Anaemia is a frequent complication in cancer patients, and particularly exacerbated at late stages of lung carcinoma. Erythropoiesis-Stimulating Agents (ESAs) are widely used to correct chemotherapy-associated anaemia. However, it was reported that 30-50% of patients do not respond. An increased risk of mortality, thromboembolic events and tumour progression was associated with ESA treatments in the context of cancer and low levels of erythropoietin receptor (EpoR) expression was observed in cancer cells, raising safety concerns on the use of ESAs in cancer. Here we establish by mathematical modelling an innovative approach to optimize a personalized ESA treatment for anaemia in Non-Small Cell Lung Carcinoma (NSCLC) patients. Based on in-vitro experiments we calibrate a mechanistic dynamic pathway model that enables the estimation of ESA binding sites and the determination of the binding properties of ESAs. We show that ESAs with low affinity towards the EpoR activate signal transduction more efficiently in cells exhibiting high levels of ESA binding sites, such as primary erythroid progenitor cells, and that in a defined range of concentrations the risk of ESA-induced activation of the EpoR in the context of NSCLC cells is reduced. By combining mechanistic dynamic pathway modelling with pharmacokinetic and pharmacodynamic data of ESAs in human subjects, we identify the number of ESA binding sites per patient and the haemoglobin degradation rate as key patient-specific parameters. The integrative model enables a personalized prediction of the minimum efficacious ESA dose, and the stratification of patients into groups of low and high risk of fatal outcome. In sum, our integrative mechanistic model quantitatively describes the dynamic interaction of ESAs at molecular, cellular and systemic level in the human body and provides a quantitative tool to optimize the dosing regimens in clinical trials, and to personalize ESA treatment in cancer.