heart failure, a known treatment-related toxicity for HP, but no treatment-related grade 4 or 5 events. The most frequent all grade treatment-emergent AEs included diarrhea (31%), infusion-related reaction (28% [majority grade 1/2]) and fatigue (23%, Supplementary Table 4).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Efficacy

Eligible and treated patients enrolled based on the central MATCH assay *OR* outside assays with molecular abnormalities *confirmed* by MATCH assay were included in the primary efficacy analyses (n=25). The confirmed ORR in this population was 12% (3/25 partial responses [colorectal, cholangiocarcinoma and urothelial cancers], 90% CI 3.4–28.2%, Figure 2 and Supplementary Table 6), with a median duration of response of 5.2 months (Figure 3). There was one additional partial response (PR) in a patient with urothelial cancer whose ERBB2 copy number (outside assay) was not confirmed by MATCH assay. Nine additional patients in the primary analysis population had evidence of stable disease, another nine with progressive disease, and four patients who were not evaluable due to lack of follow-up assessment. For the overall cohort of 32 patients, the ORR was 12.5% (90% CI 4.4–26.4%). The median PFS for the 25 patients in the primary analysis was 3.3 months (90% CI 2.0 – 4.1), the 6-month PFS was 25.3% (90% CI 10.7 – 40.0), and the median OS was 9.4 months (90% CI 5.0 – 18.9) (Supplementary Figure 4). The median PFS amongst all 32 analyzable patients was 2.1 months (90% CI 1.8 – 4.1), the 6-month PFS was 22.9% (90% CI 10.4 – 35.4), and the median OS was 8.7 months (90% CI 5.0 – 13.8) (Supplementary Figure 5), with median follow up period for OS of 24.1 months (range 8.2–35.6).

Although no complete responses were observed in this NCI MATCH treatment arm, the patient with colorectal adenocarcinoma who achieved PR had 99% reduction from baseline on imaging (Figure 2, Supplementary Figure 2). This patient was enrolled prior to the amendment excluding additional patients with colorectal cancer. Molecular profiling revealed intact mismatch repair and mutations in *APC, SMAD4, FBXW7* and *TP53*, but not *BRAF/KRAS*, and *HER2* copy number was 41. The patient with cholangiocarcinoma had 59% tumor shrinkage from baseline, remained on therapy for > 15 cycles and harbored *SMAD4, TP53, CDK12* mutations, with HER2 copy number of 18. The patients with urothelial cancer who achieved PR harbored CCNE1 copy number variant (best tumor shrinkage 62.5%, HER2 copy number 12) and TP53 mutation (best tumor shrinkage 47.5%, HER2 copy number 82 but uncomfirmed). A number of other durable responses and stable disease were observed, including in patients with endocervical papillary adenocarcinoma and gallbladder cancer (Figure 3, Supplementary Figure 3).

Correlative Analysis

There was no significant association observed between *HER2* copy number and treatment response, with results from the primary analysis population presented in Supplementary Figure 6 (p=0.87 for comparison of PR versus not). Co-occurring mutation data were available for the 25 patients included in the primary analysis (25/32). In this cohort, all 25 patients were identified as having an additional genetic alteration, alongside the *HER2* amplification (CN ≥7) required for eligibility. The most common co-occurring mutation was a mutation in *TP53,* detected in 21 patients. *SMAD4* mutation was present in two patients with PR (Figure 4), including the patient with colorectal adenocarcinoma noted above and a patient with cholangiocarcinoma. Four patients had co-occurring mutations in *PIK3CA,* and no tumors had deficient mismatch repair/high levels of microsatellite instability. Co-occurring mutation data for the overall cohort is also presented in Supplementary Figure 7.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Discussion

The Arm J (EAY131-J) NCI-MATCH subprotocol investigating the combination of dual *HER2*-directed therapy with HP across *HER2*-amplified advanced tumors (non-breast/gastroesophageal) did not meet the predefined efficacy benchmark for ORR of 16% (4/25) required to reject the null ORR of 5%. Three patients achieved confirmed partial responses (colorectal adenocarcinoma, cholangiocarcinoma, and urothelial cancer), with a 4th tumor response unconfirmed, thus, falling just short of considering HP worthy of further evaluation. Although the patient with colorectal carcinoma achieving partial response was noted to have a high *HER2* copy number of 41, overall, there was no significant correlation between *HER2* copy number and treatment response.

