Pharmacokinetics of regorafenib in the phase 3 CONCUR and CORRECT trials in patients with metastatic colorectal cancer (mCRC)

Isrid Sturm[1], Adriaan Cleton[1], Zuzana Jirakova Trnkova[1], Joachim Grevel[2], Sabine Fiala-Buskies[3], John Lettieri[4]

[1]Bayer Pharma AG, Berlin, Germany; [2]BAST Inc. Limited, Loughborough, UK; [3]Bayer Pharma AG, Wuppertal, Germany; [4]Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA

P-261

BACKGROUND

- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in the regulation of angiogenesis, oncogenesis, and the tumor microenvironment[1]
- The randomized, double-blind, placebo-controlled, multicenter phase 3 CORRECT and CONCUR trials showed that regorafenib 160 mg once daily (3 weeks on/1 week off) improves overall survival in patients with treatment-refractory mCRC[2,3]
- The CORRECT trial (NCT01103323) included 760 patients from North America, Europe, Israel, Australia, and Asia (China, n=4; Japan, n=100)[2]
- The CONCUR trial (NCT01584830) included Asian patients (n=204) mostly from mainland China (n=129), but also included patients from Hong Kong (n=23), South Korea (n=20), Taiwan (n=20), and Vietnam (n=12)[3]

OBJECTIVE

- The aim of this analysis was to estimate and compare the exposure (AUC) of regorafenib and its two pharmacologically active metabolites (M-2 and M-5) in the CONCUR and CORRECT patient populations, including in a subset of CONCUR patients from mainland China

METHODS

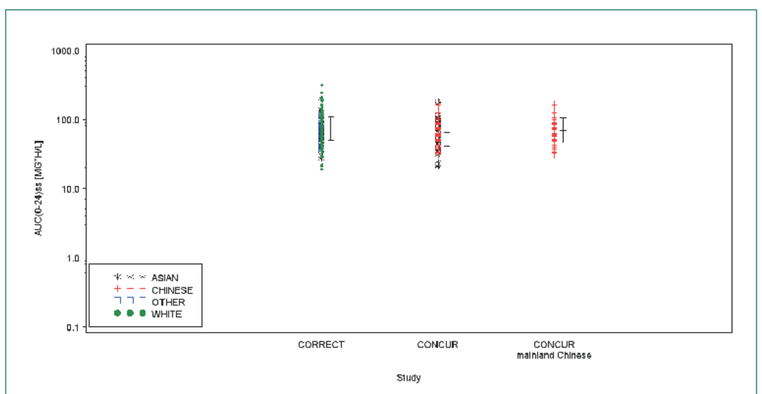
- In CONCUR and CORRECT, patients with treatment-refractory mCRC received regorafenib 160 mg once daily (3 weeks on/1 week off); sparse pharmacokinetic (PK) sampling for population PK (pop-PK) analysis was included for a subset of these patients (N=479):
  - CORRECT, n=381
    - White, n=310
    - Asian, n=45 (41 from Japan, none from mainland China)
    - Other, n=26
  - CONCUR, n=98 (all Asian)
    - Mainland China, n=54
    - South Korea, n=14
    - Taiwan, n=13
    - Hong Kong, n=8
    - Vietnam, n=9
- The $AUC_{(0–24),ss}$ values for regorafenib M-2 and M-5 were estimated using a pop-PK analysis based on sparse samples (2–5 samples per patient in CORRECT and 4 samples per patient in CONCUR) determined by a previously developed pop-PK model for regorafenib
- The pop-PK model was developed to describe the PK of regorafenib, M-2, and M-5[4]
  - The model was based on 617 patients who were enrolled in 2 phase 1 and 2 phase 3 studies and who received oral regorafenib 10–220 mg QD (3 weeks on/1 week off)
  - The pop-PK model accurately described the individual PK observations; covariate analysis identified a number of patient demographics and clinical characteristics with significant impact on exposure to regorafenib and its metabolites; however, these covariates accounted for only a small portion of the overall variability in regorafenib exposure

