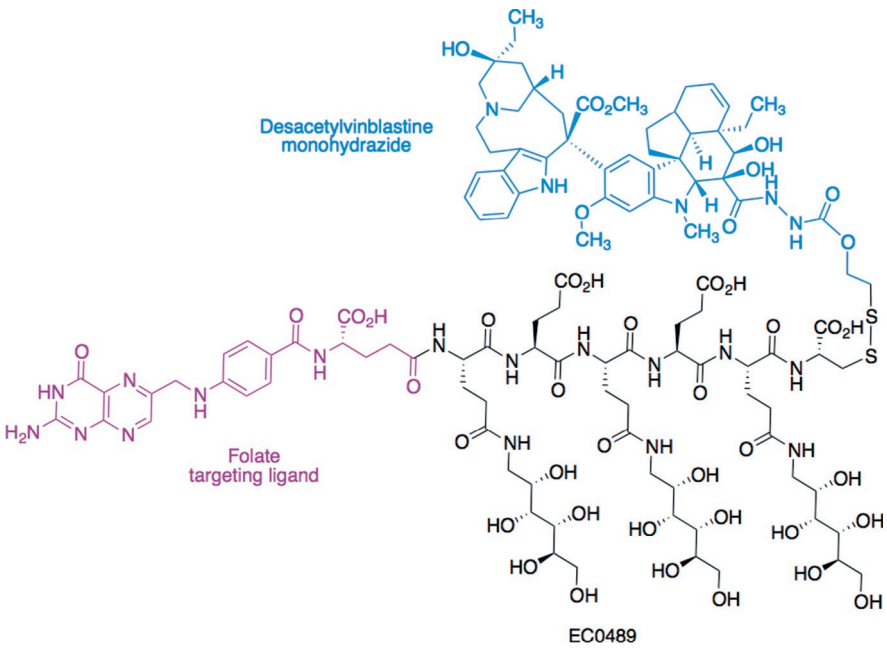

Vintafolide is being studied in association with etarfolatide (^{99m}Tc-EC20), a folate-targeted radiopharmaceutical imaging agent used to identify FR^+ cancers. This allows identifying tumors that overexpress this receptor without the need for a tissue biopsy and hence to select the patients who will be most likely to respond to folate-targeted therapy.[83] Etarfolatide, similarly to most ^{99m}Tc radiopharmaceuticals of diagnostic importance, needs to be prepared immediately before its administration from the chelating agent EC20 and radioactive ^{99m}Tc, together with $SnCl_2$ for the reduction of Tc^{7+} to a lower valency state, which facilitates its chelation (Figure 13.39). Etarfolatide has undergone a number of clinical trials[84] and is being developed together with vintafolide. This combination received orphan drug status in Europe in 2012.[85]

Constipation was identified as the dose-limiting toxicity of vintafolide during a phase I trial. Interestingly, the origin of this problem was identified to be the release of unconjugated vinca alkaloid to the bile following hepatic hydrolysis of the carbamate moiety that connects the alkaloid to the spacer, which led to the development of analogs with an increased hydrolytic stability such as EC0489 is another desacetyl vinblastine hydrazide-derived conjugated drug containing a folate structural fragment as a targeting unit. This compound was designed to have reduced hepatic clearance by placing carbohydrate spacers formed by 1-amino-1-deoxyglucitolyl-γ-glutamate units between the folate and the alkaloid moieties.[86] This new conjugate has entered phase I trials in patients with refractory or metastatic solid tumors who have exhausted standard therapeutic options.[87]

The folate–drug conjugate EC-0225 is unique in that it contains two active moieties (the vinca alkaloid and mitomycin C) and a single folate molecule. In preclinical studies in animals, results were similar to those of vintafolide with doses approximately threefold lower, which justified starting a phase I trial.