As this treatment arm of the NCI MATCH trial was starting to accrue, emerging data supporting the role of *HER2*-directed therapy in *HER2*-overexpressing or amplified advanced colorectal cancer was noted. In MyPathway, an industry-sponsored non-randomised phase 2a multiple basket study, the investigators reported an ORR of 32% in this cohort with HP alone.(9,15) The HERACLES trial also reported a 30% ORR in patients with heavily pre-treated *HER2*-positive and *RAS* wild type metastatic colorectal cancer with the combination of trastuzumab and lapatinib.(14) This emerging data led to capping of enrollment of patients with colorectal cancer to this Arm J (EAY131-J) of the NCI-MATCH subprotocol to ensure enrollment slots were available for cancer types not known to respond to HP, in keeping with the overall goal of NCI MATCH. This decision may also have contributed to this Arm of the MATCH trial not meeting its predefined efficacy objective in a heterogenous advanced solid tumor cohort where *new* efficacy signals were being sought. Differences in enrolment criteria between studies investigating HP in advanced solid tumors should also be considered. The MyPathway trial enrolled patients based on HER2 overexpression by immunohistochemistry 3+ staining or *HER2* amplification based on in-situ hybridization (ISH) or NGS in archival or fresh tumor tissue samples (most recent biopsy recommended), supplemented with central NGS testing following enrollment where archival tissue was available; whereas the NCI MATCH eligibility was based on NGS from fresh tumor biopsies at the time of screening.

Investigation of biomarkers of response and resistance to *HER2*-directed therapies is a research priority of the oncology community. In this small cohort, there was no association observed between *HER2* copy number and treatment response, a biomarker of increasing interest in the breast cancer literature.(16) The selection of CN≥7 for *HER2* gene was based on early feasibility data using the Oncomine assay that suggested excellent sensitivity and specificity using this CN cut-off, resulting in a consensus-based decision albeit without focused clinical validation at the time.(10,12) That traditional biomarkers of response to *HER2*-directed therapies were not assessed in this study, including protein overexpression by IHC, is a potential limitation of the study design.(17) It may be that tumor type specificity is more important than previously thought to determine sensitivity to dual *HER2*-directed therapies, when one considers the excellent outcomes with these therapies in responsive cancers. However, it should be acknowledged that even in cancer types felt to be responsive to dual HER2-directed therapies such as breast cancer, the ORR to HP is approximately 24%; an outcome not too different to what has been presented in our

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

cohort. Additional limitations include the relatively small sample size and single arm non-randomized design, potential selection bias and confounders, heterogeneity of tumor types enrolled, variability of laboratory assay algorithms to assess *HER2* CN, and inadequate molecular profiling of tumor tissue at the time of progression. Furthermore, differences in assay algorithms and adjustment for cellularity led to the need to adjust for HER2 CN with some of the NCI designated laboratories.

Other putative predictive biomarkers of response to *HER2*-directed therapies of interest include gene expression signatures such as intrinsic subtyping, novel “immune signatures”, the presence of tumor infiltrating lymphocytes, and other characteristics of the tumor microenvironment.(18,19) Dysregulation of the downstream PI3K pathway may also lead to constitutive activation of the PI3K/AKT pathway leading to treatment resistance, as one example of downstream mutational activation leading to lower response rates to anticancer targeted therapies.(20) Co-occurring *PIK3CA* mutations were detected in four patients in our study, all with gynecologic malignancies (adenocarcinoma cervix, carcinosarcoma uterus, vulvar cancer, uterine cancer) and none of whom responded to treatment. The most common co-occurring mutation overall was a mutation in *TP53*, with *SMAD4* co-mutations detected in two patients with PR. Additional translational studies in this cohort (using tumor tissue and cell-free circulating tumor DNA) will focus further on potential mechanisms of response and resistance, acknowledging the small sample size and heterogeneous tumor types enrolled.