RESULTS

Regorafenib

- The range of individual $AUC_{(0–24),ss}$ values for regorafenib was similar between patients in CONCUR (20.7–184 mg·h/L) in comparison to patients in CORRECT (19.2–311 mg·h/L) (Figure 1)
- Regorafenib exposure in mainland Chinese patients from CONCUR was similar to the values in patients (Asian and non-Asian) from either CONCUR or CORRECT (Figure 1)
- The geometric mean $AUC_{(0–24),ss}$ was 64.4 mg·h/L in all CONCUR patients and 69.5 mg·h/L in the CONCUR patients from mainland China; 72.9 mg·h/L in all CORRECT patients and 69.5 mg·h/L in CORRECT patients from Asia (Table 1)
- Variability in regorafenib exposure was characterized by coefficient of variation (CV) ranging from 41% to 48%

***Figure 1:** Individual patient $AUC_{(0–24),ss}$ estimates for regorafenib from patients in CORRECT, CONCUR, and from the subset of patients from mainland China in CONCUR*



Plot presents individual and geometric mean ± geometric standard deviation.
Race 'Other' combines American Indian or Alaska native, black or African American, multiple or not reported.

***Table 1:** Summary statistics for regorafenib $AUC_{(0–24),ss}$ in all patients and patient subsets from CORRECT and CONCUR*

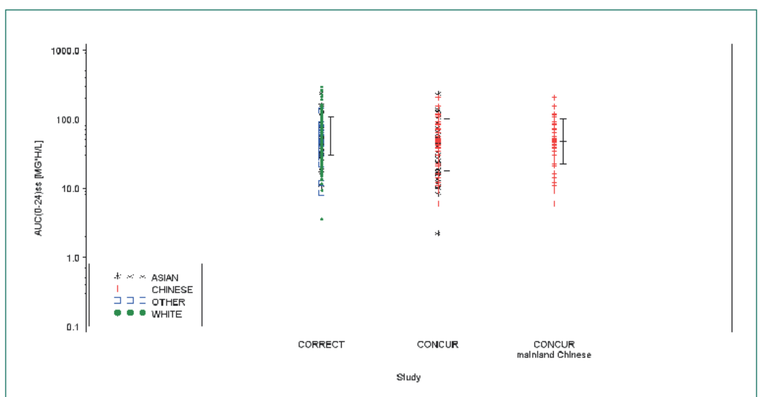
Study	n	Population	Geometric mean, mg·h/L	CV, %	Range, mg·h/L
CORRECT	381	All*	72.9	41	(19.2–311)
CORRECT	45	Asian	68.1	43	(27.4–200)
CONCUR	98	All (Asian)†	64.4	48	(20.7–184)
CONCUR	54	Mainland Chinese	69.5	42	(30.0–172)

*Includes white, Asian, and black patients.
†Includes Hong Kong, Taiwan, South Korea, Vietnam, and mainland China.
CV, coefficient of variation.

M-2

- The M-2 metabolite exposure was similar in the CONCUR (2.2–233 mg·h/L) and CORRECT (3.5–295 mg·h/L) patient populations (Figure 2)
- Geometric mean $AUC_{(0–24),ss}$ estimate for M-2 in CONCUR patients from mainland China (47.8 mg·h/L) was similar to that observed in all CONCUR patients (42.4 mg·h/L), as well as similar to the values in Asian patients and overall patient population from CORRECT (49.7 mg·h/L and 56.7 mg·h/L, respectively) (Table 2)
- Variability in M-2 was higher than for regorafenib, as evidenced by CVs ranging from 71% to 108% for M-2 $AUC_{(0–24),ss}$

***Figure 2:** Individual patient $AUC_{(0–24),ss}$ estimates for regorafenib metabolite M-2 from patients in CORRECT, CONCUR, and from the subset of patients from mainland China in CONCUR*



Plot presents individual and geometric mean ± geometric standard deviation.
Race 'Other' combines American Indian or Alaska native, black or African American, multiple or not reported.

