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Roxadustat for Chemotherapy-Induced Anemia in Patients with Non-Myeloid Malignancies: A Randomized, Open-Label, Active-Controlled, Phase III Study

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DECLARATION OF INTERESTS

Shun Lu reports speaker fees from AstraZeneca, Hansoh, and Hengrui Therapeutics; served as advisor/consultant for AstraZeneca, Pfizer, Boehringer Ingelheim, Hutchison, ZaiLab, GenomiCare, Yuhan Corporation, Menarini, InventisBio Co., Simcere Zaiming, and Roche; and received research support from AstraZeneca, Hutchison, BMS, Heng Rui, Beigene, Roche, Hansoh, Lilly Suzhou, and FibroGen

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CIA represents a significant unmet need in China and worldwide

CIA is common and associated with substantial health burden

- Up to 98% of patients with solid tumors receiving myelosuppressive chemotherapy experience CIA[1-3]
- CIA is associated with reduced HRQoL[4-6] and decreased survival[7]

Current treatments are limited in China; only 7.2% of Chinese patients with cancer-related anemia receive treatment[2]

- Blood supply in China is extremely limited
- ESAs require subcutaneous/intravenous injection in hospitals, which can lead to low treatment compliance

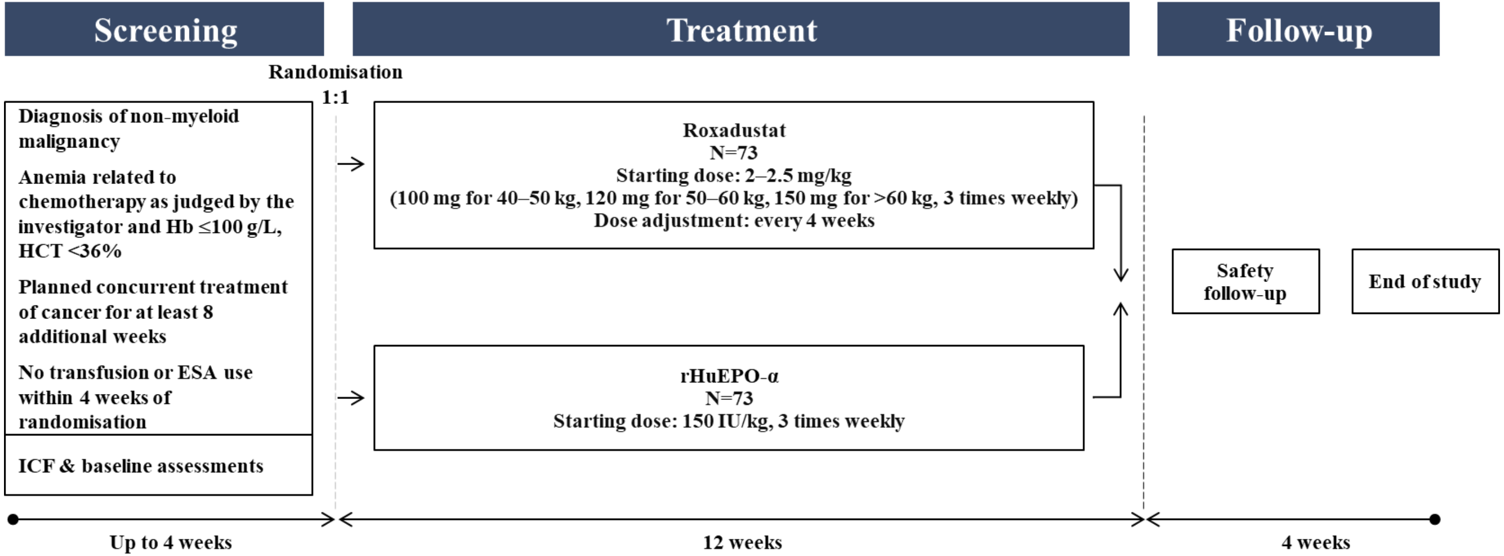
Roxadustat (FG-4592) belongs to a new pharmacologic class of small molecule enzyme inhibitors, HIF PHIs

- First approved for the treatment of anemia associated with CKD in China in December 2018 and by the EMA in August 2021

CIA, chemotherapy-induced anemia; CKD, chronic kidney disease; EMA, European Medicines Agency; ESAs, erythropoietin-stimulating agents; HIF PHI, hypoxia-inducible factor prolyl hydroxylase inhibitors; HRQoL, health-related quality of life

1. Clinical guidelines on tumor associated anemia (version 2015–2016) Chin J Pract Intern Med 2015; 35: 921–30. **2.** Song ZB, et al. China. China Cancer 2019; 28: 718–22. **3.** Xu H, et al. Clin Epidemiol 2016; 8: 61–71. **4.** Busti F, et al. Pharmaceuticals (Basel) 2018; 11. **5.** Tran KT, et al. Blood 2006; 108: 3355. **6.** Ludwig H, et al. Semin Oncol 2001; 28 (2 suppl 8): 7–14. **7.** Groopman JE, et al. J Natl Cancer Inst 1999; 91: 1616–34.

