Abstract 10038

The objective response categories are as described by Houghton, et al. 2007. Solid tumor xenograft models were commonly utilized to assess the potential activity of anti-cancer agents in Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma. (Houghton et al, 2007)

Regorafenib is a small molecule multi-kinase inhibitor and differs in its chemical structure over sorafenib by the addition of a fluorine atom. Regorafenib inhibits several kinases including BRAF, EGFR1, KIT, PDGFRα, RAF-1, RET, and VEGFR1,2 with higher potency than sorafenib.

Regorafenib has been found to have significant antitumor activity, both in vitro and in vivo, in multiple cancer models

Prior studies assessing the in vivo activity of sorafenib within the Pediatric Preclinical Testing Consortium (PPTC) demonstrated intermediate to high activity for tumor growth inhibition in more than 50% of the sarcoma models tested at a dose of 60mg/kg by oral gavage daily (5 days/wk for 6 consecutive weeks). (Keir et al, 2011)

Hypothesis: Regorafenib will inhibit tumor growth in PDX sarcoma models

Specific Aim: Determine the effect of Regorafenib on tumor growth in orthotopic PDX models

PD2 = when PD, but, additionally, time-to-event is > 200% of the Kaplan-Meier median time-to-event in control group (For ALL, %huCD45+ never drops < 1% of baseline level in PB for at least 2 consecutive weekly readings during the study period)

PD1 = when PD, but, additionally, time-to-event is > 200% of the Kaplan-Meier median time-to-event in control group (For ALL, %huCD45+ never drops < 1% of baseline level in PB for at least 3 consecutive weekly readings at any time after treatment has been completed).

The Kaplan-Meier method was used to compare time-to-event between treated and control groups. For comparing treatment groups, comparison between treatment groups used a p-value of 0.0167 for declaring significance to correct for the multiple comparisons made.

The objective response categories are as described by Houghton, et al. 2007.

PD = progressive disease, <50% tumor regression throughout study and >25% tumor growth at end of study

PD1 = when PD and the mouse’s time to event > 200% of the Kaplan-Meier median time-to-event in control group (For ALL, %huCD45+ never drops < 1% of baseline level in PB for at least 3 consecutive weekly readings during the study period)

SD = stable disease, <50% tumor regression throughout study and ≤25% tumor growth at end of study (For ALL, %huCD45+ in PB < 1% of baseline level in PB never reaches event during the study period)

PR = partial response, ≥50% tumor regression at any point during study but measurable tumor throughout study period (For ALL, %huCD45+ in PB < 1% once the study period)

CR = complete response, disappearance of measurable tumor mass during study period (For ALL, %huCD45+ in PB < 1% at least 3 consecutive weekly readings at any time after treatment has been completed)

CRN = maintained complete response, no measurable tumor mass for at least 3 consecutive weekly readings at any time after treatment has been completed (For ALL, %huCD45+ in PB < 1% at least 3 consecutive weekly readings at any time after treatment has been completed).

The in vivo antitumor effects of regorafenib were assessed in a panel of 6 osteosarcoma models (OS2, OS9, OS31, OS33, OS36, OS60), three rhabdomyosarcoma models (RH38, RH30, RH41), and one Ewing sarcoma model (EWS).

Solid tumor xenograft models were heterologously injected into the flanks of CB17SCID-scid/- female mice (Taconic Farms, Germantown, NY).

Regorafen solution (5 mg/ml) was administered by oral gavage at a dose of 30mg/kg for 21 days followed by 21 days of washout (EFS) compared to control in 100% (10/10) of sarcoma models tested (Figure 1).

Most models showed pronounced slowing of tumor growth compared to control during the 21 days of regorafenib treatment (Figure 2), with tumor growth generally approximating control rates soon after completion of regorafenib treatment (Figure 2).

Minimum relative tumor volumes ranged from 0.74 to 1.60, with no events were defined as 4-fold increase in tumor volume from treatment day 0.

Treated mice from models OS33, Rh30, and Rh41experienced an objective response of PD2 (“progressive disease 2”), and treated mice from OS-60-SJ model (EW5).

OS-9 was well tolerated in vivo, without significant toxicity in the sarcoma PDX models (% < 13.9% avg. weight loss). Across 120 tested mice, three experienced toxic death.

Regorafenib induced significant improvements in event-free survival (EFS) compared to control in 100% (10/10) of sarcoma models tested (Figure 1).

Regorafenib induced modest improvements in event-free survival (EFS) compared to control in 100% (10/10) of sarcoma models tested (Figure 1).

Regorafenib induced modest improvements in event-free survival (EFS) compared to control in 100% (10/10) of sarcoma models tested (Figure 1).

Regorafenib induced modest improvements in event-free survival (EFS) compared to control in 100% (10/10) of sarcoma models tested (Figure 1).

The preclinical activity of regorafenib in pediatric sarcoma models is its inability to combine with methotrexate, which is part of the standard upfront treatment of osteosarcoma.

The preclinical activity of regorafenib in pediatric sarcoma models agent in clinical trials of refractory pediatric sarcomas.

The overall pattern of response to the multi-kinase inhibitor regorafenib against the PPTC sarcoma models appears similar to that of the kinase inhibitor sorafenib, with the primary treatment effect being pronounced slowing of tumor growth in some models that is limited to the period of agent administration

The PPTC preclinical findings are consistent with those of the SARC024 randomized phase 2 clinical trial (Davis LE, et al. J Clin Oncol 2019) that found that regorafenib prolonged time to progression compared to placebo (3.6 months versus 2.7 months, respectively) in patients with progressive metastatic osteosarcoma. Objective responses were uncommon (13%) in patients receiving regorafenib.

A challenging issue in considering regorafenib for evaluation in newly diagnosed patients with osteosarcoma is its inability to combine with methotrexate, which is part of the standard upfront treatment of osteosarcoma.

The preclinical activity of regorafenib in pediatric sarcoma models the agent in clinical trials of refractory pediatric sarcomas.

The overall pattern of response to the multi-kinase inhibitor regorafenib against the PPTC sarcoma models appears similar to that of the kinase inhibitor sorafenib, with the primary treatment effect being pronounced slowing of tumor growth in some models that is limited to the period of agent administration

The PPTC preclinical findings are consistent with those of the SARC024 randomized phase 2 clinical trial (Davis LE, et al. J Clin Oncol 2019) that found that regorafenib prolonged time to progression compared to placebo (3.6 months versus 2.7 months, respectively) in patients with progressive metastatic osteosarcoma. Objective responses were uncommon (13%) in patients receiving regorafenib.

A challenging issue in considering regorafenib for evaluation in newly diagnosed patients with osteosarcoma is its inability to combine with methotrexate, which is part of the standard upfront treatment of osteosarcoma.

The preclinical activity of regorafenib in pediatric sarcoma models

The overall pattern of response to the multi-kinase inhibitor regorafenib against the PPTC sarcoma models appears similar to that of the kinase inhibitor sorafenib, with the primary treatment effect being pronounced slowing of tumor growth in some models that is limited to the period of agent administration

The PPTC preclinical findings are consistent with those of the SARC024 randomized phase 2 clinical trial (Davis LE, et al. J Clin Oncol 2019) that found that regorafenib prolonged time to progression compared to placebo (3.6 months versus 2.7 months, respectively) in patients with progressive metastatic osteosarcoma. Objective responses were uncommon (13%) in patients receiving regorafenib.

A challenging issue in considering regorafenib for evaluation in newly diagnosed patients with osteosarcoma is its inability to combine with methotrexate, which is part of the standard upfront treatment of osteosarcoma.

The preclinical activity of regorafenib in pediatric sarcoma models