Trial Watch

MOVING FORWARDS

Joseph Tabernero and colleagues have carried out a 'first-in-man' Phase I trial of two small interfering RNAs (siRNAs) to treat patients with refractory metastatic disease that involves the liver.

In this trial, Tabernero and colleagues used lipid nanoparticles (LNPs) to encapsulate two siRNAs that target vascular endothelial growth factor (VEGF) and kinesin spindle protein (KSP; also known as KIF11). Inhibition of VEGF targets the tumour vasculature, and inhibition of KSP induces mitotic arrest. One of the limitations of using RNA interference (RNAi) in the clinic is targeting it to the desired organ or tumour. When given parenterally in animal models, the therapeutic, termed ALN-VSP, primarily localized to the liver and spleen owing to their fenestrated endothelium. It also accumulated in tumours owing to their leaky vasculature and enhanced permeability and retention effect. ALN-VSP was given to 41 patients who were enrolled sequentially and assigned one of seven dose levels (0.1–1.5 mg per kg), given as a 15-minute intravenous infusion every 2 weeks. Eleven patients whose disease had not progressed (based on computerized tomography (CT) evaluation) after four cycles (eight doses over 4 months) were allowed to continue in the expansion phase of the trial. Six of these patients received doses at 1 mg per kg and five patients at 1.25 mg per kg until disease progression or the completion of the trial.

Of the 37 patients in the dose escalation part of the trial in whom a tumour response could be assessed, four of 24 patients treated with doses ≥0.7 mg per kg had stable disease or better, according to response evaluation criteria in solid tumours (RECIST). One patient who had metastatic endometrial cancer that included several liver metastases had a complete response and completed the trial in remission after receiving 50 doses at 0.7 mg per kg over 26 months. Two patients with metastatic renal cell carcinoma had stable disease for approximately 8–12 months, and one patient with metastatic pancreatic neuroendocrine tumour had stable disease for 18 months. One patient enrolled in the trial experienced liver failure after the second dose of ALN-VSP and died. This patient had extensive liver metastases and had previously undergone a splenectomy and a partial hepatectomy. Preclinical animal toxicology studies had shown liver toxicity in rats and splenic toxicity in monkeys (this was a potentially on-target effect). On the basis of this and other data the trial was amended to prohibit the recruitment of any patients who had undergone a splenectomy or who had >50% of the liver affected by metastases. Additional dose-limiting toxicity data, including liver function tests, indicated that ALN-VSP was safe, and the recommended dose for Phase II trials was set at 1 mg per kg.

Proof of on-target effects was difficult to assess in this trial. Fifteen patients volunteered for biopsies of metastases to be carried out before and after treatment; however, only one sample contained tumour tissue alone. In two patients whose biopsy samples contained mostly normal liver tissue, evidence of *VEGF* mRNA degradation was found, indicating that the drug was delivered to the liver and had on-target effects. Degradation of *KSP* mRNA was not detected, possibly owing to the reduced expression of this mRNA relative to *VEGF* mRNA. Most of the biopsy samples showed drug accumulation, but the concentrations varied substantially. Reduced blood flow to the tumour (detected by dynamic contrast enhanced magnetic resonance imaging in 28 patients) was evident in several patients but was not dose dependent. A reduction in spleen size was evident in 25 evaluable patients and this effect also did not seem to be dose dependent.

Subsequent Phase II trials will be restricted to patients with one cancer type who have received fewer prior therapies, and all patients will receive the same dose in order to more fully assess the efficacy and on-target effects of this agent.

ORIGINAL RESEARCH PAPER Tabernero, J. *et al.* First-in-man trial of an RNA interference therapeutic targeting VEGF and KSP in cancer patients with liver involvement. *Cancer Disc.* 28 Jan 2013 (doi:10.1158/2159-8290)