









MyPathway Human Epidermal Growth Factor Receptor 2 Basket Study: Pertuzumab + Trastuzumab Treatment of a Tissue-Agnostic Cohort of Patients With Human Epidermal Growth Factor Receptor 2–Altered Advanced Solid Tumors

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The MyPathway multiple-basket study (ClinicalTrials.gov identifier: [NCT02091141](https://clinicaltrials.gov/ct2/show/study/NCT02091141)) is evaluating targeted therapies in nonindicated tumors with relevant molecular alterations. We assessed pertuzumab + trastuzumab in a tissue-agnostic cohort of adult patients with human epidermal growth factor receptor 2 (HER2)–amplified and/or –overexpressed and/or –mutated solid tumors. The primary end point was objective response rate (ORR); secondary end points included survival and safety. At data cutoff (March 2022), 346 patients with HER2 amplification and/or overexpression with/without *HER2* mutations (n = 263), or *HER2* mutations alone (n = 83) had been treated. Patients with HER2 amplification and/or overexpression had an ORR of 25.9% (68/263, 95% CI, 20.7 to 31.6), including five complete responses (urothelial [n = 2], salivary gland [n = 2], and colon [n = 1] cancers). Activity was higher in those with wild-type (ORR, 28.1%) versus mutated *KRAS* (ORR, 7.1%). Among patients with *HER2* amplification, ORR was numerically higher in patients with immunohistochemistry (IHC) 3+ (41.0%; 32/78) or 2+ (21.9%; 7/32), versus 1+ (8.3%; 1/12) or no expression (0%; 0/20). In patients with *HER2* mutations alone, ORR was 6.0% (5/83, 95% CI, 2.0 to 13.5). Pertuzumab + trastuzumab showed activity in various HER2–amplified and/or –overexpressed tumors with wild-type *KRAS*, with the range of activity dependent on tumor type, but had limited activity in the context of *KRAS* mutations, *HER2* mutations alone, or 0–1+ *HER2* expression.

ACCOMPANYING CONTENT

-  [Data Supplement](#)
-  [Protocol](#)

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2/ERBB2) amplification and/or overexpression is observed in 2%–3% of all solid tumors.^{1,2} HER2–targeted therapies are approved for HER2–positive metastatic breast, gastric, gastroesophageal, and colorectal cancers (CRC),^{3–6} but have also shown benefit in *HER2*–mutant non–small–cell lung cancer (NSCLC).^{7–9}

The MyPathway multiple-basket study is evaluating established targeted therapies in patients with advanced solid tumors and potentially actionable mutations. Previous data suggested the chemotherapy-free combination of pertuzumab + trastuzumab (P + T) has activity in multiple cancer types not indicated for HER2–targeted treatment,^{10–13}

and led to updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for HER2–positive colon, salivary, and biliary cancers.^{14–16} However, activating mutations in genes associated with resistance to EGFR–targeted therapy (eg, *KRAS* and *PIK3CA*)¹⁷ may influence HER2 as a driver,^{18–20} meaning analyses in larger populations and other tumor types are needed.

Here, we report the efficacy and safety of P + T in the overall MyPathway HER2 basket.

METHODS

MyPathway (ClinicalTrials.gov identifier: [NCT02091141](https://clinicaltrials.gov/ct2/show/study/NCT02091141)) is an open-label, nonrandomized, multicenter, multiple-basket,

US-based, tumor-agnostic phase IIa study (Data Supplement, Fig S1 [online only]). Patients in the HER2 basket were age 18 years and older, and had tumors with HER2 amplification and/or overexpression and/or activating mutations. In cases of discordant local versus central results for HER2 amplification, overexpression, or mutation status, local results took precedence (Data Supplement, Table S1). Additional methods are provided in the Data Supplement.

RESULTS

Patients

Enrollment completed between April 8, 2014, and June 3, 2019, for 346 patients, including 263 patients with HER2 amplification and/or overexpression (with or without HER2 mutations) and 83 with their sole HER2 alteration being mutation (Data Supplement, Fig S2). Baseline characteristics are provided in Table 1. Median time on treatment at data cutoff (March 24, 2022) for all patients was 2.14 months (range, 0–67.2).