***Table 2:** Summary statistics for regorafenib metabolite M-2 $AUC_{(0–24),ss}$ in all patients and patient subsets from CORRECT and CONCUR*

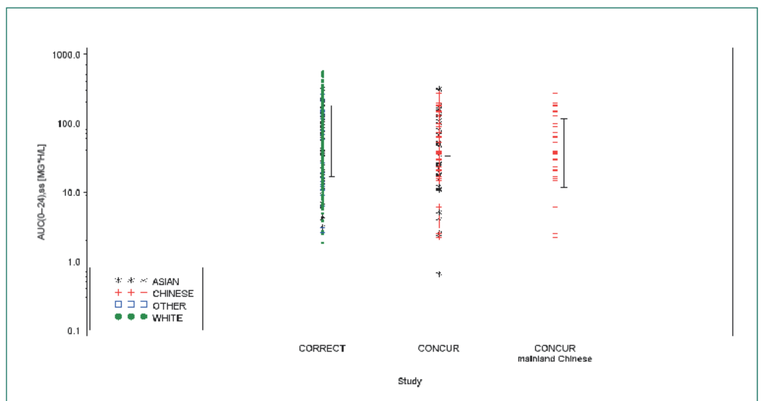
Study	n	Population	Geometric mean, mg·h/L	CV, %	Range, mg·h/L
CORRECT	381	All*	56.7	71	(3.5–295)
CORRECT	45	Asian	49.7	73	(10.9–237)
CONCUR	98	All (Asian)†	42.4	108	(2.2–233)
CONCUR	54	Mainland Chinese	47.8	88	(6.0–206)

*Includes white, Asian, and black patients.
†Includes Hong Kong, Taiwan, South Korea, Vietnam, and mainland China.
CV, coefficient of variation.

M-5

- The M-5 metabolite exposure was highly variable in both studies, with CVs ranging from 166% to 197% (Figure 3; Table 3)
- A slightly lower mean exposure of M-5 was observed in CONCUR compared with CORRECT; however, owing to the high intersubject variability, results should be interpreted with caution
- Geometric mean $AUC_{(0–24),ss}$ estimates for M-5 were 33.1 mg·h/L in the 98 CONCUR patients from Asia, 36.4 mg·h/L in the 54 CONCUR patients from mainland China, 44.9 mg·h/L in the 45 CORRECT patients from Asia, and 54.7 mg·h/L in the overall CORRECT population (Table 3)

***Figure 3:** Individual patient $AUC_{(0–24),ss}$ estimates for regorafenib metabolite M-5 from patients in CORRECT, CONCUR, and from the subset of patients from mainland China in CONCUR*



Plot presents individual and geometric mean ± geometric standard deviation.
Race 'Other' combines American Indian or Alaska native, black or African American, multiple or not reported.

***Table 3:** Summary statistics for regorafenib metabolite M-5 $AUC_{(0–24),ss}$ in all patients and patient subsets from CORRECT and CONCUR*

Study	n	Population	Geometric mean, mg·h/L	CV, %	Range, mg·h/L
CORRECT	381	All*	54.7	174	(1.9–555)
CORRECT	45	Asian	44.9	186	(3.1–315)
CONCUR	98	All (Asian)†	33.1	197	(0.7–312)
CONCUR	54	Mainland Chinese	36.4	166	(2.2–266)

*Includes white, Asian, and black patients.
†Includes Hong Kong, Taiwan, South Korea, Vietnam, and mainland China.
CV, coefficient of variation.

CONCLUSIONS

- Similar exposure values of regorafenib and its pharmacologically active metabolites M-2 and M-5 were observed in Asian patients with mCRC enrolled in CONCUR when compared with both Asian and overall mCRC patient populations from CORRECT
- No notable differences in regorafenib and M-2 and M-5 exposures were observed between patients with mCRC from mainland China and patients from other geographical areas and of different ethnicities
- These data suggest that regorafenib exposure in mCRC patients is not influenced by ethnicity

References

1. Wilhelm SM, *et al. Int J Cancer* 2011;129:245–255.
2. Grothey A, Van Cutsem E, *et al. Lancet* 2013;381:303–312.
3. Li J, *et al. Lancet Oncol* 2015;16:619–629.
4. Smeets J, *et al.* Manuscript in preparation.

Acknowledgments

This study was sponsored by Bayer HealthCare Pharmaceuticals. Editorial assistance in the preparation of this poster was provided by Choice Healthcare Solutions, with financial support from Bayer HealthCare Pharmaceuticals.

ESMO 17th World Congress on Gastrointestinal Cancer, 1–4 July 2015, Barcelona, Spain.