Additional strategies may be required where tumor heterogeneity and complex resistance mechanisms may preclude response to relatively well tolerated regimens such as HP. The addition of chemotherapy to a targeted therapy backbone may be required for optimal treatment effect in select cancer types.(6,21) Novel antibody-drug conjugates such as ado-trastuzumab emtansine (T-DM1) improve outcomes in both the early- and late-stage breast cancer setting.(22) Disappointing results were observed, however, in subprotocol Q of the NCI MATCH trial where the primary endpoint for ORR was not met for use of T-DM1 in a heavily pre-treated, mixed histology cohort.(23) More recently, trastuzumab deruxtecan has shown impressive results in the advanced disease setting across breast, lung, and GI cancers.(24,25) The impressive efficacy of such antibody-drug conjugates may relate to a “bystander effect” whereby nearby non-target cancer cells may be impacted by diffusion of free cytotoxic moiety into the surrounding tissue.

In conclusion, dual *HER2*-directed therapy with HP had activity in a minority of non-breast/gastroesophageal *HER2*-amplified tumors, noting that the majority of these responses occurred in rare tumor types. Additional strategies targeting *HER2* and potential resistance pathways are warranted in cancers that may not respond to dual *HER2*-directed therapy. Based on our results, it may be most pertinent to focus on rare cancer subtypes which is an area of unmet medical need.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Acknowledgements:

This study was coordinated by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under the following award numbers: U10CA180820, U10CA180794, UG1CA233302, UG1CA233180, UG1CA233341, UG1CA233196, UG1CA233290, UG1CA233328, UG1CA233277, U10CA180888. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank the patients who participated in this study, and the research staff and investigators at participating sites.

Abbreviations List:

CTCAE	Common Terminology Criteria for Adverse Events
CN	copy number
HER2	human epidermal growth factor receptor 2
HP	Trastuzumab and pertuzumab
IHC	immunohistochemistry
ISH	in-situ hybridization
LVEF	left ventricular ejection fraction
MSH	MutS homolog
MLH	MutL homolog
NGS	next generation sequencing
ORR	objective response rate
OS	overall survival
PR	partial response
PTEN	Phosphatase and tensin homolog
PFS	progression-free survival
RECIST	Response Evaluation Criteria in Solid Tumors

References:

1. Pernas S, Tolaney SM. HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance. Ther. Adv. Med. Oncol SAGE Publications Inc.; 2019.
2. Patel TH, Cecchini M. Targeted Therapies in Advanced Gastric Cancer. Curr Treat Options Oncol [Internet]. Curr Treat Options Oncol; 2020 [cited 2021 Dec 13];21. Available from: https://pubmed.ncbi.nlm.nih.gov/32725377/
3. Greally M, Kelly CM, Cercek A. HER2: An emerging target in colorectal cancer. Curr Probl Cancer [Internet] Curr Probl Cancer; 2018 [cited 2021 Dec 13];42:560–71. Available from: https://pubmed.ncbi.nlm.nih.gov/30100092/ [PubMed: 30100092]
4. Vernieri C, Milano M, Brambilla M, Mennitto A, Maggi C, Cona MS, et al. Resistance mechanisms to anti-HER2 therapies in HER2-positive breast cancer: Current knowledge, new research directions and therapeutic perspectives. Crit Rev Oncol Hematol [Internet] Crit Rev Oncol

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Hematol; 2019 [cited 2021 Dec 13];139:53–66. Available from: https://pubmed.ncbi.nlm.nih.gov/31112882/ [PubMed: 31112882]