Outcomes Overall and by Biomarker Status

In the entire HER2 patient cohort, objective response rate (ORR) was 21.1% and disease control rate was 42.2% (including five complete responses [CRs], 62 partial responses [PRs], 79 stable disease >4 months; Table 2). Median progression-free survival (PFS) and overall survival (OS) were 2.8 and 10.1 months, respectively (Data Supplement, Fig S3). Concordance between HER2 testing methodologies for the HER2 amplification and/or overexpression cohort (n = 263) is provided in the Data Supplement (Table S2). There was a gradient of response among patients with HER2 amplification; ORR was numerically higher in patients with immunohistochemistry (IHC) 3+ (41.0%) or 2+ expression (21.9%), versus 1+ (8.3%) or no expression (0%; Table 2).

Among patients with HER2 amplification and/or overexpression, P + T produced an ORR of 25.9% (Table 2), including five CRs (urothelial, n = 2; salivary gland, n = 2; and colon, n = 1). Median PFS and OS were 2.8 and 11.2 months, respectively (Data Supplement, Fig S3). Within this group, 28 patients also had HER2 mutations, and had similar outcomes to the other 235 patients in the group (Data Supplement [Fig S4 and Table S3]). By contrast, patients with HER2 mutations without known HER2 amplification or overexpression had an ORR of 6.0% (all PRs; Table 2). P + T activity in patients with amplification/overexpression versus HER2 mutation alone is contrasted in Table 2; PFS and OS are compared in the Data Supplement (Fig S3).

HER2 overexpression (IHC 3+) correlated with higher HER2 copy number (Data Supplement, Fig S5A). We observed a significant association between increasing HER2 copy-number cutoff and ORR (Data Supplement, Fig S5B). ORR in all patients with IHC 3+ was 41.0% (32/78; 95% CI, 30.0 to

52.7) and 26.1% (65/249; 95% CI, 20.8 to 32.0) in all patients with HER2 amplification. ORR was low (12.5%) in the 64 patients who had amplification with no or equivocal overexpression (Table 2).

Among patients with HER2 amplification and/or overexpression, 203 had KRAS wild-type, 28 had KRAS mutations, and 32 had unknown KRAS status (Data Supplement, Table S4). P + T activity was higher in patients with wild-type (ORR 28.1%) versus mutated (ORR 7.1%) KRAS (Fig 1A; Data Supplement [Table S5]); PFS and OS were also longer in KRAS wild-type tumors (Figs 1B and 1C). In patients with HER2 mutations only, 73/83 had wild-type KRAS (Data Supplement, Table S4). Of the 27 patients with disease control in the HER2-mutated group, none had KRAS-mutated tumors (Data Supplement, Table S5). There was no clinically significant difference between the ORRs of patients with HER2 amplification and/or overexpression with (21.4%) versus without (27.2%) PI3K pathway alterations (Data Supplement [Fig S6 and Table S6]). Clinical outcomes by PI3K/PIK3CA status are provided in the Data Supplement.

Responses were observed in all tumor groups of patients with HER2 amplification and/or overexpression (Fig 1D). Among the 203 patients with KRAS wild-type tumors, ORR was 63.6% (7/11) for salivary cancer (including two CRs; one ongoing at data cutoff); 31.9% (22/69) for CRC, including one CR; 30.6% (11/36) for biliary cancer; 22.7% (5/22) for NSCLC; and 21.1% (4/19) for urothelial cancer (Fig 1E; Data Supplement [Table S7]). Of three patients with pancreatic cancer, one had a PR. Of 28 patients with HER2 amplification and/or overexpression and KRAS mutations, responses were observed only in patients with CRC (Data Supplement, Table S8).

Safety

Among all 346 patients, 325 (93.9%) experienced treatment-emergent adverse events (TEAEs), with treatment-related adverse events (TRAEs) reported in 251 (72.5%), mostly diarrhea (Data Supplement, Table S9). Serious TRAEs were observed in 17 (4.9%) patients and grade ≥3 TRAEs in 42 (12.1%). Fourteen (4.0%) patients died due to TEAEs, of which two events were related to treatment (pneumonitis and sepsis). No new safety signals were observed.

