Conclusions: The safety data showed an increase in toxicity in the experimental arm, but no unexpected events. There was no excessive toxicity-rates or unacceptable risks. The risk-benefit-considerations and the conduct of the trial remain unchanged.

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439P Phase Ib/II study of ibrutinib (ibr) in combination with cetuximab (cetux) in patients (pts) with previously treated metastatic colorectal cancer (mCRC)

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Background: Third- or later-line treatments for mCRC have low response rates (1–37%) and limited PFS (1.4–5.6 mo) and OS (6.1–14.0 mo) (Arnold *Ann Oncol* 2018). Ibr is a once-daily Bruton's tyrosine kinase (BTK) inhibitor approved for the treatment of various B-cell malignancies. Ibr also inhibits other kinases, including ETK, ITK, and EGFR tyrosine kinase (Wang *Clin Cancer Res* 2018; Dubovsky *Blood* 2013; Gao *J Natl Cancer Inst* 2014), and may provide complementary activity with cetux. Dual targeting of EGFR may improve OS in mCRC (Weickhardt *J Clin Oncol* 2012). This cohort of the phase Ib/II study (NCT02599324) evaluated efficacy and safety of ibr + cetux in pts with mCRC.

Methods: Eligible pts had *KRAS* or *NRAS* wild type mCRC previously treated with 2–4 regimens and were cetux-naive. Pts received oral ibr once daily at 560 mg (starting dose) or 840 mg (recommended phase II dose) plus IV cetux (400 mg/m^2 initial dose then 250 mg/m^2 weekly) in 21-d cycles until unacceptable toxicity or progression. Efficacy (overall response rate [ORR], PFS, duration of response [DOR], disease control rate [DCR], and OS) and safety are reported.

Results: 58 pts received ibr + cetux (ibr 560 mg, n=8; ibr 840 mg, n=50). Median age was 62 y; 38%, 40%, and 22% of pts had received 2, 3, and 4 prior regimens for mCRC, respectively. Median follow-up was 20.9 mo. ORR was 16% (Table). Median PFS was 4.8 mo (range 3.9–5.6). Median treatment duration was 3.2 mo for ibr and 3.0 mo for cetux. Grade ≥3 adverse events (AEs) occurred in 41 pts (71%); the only grade ≥3 AE occurring in ≥10% of pts was dermatitis acneiform (15 pts [26%]). Two pts (3%) had AEs leading to death; neither were related to study drug. Two pts (3%) had major hemorrhage and 53 pts (91%) had rash of any grade (grade ≥3 in 17 pts [29%]).

Table: 439P

Efficacy Outcomes	Ibr + cetux N = 58
Confirmed ORR*, n (%; 90% CI)	9 (16; 8–26)
Complete response	0
Partial response	9 (16)
Stable disease	36 (62)
Progressive disease	10 (17)
Not evaluable	0
Unknown/missing	3 (5)
Confirmed DCR*, n (%; 90% CI)	45 (78; 67–86)
Median DOR, mo (90% CI)	5.4 (3.2–12.2)
Median PFS, mo (90% CI)	4.8 (3.9–5.6)
Median OS, mo (90% CI)	15.1 (10.5–17.3)

*Confirmed by repeat assessments ≥28 days apart.

Conclusions: Ibr + cetux was moderately active in heavily pretreated, refractory, cetux-naive pts with mCRC. There were no new safety signals and the safety profile was consistent with those of the individual drugs.

Clinical trial identification: NCT02599324.

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