5. O'Sullivan CC, Connolly RM. Pertuzumab and its accelerated approval: evolving treatment paradigms and new challenges in the management of HER2-positive breast cancer. Oncol (willist Park [Internet] 2014/05/27. 2014;28:186–94, 196. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24855725
6. Swain SM, Kim SB, Cortes J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol [Internet] 2013/04/23. 2013;14:461–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23602601 [PubMed: 23602601]
7. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Hear J [Internet] 2016/02/24. 2016;37:1671–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26903532
8. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol [Internet] 2011/12/14. 2012;13:25–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22153890 [PubMed: 22153890]
9. Meric-Bernstam F, Hurwitz H, Raghav KPS, McWilliams RR, Fakih M, VanderWalde A, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol [Internet] Lancet Oncol; 2019 [cited 2021 Dec 13];20:518–30. Available from: https://pubmed.ncbi.nlm.nih.gov/30857956/ [PubMed: 30857956]
10. Lih CJ, Harrington RD, Sims DJ, Harper KN, Bouk CH, Datta V, et al. Analytical Validation of the Next-Generation Sequencing Assay for a Nationwide Signal-Finding Clinical Trial: Molecular Analysis for Therapy Choice Clinical Trial. J Mol Diagnostics [Internet] Elsevier B.V.; 2017 [cited 2021 May 23];19:313–27. Available from: https://pubmed.ncbi.nlm.nih.gov/28188106/
11. Conley BA, Doroshow JH. Molecular analysis for therapy choice: NCI MATCH [Internet]. Semin. Oncol. W.B. Saunders; 2014 [cited 2021 May 23]. page 297–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25023344/
12. Lih CJ, Si H, Das B, Harrington RD, Harper KN, Sims DJ, et al. Certified DNA Reference Materials to Compare HER2 Gene Amplification Measurements Using Next-Generation Sequencing Methods. J Mol Diagnostics Elsevier; 2016;18:753–61.
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer [Internet] 2008/12/23. 2009;45:228–47. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19097774 [PubMed: 19097774]
14. Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol [Internet] Lancet Oncol; 2016 [cited 2021 Dec 13];17:738–46. Available from: https://pubmed.ncbi.nlm.nih.gov/27108243/ [PubMed: 27108243]
15. Hainsworth JD, Meric-Bernstam F, Swanton C, Hurwitz H, Spigel DR, Sweeney C, et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol [Internet] J Clin Oncol; 2018 [cited 2021 Dec 13];36:536–42. Available from: https://pubmed.ncbi.nlm.nih.gov/29320312/ [PubMed: 29320312]
16. Hurvitz SA, Caswell-Jin JL, McNamara KL, Zoeller JJ, Bean GR, Dichmann R, et al. Pathologic and molecular responses to neoadjuvant trastuzumab and/or lapatinib from a phase II randomized trial in HER2-positive breast cancer (TRIO-US B07). Nat Commun [Internet] Nat Commun; 2020 [cited 2021 Dec 13];11. Available from: https://pubmed.ncbi.nlm.nih.gov/33203854/

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

17. Wolff AC, Hammond MEH, Allison KH, Harvey BE, McShane LM, Dowsett M. HER2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update Summary. J Oncol Pract. American Society of Clinical Oncology; 2018;JOP1800206.

18. Llombart-Cussac A, Cortes J, Pare L, Galvan P, Bermejo B, Martinez N, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Lancet Oncol [Internet] 2017/02/28. 2017;18:545–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28238593 [PubMed: 28238593]

19. Nitz UA, Gluz O, Christgen M, Grischke EM, Augustin D, Kuemmel S, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab +/− weekly paclitaxel. Ann Oncol [Internet] 2017/09/26. 2017;28:2768–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28945833 [PubMed: 28945833]

20. Majewski IJ, Nuciforo P, Mittempergher L, Bosma AJ, Eidtmann H, Holmes E, et al. PIK3CA mutations are associated with decreased benefit to neoadjuvant human epidermal growth factor receptor 2-targeted therapies in breast cancer. J Clin Oncol [Internet] 2015/01/07. 2015;33:1334–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25559818 [PubMed: 25559818]