DISCUSSION

P + T showed activity in various KRAS wild-type HER2-amplified and/or -overexpressed advanced solid tumors, ranging from 5.9% in uterine cancer to 63.6% in salivary gland tumors, suggesting that tumor origin is important. However, P + T had limited activity in patients with HER2-amplified and/or -overexpressed tumors carrying KRAS mutations and patients with HER2-activating mutations without HER2 amplification/overexpression. Safety was consistent with previously reported profiles for pertuzumab and trastuzumab.

TABLE 1. Baseline Demographics and Clinical Characteristics

Characteristic	HER2-Amplified and/or -Overexpressed (n = 263)	HER2-Mutated Alone (n = 83)	All HER2-Altered (N = 346)
Age, years, median (range)	63 (23-87)	61 (36-89)	62 (23-89)
Sex, No. (%)			
Female	130 (49.4)	44 (53.0)	174 (50.3)
Male	133 (50.6)	39 (47.0)	172 (49.7)
Race, No. (%)	n = 262		n = 345
White	215 (82.1)	65 (78.3)	280 (81.2)
Black/African American	19 (7.3)	8 (9.6)	27 (7.8)
Asian	14 (5.3)	7 (8.4)	21 (6.1)
American Indian/Alaska Native	3 (1.1)	0	3 (0.9)
Other	11 (4.2)	3 (3.6)	14 (4.1)
Ethnicity, No. (%)			
Not Hispanic or Latino	234 (89.0)	76 (91.6)	310 (89.6)
Hispanic or Latino	12 (4.6)	6 (7.2)	18 (5.2)
Not reported/unknown	17 (6.5)	1 (1.2)	18 (5.2)
ECOG performance status, No. (%)	n = 262	n = 81	n = 343
0	89 (34.0)	21 (25.9)	110 (32.1)
1	157 (59.9)	52 (64.2)	209 (60.9)
2	16 (6.1)	8 (9.9)	24 (7.0)
Previous lines of therapy, median (range)	2 (0-7)	2 (0-8)	2 (0-8)
Previous lines of therapy, No. (%)	n = 246	n = 80	n = 326
1	68 (27.6)	29 (36.3)	97 (29.8)
2	58 (24.0)	17 (21.3)	76 (23.3)
3	60 (24.4)	17 (21.3)	77 (23.6)
4	50 (20.3)	10 (12.5)	60 (18.4)
5+	9 (3.7)	7 (8.8)	16 (4.9)
Tumor type, No. (%)			
Biliary	42 (16.0)	9 (10.8)	51 (14.7)
Colorectal	86 (32.7)	9 (10.8)	95 (27.5)
Gynecologic	38 (14.4)	6 (7.2)	44 (12.7)
NSCLC	28 (10.6)	32 (38.6)	60 (17.3)
Other	19 (7.2)	15 (18.1)	34 (9.8)
Pancreas	10 (3.8)	1 (1.2)	11 (3.2)
Salivary	18 (6.8)	1 (1.2)	19 (5.5)
Urothelial	22 (8.4)	10 (12.0)	32 (9.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung cancer.

In patients with *HER2* amplification, ORRs were higher among those with confirmed *HER2* overexpression (39.1%) versus no or equivocal *HER2* overexpression (12.5%). Higher *HER2* copy number was associated with higher likelihood of *HER2* overexpression, and response rate significantly increased with higher copy-number cutoff. Thus, it may be informative to perform IHC testing even in patients with confirmed amplifications on next-generation sequencing.

Conflicting data have been reported concerning the predictive value of *HER2*-activating mutations.^{8,19,21-27} In our data set, patients with *HER2* amplification or overexpression

and concomitant *HER2* mutations had similar ORR to the overall *HER2* amplification and/or overexpression group (35.7% v 25.9%). Although *HER2* mutations alone were not associated with response in the overall population, the therapeutic relevance of the few mutations associated with response should be further investigated.

