KDDF
Korea Drug Development Fund

Asset #33
NIH

Small Molecule Ephrin (Eph) Tyrosine Kinase Inhibitors for the Treatment of Colorectal Cancer and Other Eph Growth-dependent Solid Tumors

Therapeutic Area	Oncology	**Indications**	Solid Turmors
Modality	Small Molecule	**Development Stage**	Pre-clinical

Overview

Background

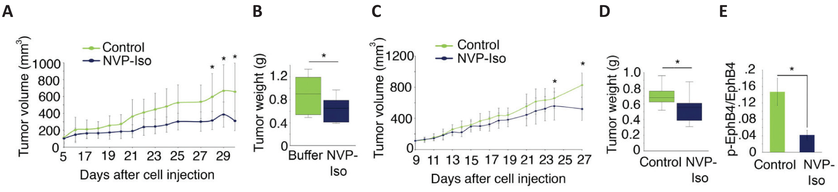
- Advanced colorectal carcinoma is currently incurable, and new therapies are urgently needed. Ephrin (Eph) receptors are a clinically relevant class of receptor tyrosine kinases. Related signaling pathways are associated with oncogenesis of a number of cancers. NCI investigators found that phosphotyrosine-dependent Eph receptor signaling sustains colorectal carcinoma cell survival, thereby uncovering a survival pathway active in colorectal carcinoma cells. Furthermore, colorectal cancers express the EphrinB2 ligand and its Eph receptors at significantly higher levels than numerous other cancer types. Colorectal cancer patients with the highest levels of EphrinB2 expression in their tumor have a lower probability of survival than those with the lowest levels.

Technology Advantages

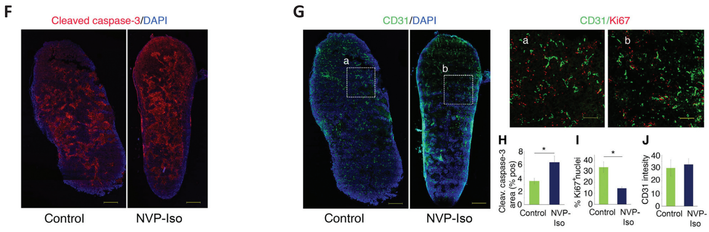
- Differs in targeting selectivity from many other tyrosine kinase inhibitors
- Distinct mechanism of action from Regorafenib, the only existing receptor tyrosine inhibitor approved to treat metastatic colorectal cancer; Regorafenib is a multi-targeted tyrosine kinase inhibitor developed to inhibit VEGF-dependent tumor angiogenesis
- Promising combination therapy when used with other tyrosine kinase inhibitors and antibodies – such as Cetuximab (approved for metastatic colorectal cancer)
- Overcome resistance to EGFR or BRAF treatment in various tumor types; attributed to EphA2 kinase activity

Key Data

EphB tyrosine kinase inhibition reduces colorectal carcinoma growth in mice



The Eph TKI NVP-Iso reduces colorectal cancer growth. (A–D) Colo 205 (A, B) or HT-29 (C, D) cells (10 x 106) were injected s.c. in nu/nu mice. When the average tumor volume reached 100 mm3 , mice (10/group) were randomized to receive daily i.p. injections of NVP-Iso (15 mgkg1) or vehicle only. Results show the average tumor volume (SD) as a function of time from tumor cell injection (A, C) and tumor weight after tumor harvest (B, D).
(E) HT-29 tumor extracts from control or NVP-Iso-treated mice (experiment in panel D) were tested for tyrosine-phosphorylated EphB4 and total EphB4 content. Results are expressed as the mean (SD) ratio of tyrosine-phosphorylated EphB4/total EphB4 (measured in pg from 50 lg tumor lysate; 10 drug-treated mice and 10 controls tested).



(F, G) Cleaved caspase-3 (red) (F); CD31 (green) and Ki67 (red) (G) immunostaining of representative HT29 tumor sections from control and NVP-Iso-treated mice; cell nuclei (DAPI+) are blue. Tumors were removed after completion of treatment (experiment in panel D). Boxed tumor areas (a and b) are magnified on the right of panel (G). Scale bars 1000 mm (F, G); 200 mm (magnified panels in G). (H–J) Quantitation of cleaved caspase-3+ (H), Ki67+ (I), and CD31+ (J) immunostaining in control (n = 5) and NVP-Iso-treated (n = 5) tumors (experiment shown in C, D). Results are expressed as: mean % (SD) cleaved caspase-3+ tumor area; mean % (SD) Ki67+ cell nuclei in tumor sections; and average (SD) CD31+ fluorescence intensity in tumor sections; *P < 0.05.

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-US2020-050439 (2020.09.11)

Patent Family
PCT, US, EP, CA

Publication(s)

- DiPrima, M. et al. (2019). Identification of Eph receptor signaling as a regulator of autophagy and a therapeutic target in colorectal carcinoma. Molecular Oncology, 13(11), 2441–2459.