21. Connolly RM, Leal JP, Solnes L, Huang C-Y, Carpenter A, Gaffney K, et al. Updated Results of TBCRC026: Phase II Trial Correlating Standardized Uptake Value With Pathological Complete Response to Pertuzumab and Trastuzumab in Breast Cancer. J Clin Oncol [Internet] J Clin Oncol; 2021 [cited 2021 May 23];JCO.21.00280. Available from: 10.1200/JCO.21.00280

22. Pondé N, Aftimos P, Piccart M. Antibody-Drug Conjugates in Breast Cancer: a Comprehensive Review. Curr Treat Options Oncol [Internet]. Curr Treat Options Oncol; 2019 [cited 2021 Dec 13];20. Available from: https://pubmed.ncbi.nlm.nih.gov/30931493/

23. Jhaveri KL, Wang XV., Makker V, Luoh SW, Mitchell EP, Zwiebel JA, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Ann Oncol Off J Eur Soc Med Oncol [Internet] Ann Oncol; 2019 [cited 2021 Dec 13];30:1821–30. Available from: https://pubmed.ncbi.nlm.nih.gov/31504139/

24. Modi S, Saura C, Yamashita T, Park YH, Kim S-B, Tamura K, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med [Internet] N Engl J Med; 2020 [cited 2021 Dec 13];382:610–21. Available from: https://pubmed.ncbi.nlm.nih.gov/31825192/ [PubMed: 31825192]

25. Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med [Internet] N Engl J Med; 2020 [cited 2021 Dec 13];382:2419–30. Available from: https://pubmed.ncbi.nlm.nih.gov/32469182/ [PubMed: 32469182]