We observed meaningful objective responses in patients with a variety of refractory solid tumors (Data Supplement, Table S7). Earlier published ORRs for the salivary (60%; 9/15), colorectal (32%; 18/57), and biliary cancer (23%; 9/39) subgroups were confirmed in this updated analysis.¹¹⁻¹³ The NSCLC and urothelial cancer cohorts had ORRs of 22.7% and 21.1%,

TABLE 2. Clinical Outcomes by *HER2* Alteration Group (N = 346)

<i>HER2</i> Alteration Group	ORR ^a		DCR		DOR		PFS		OS	
	No. (%)	95% CI	No. (%)	95% CI	Median, Months	95% CI	Median, Months	95% CI	Median, Months	95% CI
All <i>HER2</i> -altered (N = 346)	73 (21.1)	16.9 to 25.8	146 (42.2)	36.9 to 47.6	7.4	5.9 to 9.2	2.8	2.7 to 3.5	10.1	8.6 to 12.1
Patients with <i>HER2</i> amplification and/or overexpression (n = 263)	68 (25.9)	20.7 to 31.6	119 (45.2)	39.1 to 51.5	7.4	5.9 to 9.2	2.8	2.7 to 4.0	11.2	9.4 to 14.2
Patients with <i>HER2</i> amplification and overexpression, and/or mutation (n = 78)	32 (41.0)	30.0 to 52.7	47 (60.3)	48.5 to 17.2	6.9	4.2 to 9.2	5.6	3.9 to 6.9	17.2	10.9 to 23.6
Patients with <i>HER2</i> amplification and overexpression (n = 69)	27 (39.1)	27.6 to 51.6	40 (58.0)	45.5 to 69.8	7.3	4.4 to 11.3	5.3	3.5 to 7.1	17.2	10.4 to 24.1
Patients with <i>HER2</i> amplification, overexpression, and mutation (n = 9)	5 (55.6)	21.2 to 86.3	7 (77.8)	40.0 to 97.2	4.2	2.8 to NE	5.9	1.0 to 9.7	20.9	2.3 to 26.2
Patients with <i>HER2</i> amplification and no/equivocal expression (n = 64)	8 (12.5)	5.6 to 23.2	19 (29.7)	18.9 to 42.4	6.6	0.7 to 11.3	2.0	1.5 to 2.7	8.1	5.0 to 12.5
IHC 2+ (n = 32)	7 (21.9)	9.3 to 40.0	12 (37.5)	21.1 to 56.3	6.2	0.7 to 9.3	1.8	1.4 to 5.4	7.3	4.2 to 14.7
IHC 1+ (n = 12)	1 (8.3)	0.2 to 38.5	3 (25.0)	5.5 to 75.2	11.3	NE to NE	2.3	1.2 to 7.1	10.3	3.8 to 15.7
IHC 0 or 0+ (n = 20)	0	0	4 (20.0)	5.7 to 43.7	—	—	2.7	1.4 to 2.8	10.3	3.8 to 15.7
Patients with <i>HER2</i> amplification and unknown overexpression status (n = 107)	25 (23.4)	15.7 to 32.5	44 (44.1)	31.7 to 51.0	8.5	5.8 to 15.4	2.7	2.5 to 4.0	10.7	7.7 to 14.2
Patients with <i>HER2</i> overexpression and no amplification (n = 3)	1 (33.3)	0.8 to 90.6	2 (66.7)	9.4 to 99.2	25.9	NE to NE	19.7	1.4 to NE	37.9	1.5 to NE
Patients with <i>HER2</i> overexpression and unknown amplification status (n = 11)	2 (18.2)	2.3 to 51.8	7 (63.6)	30.8 to 89.1	5.4	2.5 to NE	4.2	1.2 to 8.3	10.1	2.2 to 23.5
Patients with <i>HER2</i> mutation only (n = 83)	5 (6.0)	2.0 to 13.5	27 (32.5)	22.6 to 43.7	7.4	1.4 to NE	2.8	1.7 to 3.5	7.7	5.1 to 9.4
Patients with <i>HER2</i> IHC 1+ or 2+ (n = 7)	0	0	2 (28.6)	3.7 to 71.0	NE	NE	2.7	1.3 to 4.1	6.9	1.4 to 12.1

Abbreviations: DCR, disease control rate; DOR, duration of response; *HER2*, human epidermal growth factor receptor 2; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

^aResponse was assessed by the investigator using RECIST v1.1.

