

INTEGRATE IIa: A randomised, double-blind, phase III study of regorafenib versus placebo in refractory advanced gastro-oesophageal cancer (AGOC)—A study led by the Australasian Gastro-intestinal Trials Group (AGITG).

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Background: AGOC has limited options after second-line therapy. Regorafenib (Rego), an oral multi-targeted tyrosine kinase inhibitor (TKI) targeting angiogenic, stromal and oncogenic receptor TKs, prolonged progression free survival (PFS) versus placebo (PBO) across all regions/subgroups in the INTEGRATE phase 2 randomised trial (JCO 2016 43(23):2728-2735). INTEGRATE IIa was designed to examine if Rego improves overall survival (OS). **Methods:** Double-blind placebo-controlled phase 3 trial comparing Rego + best supportive care (BSC) vs PBO + BSC using 2:1 randomisation, stratified by tumour location (GO junction vs gastric), geographic region (Asia vs rest of world), prior VEGF inhibitors (Y/N). Eligibility criteria: histologically/cytologically confirmed AGOC, evaluable metastatic/locally advanced disease, failure/intolerance of ≥ 2 prior lines of therapy with a platinum agent + fluoropyrimidine. Primary objective: OS in the whole study population. OS among Asian sub-population is a key secondary objective. Target of at least 221 events from 250 patients provides 80% power to detect an OS hazard ratio (HR) of 0.67. Pooled OS analysis incorporating INTEGRATE phase 2 data is also planned. Secondary endpoints include PFS, objective response rate, safety and quality of life. **Results:** 251 patients enrolled (Oct16 - Sep21) from 5 countries: 157 from Asia (Korea, Taiwan, Japan); 169 Rego and 82 PBO. After 238 events, median OS (in months) for Rego vs PBO was 4.5 vs 4.0 (HR 0.70 [95%CI: 0.53 to 0.92]; $p = 0.011$) in the whole study population, with a 12 mo survival of 19% vs 6%. Median PFS was 1.8 v 1.6 (HR = 0.52; [95%CI: 0.40-0.69]; $p = < .0001$). After pre-planned adjustment for multiplicity, there were no statistically significant differences across regions (Asia versus non-Asia) or other pre-specified subgroups. Pooled analysis median OS was 5.0 v 4.1 (HR 0.69 [95% CI: 0.56 to 0.87]; $p = 0.001$). Rego toxicity was similar to previously reported. **Conclusions:** Rego improves survival compared with PBO in advanced refractory AGOC, offering a new treatment option. This result creates a therapeutic platform for combination studies. INTEGRATE IIb is an ongoing international randomised Phase 3 trial in pre-treated patients with AGOC comparing Rego + nivolumab to standard chemotherapy (NCT0487936). Clinical trial information: NCT02773524. Research Sponsor: Bayer.