Study design: randomized, open-label, active-controlled, multicenter phase 3 study



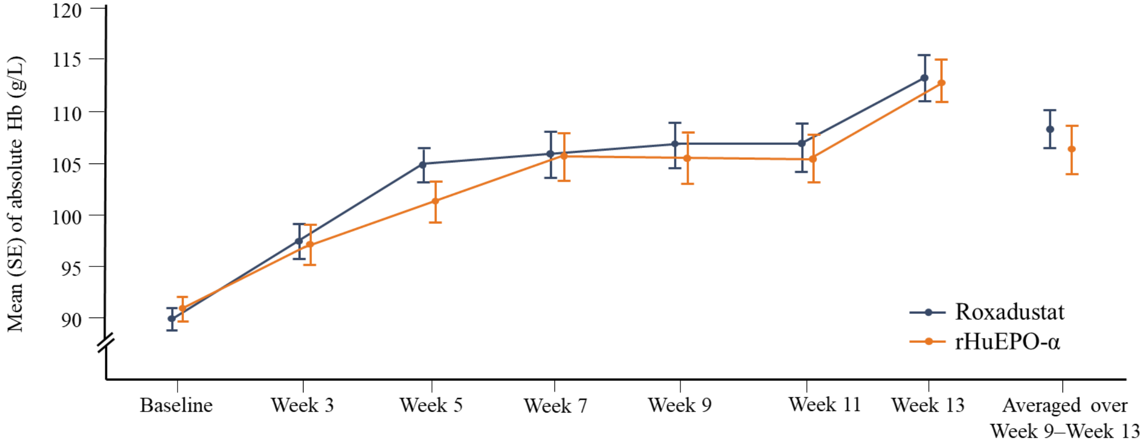
Primary efficacy endpoint: mean change in Hb concentration from baseline to that averaged over Weeks 9–13 (stratified by screening Hb level (<90 g/L or ≥ 90 g/L); tumor type (lung, breast or others); and chemotherapy regimen (platinum vs. non-platinum)

- Of 159 patients randomized, 140 were included in the per-protocol set (n=78, roxadustat; n=62, rHuEPO-α)

EOS, end of study; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; HCT, hematocrit; ICF, informed consent form; rHuEPO-α, recombinant human erythropoietin-α.

Oral roxadustat is non-inferior to subcutaneous rHuEPO-α

Mean (SE) of absolute Hb by scheduled visit (per-protocol set)



	Baseline	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Averaged over Week 9–Week 13
Roxadustat, n	78	71	65	61	55	53	51	65
rHuEPO-α, n	62	57	55	49	51	41	40	52

- The LSM (95% two-sided CI) change from baseline to Weeks 9–13 in Hb concentration was 17.1 (13.58, 20.71) g/L with roxadustat and 15.4 (11.34, 19.50) g/L with rHuEPO-α
- The lower bound of the 1-sided 97.5% CI for the treatment difference (–3.4 g/L) was greater than the predefined non-inferiority margin of –6.6 g/L, establishing non-inferiority

- A numerically greater percentage of patients in the roxadustat group achieved ≥10-g/L, ≥15-g/L, and ≥20-g/L Hb increase
- A numerically shorter median time to first 15 g/L and 20 g/L Hb increase was observed in the roxadustat group in the FAS population (42.0 and 57.0 days for Roxadustat vs. 52.0 and 77.0 days for rHuEPO-α)

CI, confidence interval; EOS, end of study; ESA, erythropoietin-stimulating agent; FAS, full analysis set; Hb, hemoglobin; LSM, least-squares mean; rHuEPO-α, recombinant human erythropoietin-α; SE, standard error

