Product Data Sheet

Product Name: Lerociclib (G1T38)
Cat. No.: GC34163

Chemical Properties

Cas. No.	1628256-23-4		
SMILES	O=C1NCC2(N3C1=CC4=CN=C(NC5=NC=C(N6CCN(C(C)C)CC6)C=C5)N=C43)CCCCC2		
Formula	$C_{26}H_{34}N_8O$	M.Wt	474.6
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	Lerociclib (G1T38)		

Protocol

Cell experiment:	SupT1, Daudi, MCF7, ZR-75-1, A2058, WM2664, and H69 cells are seeded at 1000 cells per well; MV-4-11 and BV173 cells are plated at 4000 cells per well; Tom-1 cells are plated at 8,000 cells per well; NALM-1 cells are plated at 20,000 cells per well in Costar 3903 96 well plates. After 24 hours, plates are dosed with Lerociclib (G1T38) at a nine-point dose concentration from 10 μM to 1 nM. Cell viability is determined after four or six days. Plates are processed on BioTek Synergy2 multi-mode plate reader and data analyzed using GraphPad Prism 5 statistical software[1].

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Animal experiment:

Mice[1]Female MMTV-NEU mice are used to test the efficacy of Lerocyclib (G1T38) (100 mpk, medicated diet). At time of treatment, body composition is assessed and weight measurements (in grams) are recorded and used as a measure of gross toxicity. Female nude mice are implanted with NSCLC PDX CTG0159 tumor. Mice are then randomized into treatment groups and dosing initiated once tumors reached a volume that fell within the range of 150-300 mm3. 100 mg/kg Lerociclib (G1T38) or vehicle is orally administered for 28 consecutive days. Female NCI Ath/nu mice are implanted with H1975 NSC lung adenocarcinoma model. Once tumors reach an average size of 100-150 mm3, mice are randomized into treatment cohorts. Mice are orally administered daily afatinib (20 mg/kg), erlotinib (70 mg/kg), or Lerociclib (50 or 100 mg/kg), as single agents or in combination (Lerociclib+erlotinib or Lerociclib+afatinib) for the duration of the study. All tumors are measured twice weekly until mice reach tumor burden of 1500 mm3.

References:

[1]. Bisi JE, et al. Preclinical development of G1T38: A novel, potent and selective inhibitor of cyclin dependent kinases 4/6 for use as an oral antineoplastic in patients with CDK4/6 sensitive tumors. Oncotarget. 2017 Jun 27;8(26):42343-42358.

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Background

G1T38 (Lerociclib) is a novel, potent, selective, and orally bioavailable CDK4/6 inhibitor with IC50 values of 0.001 μM, 0.002 μM and 0.028 μM for CDK4, CDK6 and CDK9 respectively.

G1T38 is highly potent and selective for CDK4/cyclin D1 and CDK6/cyclin D3 over CDK1, CDK2, CDK5 and CDK7 and their respective binding partners. In vitro, G1T38 decreases RB1 (RB) phosphorylation, causes a precise G1 arrest, and inhibits cell proliferation in a variety of CDK4/6-dependent tumorigenic cell lines including breast, melanoma, leukemia, and lymphoma cells with EC50 concentrations as low as 23 nM[1].

In vivo, G1T38 treatment leads to equivalent or improved tumor efficacy compared to the first-in-class CDK4/6 inhibitor, palbociclib, in an ER+ breast cancer xenograft model. Furthermore, G1T38 accumulates in mouse xenograft tumors but not plasma, resulting in less inhibition of mouse myeloid progenitors than after palbociclib treatment. In larger mammals, this difference in pharmacokinetics allows for 28 day continuous dosing of G1T38 in beagle dogs without producing severe neutropenia[1].

[1] John E. Bisi, et al. Oncotarget. 2017, 8(26): 42343-42358.

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