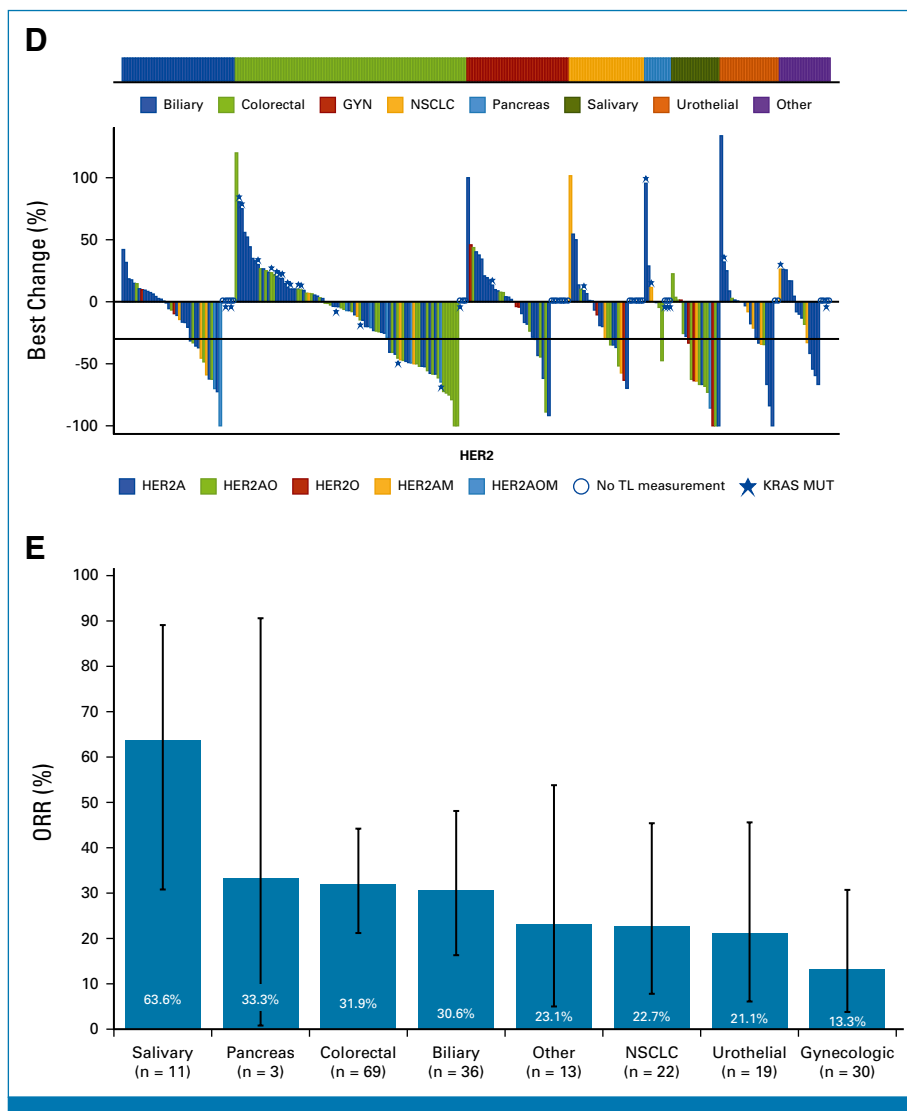


FIG 1. (Continued). the 30% decrease in the sum of diameters of target lesions, from baseline. (E) ORR in patients with HER2-amplified and/or -overexpressed + *KRAS* wild-type tumors by tumor group (n = 202). ^aResponse was assessed by the investigator using RECIST v1.1. ^bData for patients without disease progression or death were censored at the date of the last tumor assessment (or, if no tumor assessments were performed, after the baseline visit, at the date of first treatment). Kaplan-Meier curves are for descriptive purposes only. Bar graph whiskers represent 95% CI. A/O, amplified and/or overexpressed; GYN, gynecologic; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; NE, not estimable; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TL, target lesion; UNK, unknown; WT, wild-type.

respectively. Responses were also seen in patients with pancreatic, cervical, and unknown primary tumors, but the numbers in these cohorts were too small to allow an estimate of the response rates.