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

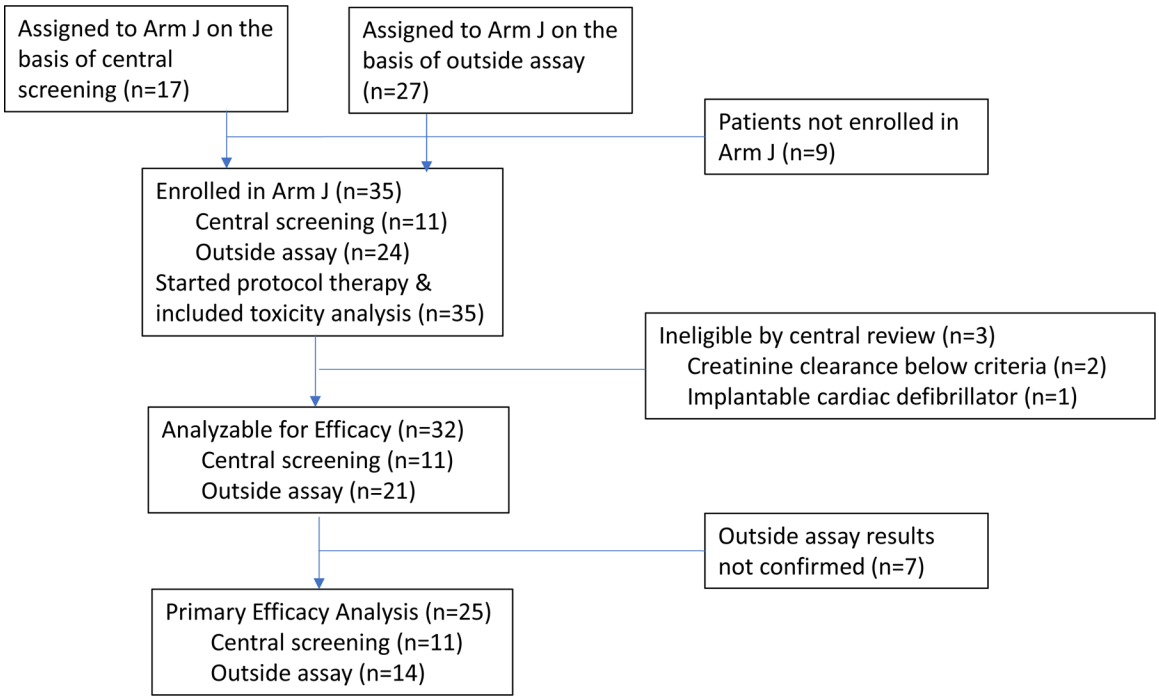


Figure 1:
CONSORT Diagram

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

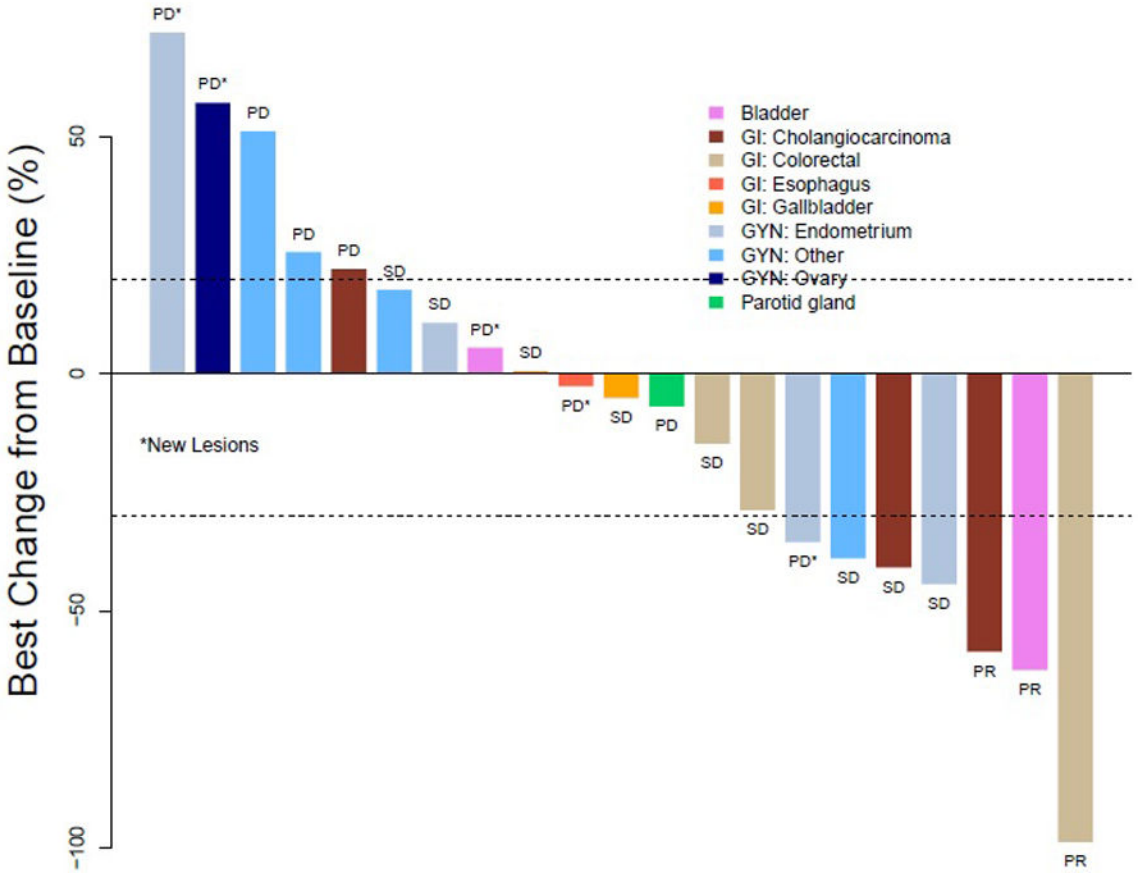


Figure 2:

Waterfall plot of best percentage change from baseline in 21 patients with centrally confirmed HER2 result (primary analysis population) and evaluable measurements. This plot excludes patients who did not have follow-up tumor measurements available (n=4). PD, progressive disease; PR, partial response; SD, stable disease.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

