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A randomized phase 2 study of trastuzumab and pertuzumab (TP) compared to cetuximab and irinotecan (CETIRI) in advanced/metastatic colorectal cancer (mCRC) with HER2 amplification: SWOG S1613.

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Background: HER2 (*ERBB2*) over-expression and amplification (HER2+) is seen in a small but distinct subset (2-3%) of mCRC and is enriched in *RAS/BRAF* wild type (WT) tumors. This subset is characterized by a limited response to anti-epidermal growth factor receptor monoclonal antibody-based (anti-EGFR) therapy and a promising response to dual-HER2 inhibition. **Methods:** In this multicenter, open label, randomized, phase 2 trial, we enrolled 54 patients with *RAS/BRAF* WT HER2+ mCRC who had had disease progression after 1 or 2 previous therapies. HER2 status was confirmed centrally with immunohistochemistry (IHC) and in-situ hybridization (ISH). HER2+ was defined as IHC 3+ or 2+ and ISH amplified (dual-probe HER2/CEP17 ratio $>$ 2.0). Patients were then randomly assigned in a 1:1 ratio to receive either TP (trastuzumab [loading 8 mg/kg then 6 mg/kg] + pertuzumab [loading 840 mg then 420 mg] every 3 weeks) or CETIRI (cetuximab 500 mg/m^2 + irinotecan 180 mg/m^2 every 2 weeks). Crossover was allowed for patients on CETIRI arm to TP (cTP) after progression. Restaging (per RECIST v1.1) was performed at 6 and 12 weeks and then every 8 weeks until progression. The primary endpoint was progression-free survival (PFS). Key secondary endpoints were overall response rate (ORR), overall survival (OS) and safety. **Results:** A total of 54 (out of planned 62 due to low accrual) patients were randomized to TP (26) and CETIRI (28) between 10/2017 and 12/2021. By 8/18/2022, 20 patients had crossed over to cTP arm. One CETIRI patient was not analyzable. The results for key endpoints by protocol defined stratification factors, prior irinotecan (Piri) (yes or no) and HER2/CEP17 ratio (HCR) ($>$5 or $\leq$5), are summarized as of data cut-off of 9/6/2022. PFS did not vary significantly by treatment: medians 4.4 (95%CI: 1.9 – 7.6) months in TP group and 3.7 (95%CI: 1.6 – 6.7) months in CETIRI group (p = 0.35). Grade $\geq$3 adverse events occurred in 23%, 46% and 40% of patients in TP, CETIRI and cTP groups. **Conclusions:** Dual-HER2 inhibition with TP appears to be a safe and effective treatment option for patients with *RAS/BRAF* WT HER2+ mCRC with a promising response rate of 31%. Higher level of *HER2* amplification may provide a greater degree of clinical benefit from TP compared to CETIRI. Future correlative efforts will explore biomarkers of response/resistance with this strategy. Clinical trial information: NCT03365882. Research Sponsor: U.S. National Institutes of Health; Genentech, Inc.

	TP					CETIRI					
		HCR		Piri			HCR		Piri		Crossover
Endpoint	All	> 5	≤ 5	Yes	No	All	> 5	≤ 5	Yes	No	TP
N	26	19	7	11	15	27	20	7	13	14	20
mPFS[1]	4.4	7.5	2.8	3.0	7.5	3.7	3.5	6.6	3.1	4.7	5.7
6mo-PFS[2]	37	51	0	18	51	37	30	57	31	43	48
ORR[2]	31	42	0	27	33	24	21	33	15	33	29
mOS[1]	NR	NR	32.3	20.0	NR	24.7	24.8	23.2	17.5	33.8	NA
2yr-OS[2]	64%	62	71	49	77	52%	61	36	30	64	NA

1, in months; 2, in %; m, median; mo, months; N, number of patients; NA, not applicable; NR, not reached; yr, year.