Limitations include potential bias toward recruiting patients with tumor types known to respond to P + T, as well as risk in aggregating tumor response rates across different tumor types. Furthermore, as many of these

analyses were not prespecified, and as this was a single-arm study, the results are purely exploratory and hypothesis-generating.

HER2-targeted therapy may have utility in a variety of *KRAS* wild-type, HER2-amplified and -overexpressed solid tumors. Substantial activity was seen in patients with refractory salivary gland, colorectal, biliary, NSCLC, and urothelial cancers.

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PRIOR PRESENTATION

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CLINICAL TRIAL INFORMATION

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REFERENCES

- Dumbrava EEI, Balaji K, Raghav K, et al: Targeting ERBB2 (HER2) amplification identified by next-generation sequencing in patients with advanced or metastatic solid tumors beyond conventional indications. *JCO Precis Oncol* 10.1200/PO.18.00345
- Yan M, Schwaederle M, Arguello D, et al: HER2 expression status in diverse cancers: Review of results from 37,992 patients. *Cancer Metastasis Rev* 34:157-164, 2015
- Baselga J, Gelmon KA, Verma S, et al: Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol* 28:1138-1144, 2010
- Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001
- Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *Lancet* 376:687-697, 2010
- Strickler JH, Cercek A, Siena S, et al: MOUNTAINEER: Open-label, phase 2 study of tucatinib in combination with trastuzumab for HER2-positive metastatic colorectal cancer. Presented at the ESMO World Congress on Gastrointestinal Cancers Barcelona, July 2, 2022
- Mazieres J, Barlesi F, Filleron T, et al: Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: Results from the European EUHER2 cohort. *Ann Oncol* 27:281-286, 2016
- Li BT, Smit EF, Goto Y, et al: Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. *N Engl J Med* 386:241-251, 2022
- Cooper AJ, Gainor JF: Human epidermal growth factor receptor 2-mutant non-small-cell lung cancer: Continued progress but challenges remain. *J Clin Oncol* 40:693-697, 2022
- Hainsworth JD, Meric-Bernstam F, Swanton 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* 36:536-542, 2018
- Meric-Bernstam F, Hurwitz H, Raghav KPS, 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* 20:518-530, 2019
- Kurzrock R, Bowles DW, Kang H, et al: Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: Results from MyPathway, a phase IIa multiple basket study. *Ann Oncol* 31:412-421, 2020
- Javle M, Borad MJ, Azad NS, et al: Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): A multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 22:1290-1300, 2021
- National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in oncology (NCCN Guidelines): Colon cancer V.2.2023. 2023. <http://NCCN.org>
- National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in oncology (NCCN Guidelines): Head and Neck Cancers V.2.2023. 2023. <http://NCCN.org>
- National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in oncology (NCCN Guidelines): Biliary Tract Cancers V.2.2023. 2023. <http://NCCN.org>
- Zhao B, Wang L, Qiu H, et al: Mechanisms of resistance to anti-EGFR therapy in colorectal cancer. *Oncotarget* 8:3980-4000, 2017
- Berns K, Horlings HM, Hennessy BT, et al: A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. *Cancer Cell* 12:395-402, 2007
- Smith AE, Ferraro E, Safonov A, et al: HER2 + breast cancers evade anti-HER2 therapy via a switch in driver pathway. *Nat Commun* 12:6667, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.22.02636>.