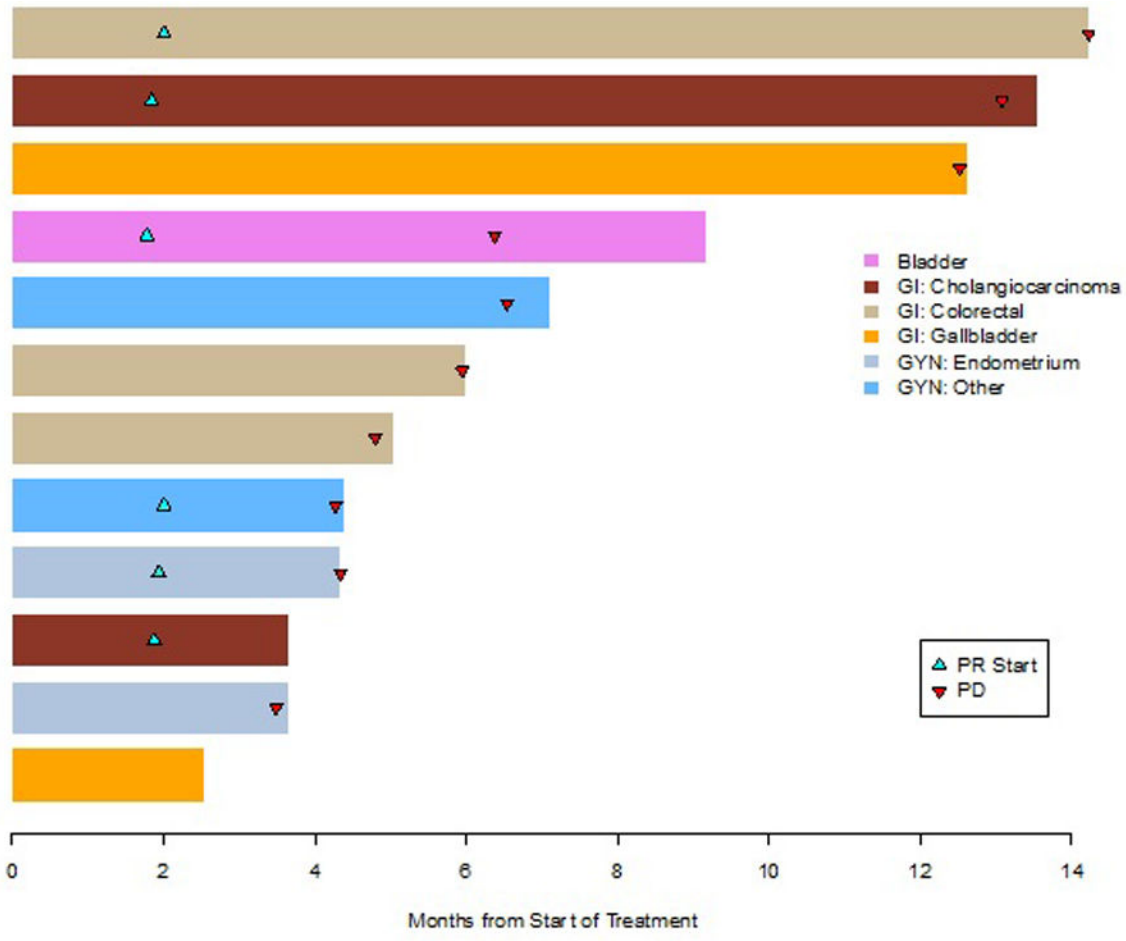


Figure 3:

Swimmers plot of duration of treatment in patients who achieved partial response (PR) or stable disease (n=12) and had centrally confirmed HER2 result (primary analysis population).