Roxadustat non-inferiority in key secondary endpoints

PPS analysis	Roxadustat (n=78)	rHuEPO-α (n=62)	% difference (95% two-sided CI)
Patients with Hb increase ≥10 g/L from baseline through Week 13, n (%), (95% CI)	69 (88.5) (79.2, 94.6)	51 (82.3) (70.5, 90.8)	6.5 (–6.4, 19.5)
FACT-An anemia subscale averaged Weeks 9–13, LSM (95% CI)	–0.58 (–3.13, 1.98)	–0.92 (–3.88, 2.03)	0.35 (–3.33, 4.02)
FACIT-F fatigue subscale averaged Weeks 9–13, LSM (95% CI)	–0.24 (–2.19, 1.71)	–0.27 (–2.52, 1.98)	0.03 (–2.77, 2.83)
FACT-An total score averaged Weeks 9–13, LSM (95% CI)	–0.96 (–6.33, 4.41)	–5.38 (–11.61, 0.85)	4.42 (–3.30, 12.15)

- Patients treated with roxadustat had greater treatment compliance compared with those treated with rHuEPO-α (≥85% to ≤100% compliance, 65.4% vs. 39.2%, respectively)
- Roxadustat may decrease the burden of RBC transfusion compared with rHuEPO-α (incidence of RBC transfusions[a], 0.004 vs. 0.019; rate ratio 0.225 [95% CI: 0.084 to 0.603])

Non-inferiority was established if the lower bound of the one-sided 97.5% CI for the difference between roxadustat and rHuEPO-α was greater than –15% (patients with Hb increase ≥10 g/L), –4 (FACT-An anaemia), –3 (FACIT-F), or –7 (FACT-An total)

[a]Incidence of RBC transfusions was defined as the number of RBC transfusions divided by the duration of treatment in week

CI, confidence interval; FACT-An, Functional Assessment of Cancer Therapy-Anemia; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; PPS, per-protocol set; rHuEPO-α, recombinant human erythropoietin-α

Roxadustat safety profile is acceptable and consistent with previous findings

	Roxadustat (n=81, PEY=15.8)		rHuEPO-α (n=74, PEY=12.1)	
Category of AEs	n (%)	Patients*100/PEY	n (%)	Patients *100/PEY
Patients with any TEAE	77 (95.1)	488.4	69 (93.2)	568.4
Drug-related TEAEs*	12 (14.8)	76.1	13 (17.6)	107.1
TEAEs with CTCAE Grade 3 or greater†	44 (54.3)	279.1	33 (44.6)	271.8
Drug-related TEAEs with CTCAE ≥Grade 3*,†	2 (2.5)	12.7	2 (2.7)	16.5
TESAEs	24 (29.6)	152.2	16 (21.6)	131.8
TEAEs leading to discontinuation	1 (1.2)	6.3	3 (4.1)	24.7
TEAEs leading to death‡	9 (11.1)	57.1	2 (2.7)	16.5
TEAEs of special interest	2 (2.5)	12.7	1 (1.4)	8.2
DVT and PE	2 (2.5)	12.7	1 (1.4)	8.2

*TEAEs with unknown relationship to study treatment were counted as "Related." †TEAEs with unknown severity were counted as "Severe." ‡No deaths were determined to be related to study treatment.
TEAEs were defined as AEs occurring on or after the first doses of study medication but within 28 days after the last doses of study drug. AEs were coded with MedDRA Version 26.0. CTCAE Version 5.0 served as guidance for specific severity assessment criteria for AEs.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DVT, deep vein thrombosis; MedDRA, Medical Dictionary for Regulatory Activities; PE, pulmonary embolism; PEY, patient-exposure-year (Last Dose Date – First Dose Date + 1)/365.25; rHuEPO-α, recombinant human erythropoietin-α; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Conclusions

In this first randomized, controlled study analyzing roxadustat for the treatment of CIA among patients with non-myeloid malignancies

- Oral roxadustat was non-inferior to subcutaneous rHuEPO-α
- Patients treated with roxadustat had greater treatment compliance
- The safety profile of roxadustat was acceptable and consistent with previous findings
    - The incidence of any TEAEs was similar between treatment arms; TESAEs were numerically greater in roxadustat group and were consistent with those reported for patients undergoing chemotherapy
    - Deaths were numerically greater in the roxadustat group compared to the rHuEPO-α group (n=9 vs. n=2), but no deaths were assessed to be drug related by either investigator or sponsor

These results suggest a positive benefit:risk ratio in this patient population and support a secondary indication for this new class of therapeutics, with roxadustat potentially representing a new treatment paradigm

AE, adverse event; rHuEPO-α, recombinant human erythropoietin-α; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event