DATA SHARING STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (<https://vivli.org>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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20. Majewski IJ, Nuciforo P, Mittempergher L, 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* 33:1334-1339, 2015
 21. Bose R, Kavuri SM, Searleman AC, et al: Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov* 3:224-237, 2013
 22. Hyman DM, Piha-Paul SA, Won H, et al: HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature* 554:189-194, 2018
 23. Li BT, Shen R, Buonocore D, et al: Ado-trastuzumab emtansine for patients with HER2-mutant lung cancers: Results from a phase II basket trial. *J Clin Oncol* 36:2532-2537, 2018
 24. Smyth LM, Piha-Paul SA, Won HH, et al: Efficacy and determinants of response to HER kinase inhibition in HER2-mutant metastatic breast cancer. *Cancer Discov* 10:198-213, 2020
 25. Xu X, De Angelis C, Burke KA, et al: HER2 reactivation through acquisition of the HER2 L755S mutation as a mechanism of acquired resistance to HER2-targeted therapy in HER2(+) breast cancer. *Clin Cancer Res* 23:5123-5134, 2017
 26. Zhang Y, Wu S, Zhuang X, et al: Identification of an activating mutation in the extracellular domain of HER2 conferring resistance to pertuzumab. *Onco Targets Ther* 12:11597-11608, 2019
 27. Meric-Bernstam F, Johnson AM, Dumbrava EE, et al: Advances in HER2-targeted therapy: Novel agents and opportunities beyond breast and gastric cancer. *Clin Cancer Res* 25:2033-2041, 2019
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

MyPathway Human Epidermal Growth Factor Receptor 2 Basket Study: Pertuzumab + Trastuzumab Treatment of a Tissue-Agnostic Cohort of Patients With Human Epidermal Growth Factor Receptor 2–Altered Advanced Solid Tumors

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Stock and Other Ownership Interests: Leuchemix

Consulting or Advisory Role: Sanofi, Janssen Biotech, Astellas Pharma, Bayer, Genentech/Roche, AstraZeneca, Pfizer, Amgen, Lilly, POINT Biopharma, Cadence Pharma

Research Funding: Janssen Biotech (Inst), Astellas Pharma (Inst), Sanofi (Inst), Bayer (Inst), Dendreon, Pfizer (Inst)

Patents, Royalties, Other Intellectual Property: Leuchemix, Parthenolide, Dimethylaminoparthenolide. Exelixis: Abiraterone plus cabozantinib combination

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Open Payments Link: <https://openpaymentsdata.cms.gov/physician/201030/>

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Research Funding: Boehringer Ingelheim, BMS, Roche, AstraZeneca, Ono Pharmaceutical, Archer, Pfizer, Personalis

Patents, Royalties, Other Intellectual Property: Founder of Achilles Therapeutics: a biotechnology company funded by Syncona/Wellcome Trust to target clonal Neoantigens through vaccine and cell therapy approaches, Method for treating cancer based on identification of clonal neo-antigens (PCT/EP2016/059401), Immune checkpoint intervention in cancer (PCT/EP2016/071471), Methods for lung cancer detection (PCT/US2017/028013), Method of detecting tumour recurrence (PCT/GB2017/053289), Method for treating cancer (PCT/EP2016/059401), Method of identifying insertion/deletion mutation targets (PCT/GB2018/051892), Method for determining whether an HLA allele is lost in a tumour (PCT/GB2018/052004), Method for identifying responders to cancer treatment (PCT/GB2018/051912), Method of predicting survival rates for cancer patients (PCT/GB2020/050221)

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Open Payments Link: <https://openpaymentsdata.cms.gov/physician/477023/>

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Research Funding: Novartis (Inst), AstraZeneca (Inst), Taiho Pharmaceutical (Inst), Genentech (Inst), Calithera Biosciences (Inst), Debiopharm Group (Inst), Bayer (Inst), Aileron Therapeutics (Inst), PUMA Biotechnology (Inst), CytomX Therapeutics (Inst), Jounce Therapeutics (Inst), Zymeworks (Inst), Curis (Inst), Pfizer (Inst), eFFECTOR Therapeutics (Inst), AbbVie (Inst), Boehringer Ingelheim (Inst), Guardant Health (Inst), Daiichi Sankyo (Inst), GlaxoSmithKline (Inst), Seagen (Inst), Taiho Pharmaceutical (Inst), Klus Pharma (Inst), Takeda (Inst)

Travel, Accommodations, Expenses: European Organisation for Research and Treatment of Cancer (EORTC), ESMO, Cholangiocarcinoma Foundation

No other potential conflicts of interest were reported.

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