PD, progressive disease.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

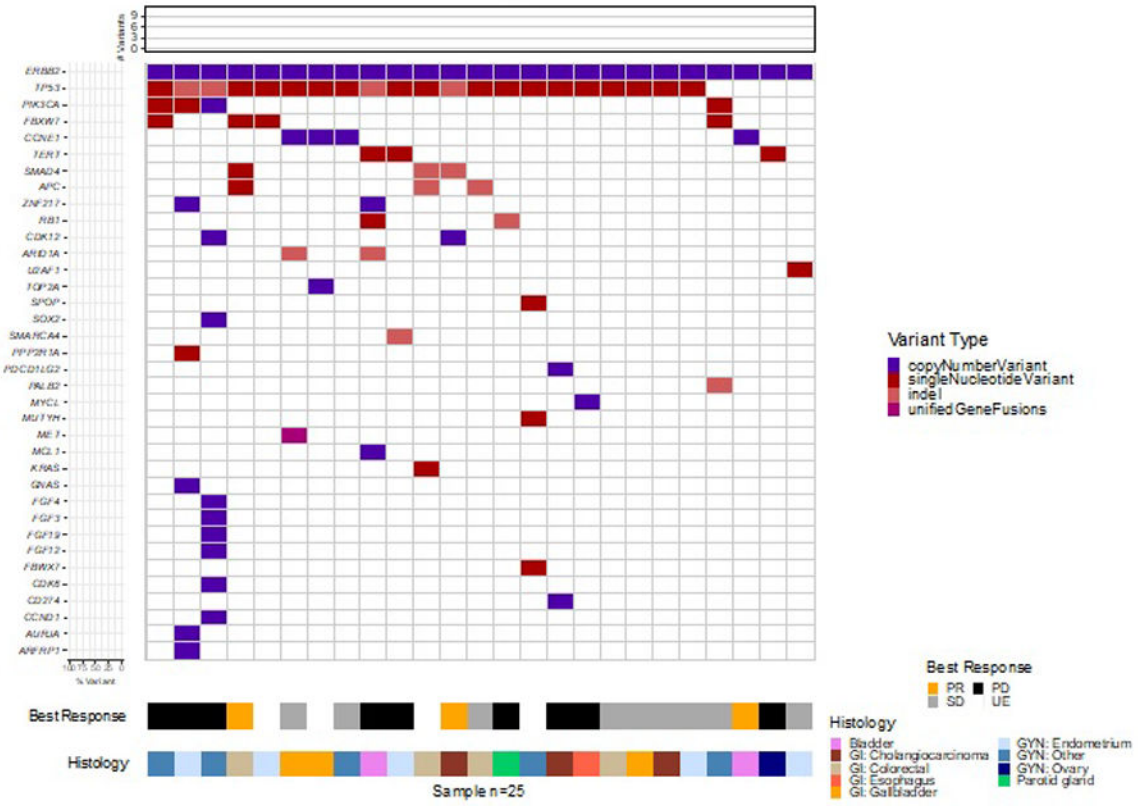


Figure 4.

Co-occurring genomic alterations with HER2 using the central NCI-MATCH assay for 25 patients. Single nucleotide variant (purple), copy number variant (dark red), insertion-deletion (light red). Response data and histology for individual patients are listed at the bottom.; PD, progressive disease; PR, partial response; SD, stable disease; UE, unevaluable.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1:

Patient Characteristics (Primary Analysis Population)

Patient Characteristic (n=25) N (%)		
Median Age (range)	Years	66 (31–80)
Sex	Female	14 (56)
	Male	11 (44)
Race	White	22 (88)
	Black	3 (12)
ECOG	0	7 (28)
	1	18 (72)
Tumor Type	Gynecologic	11 (44)
	Gastrointestinal	11 (44)
	Genitourinary	2 (8)
	Head and neck	1 (4)
Lines of Prior Therapy	1	3 (12)
	2	9 (36)
	3	6 (24)
	≥4	7 (28)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2:

Treatment Related Adverse Events

Toxicity (n=35)	**Grade 3**	**Grade 4/5**
Abdominal Pain	1	0
Alkaline Phosphatase increased	1	0
Dyspnea	1	0
Fatigue	1	0
Heart Failure	2	0
Hepatobiliary-other	1	0
Hypophosphatemia	1	0
Hypertension	1	0
Hypotension	1	0
Hypoxia	1	0
Infusion Reaction	1	0
Lymphocyte count decreased	1	0
Total	8	0

* Toxicities at least possibly related to treatment reported via Case Report Forms