TYPE Erratum
PUBLISHED 03 April 2023
DOI 10.3389/fphar.2023.1188062

Erratum: Drug resistance mechanism of kinase inhibitors in the treatment of hepatocellular carcinoma

Frontiers Production Office*

Frontiers Media SA, Lausanne, Switzerland

KEYWORDS

hepatocellular carcinoma, drug resistance, sorafenib, lenvatinib, regorafenib, cabozantinib

OPEN ACCESS

APPROVED BY
Frontiers Editorial Office,
Frontiers Media SA, Switzerland

*CORRESPONDENCE
Frontiers Production Office,
production.office@frontiersin.org

SPECIALTY SECTION
This article was submitted to Pharmacology of Anti-Cancer Drugs, a section of the journal Frontiers in Pharmacology

RECEIVED 16 March 2023
ACCEPTED 16 March 2023
PUBLISHED 03 April 2023

CITATION
Frontiers Production Office (2023), Erratum: Drug resistance mechanism of kinase inhibitors in the treatment of hepatocellular carcinoma.
Front. Pharmacol. 14:1188062.
doi: 10.3389/fphar.2023.1188062

An Erratum on
Drug resistance mechanism of kinase inhibitors in the treatment of hepatocellular carcinoma

by Jiang L, Li L, Liu Y, Lu L, Zhan M, Yuan S and Liu Y (2023). Front. Pharmacol. 14:1097277. doi: 10.3389/fphar.2023.1097277

Due to an error in the editorial process, an incorrect version of the article was published. Significant textual revisions to the published article are detailed below.

The previous version is available in the Supplementary Material of this Erratum. The article has now been updated with the correct version. The publisher apologizes for this error.

A correction has been made to the section "Primary Drug Resistance", subsection "Epidermal growth factor receptor (EGFR)". This section has been removed and its contents merged with the section entitled "Tumor heterogeneity and EGFR".

A correction has been made to the section "Acquired Drug Resistance", subsection "PI3K/AKT and MAPK/ERK signaling pathways". This section has been removed and replaced with the section entitled "EGFR and HGF/cMet mediated signaling pathway".

A spelling mistake was corrected in the keywords section of this article. "Carcinom" was corrected to "carcinoma".

Additional references have been added to the published article. Details of these references can be found in the "References" section of this article.

TABLE 1 Summary of previous studies with the mechanisms of receptor tyrosine kinase drug resistance in HCC.

Drug	Type of drug resistance	Mechanism of drug resistance	Reasons responsible	References
sorafenib	Primary drug resistance	Mutation of EGFR	Dysregulation of EGFR and HER-3	Hsieh et al. (2111)
		Enrichment of CSC	LSD1 and activation of β-catenin	Lei et al. (2015)
			EPHB2/TCF1/EPHB2/β-catenin	Leung et al. (2021)
	Acquired drug resistance	compensatory activation of the PI3K/Akt pathway	Activation of Akt	Chen et al. (2011)
		compensatory activation of the MAPK/ERK pathway	Production of HGF and phosphorylation of c-Met	Han et al. (2017)
		EMT	Ets- 1-GPX2	Gluck et al. (2019)
			TNF-α/NF-κB/EMT	Tan et al. (2019)
		Metabolic reprogramming	Activation of Rate limiting enzyme	Li et al. (2017)
			PI3K/Akt/HIF- 1α	Zhang et al. (2020)
			HDAC11/LKB1	Bi et al. (2021)
		Autophagy	The protective effect of autophagy	Lu et al. (2018), Tong et al. (2018), Lin et al. (2020b)
			The pro-death mechanism of autophagy	Neophytou et al. (2021)
		Non-coding RNAs	MicroRNAs and LncRNAs	Table 2
		Evasion of apoptosis	Deficiency of PUMA	Dudgeon et al. (2012)
			Highly expression of FGFR4	Repana and Ross (2015)
		Dysregulation of cell cycle control	E2F1-Rb-cyclin E1	Hsu et al. (2016)
Lenvatinib	Primary drug resistance	Activation of FGFR1/FGFR/VEGFR	High levels of FGFR1	Yamauchi et al. (2020)
		Enrichment of CSC	CD73-SOX9	Ma et al. (2020)
	Acquired drug resistance	High levels of EGFR	EGFR/PAK2/ERK5	Jin et al. (2021)
		Loss of NF1 and DUSP9	PI3K/AKT and MAPK/ERK	Lu et al. (2021)
		Non-coding RNAs	LncRNA MT1JP	Yu et al. (2021)
			LncRNA XIST	Duan et al. (2022)
			circMED27	Zhang et al. (2021)
regorafenib	Acquired drug resistance	EMT	Pin1/Gli1/Snail/E-cadhe rin	Wang et al. (2019)
		SphK2	NF-κB and activation of STAT3	Shi et al. (2020)
		Activation of TGF-β signaling	Wnt/β-catenin	Karabicici et al. (2021)
		TOP2A	Wnt/β-catenin	Wang et al. (2022)
cabozantinib	Primary drug resistance	Low levels of c-Met	C-Met	Gao et al. (2021)

TABLE 2 Previous studies that show the involvement of miRNAs in sorafenib resistance in HCC.

Name	Effects on sorafenib resistance	Target	Reference
miR-622	Inhibiting	KRAS	Dietrich et al. (2018)
miR-7	Inhibiting	TYRO3	Kabir et al. (2018)
miR-486-3p	Inhibiting	FGFR4/EGFR	Ji et al. (2020)
miR-138-1-3p	Inhibiting	PAK5	Li et al. (2021)
miR-122	Inhibiting	IGF-1R	Xu et al. (2016)
miR-378a-3p	Inhibiting	IGF-1R	Lin et al. (2020a)
miR-32-5p	Promoting	PTEN	Fu et al. (2018)
miR-21	Promoting	LncRNA SNHG1	Li et al. (2019)
miR-140-5p	Inhibiting	lncRNA MALAT1	Fan et al. (2020)

Tables 1, 2 have been added to the published article.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1188062/full#supplementary-material

References

Arai, H., Battaglin, F., Wang, J., Lo, J. H., Soni, S., Zhang, W., et al. (2019). Molecular insight of regorafenib treatment for colorectal cancer. *Cancer Treat. Rev.* 81, 101912. doi:10.1016/j.ctrv.2019.101912

Bi, L., Ren, Y., Feng, M., Meng, P., Wang, Q., Chen, W., et al. (2021). HDAC11 regulates glycolysis through the LKB1/AMPK signaling pathway to maintain hepatocellular carcinoma stemness. *Cancer Res.* 81 (8), 2015–2028. doi:10.1158/0008-5472.CAN-20-3044

Chen, K. F., Chen, H. L., Tai, W. T., Feng, W. C., Hsu, C. H., Chen, P. J., et al. (2011). Activation of phosphatidylinositol 3-kinase/Akt signaling pathway mediates acquired resistance to sorafenib in hepatocellular carcinoma cells. *J. Pharmacol. Ex. Ther.* 337 (1), 155–161. doi:10.1124/jpet.110.175786

Dagogo-Jack, I., and Shaw, A. T. (2018). Tumour heterogeneity and resistance to cancer therapies. *Nat. Rev. Clin. Oncol.* 15 (2), 81–94. doi:10.1038/nrclinonc.2017.166

Dietrich, P., Koch, A., Fritz, V., Hartmann, A., Bosserhoff, A. K., and Hellerbrand, C. (2018). Wild type Kirsten rat sarcoma is a novel microRNA-622-regulated therapeutic target for hepatocellular carcinoma and contributes to sorafenib resistance. *Gut* 67 (7), 1328–1341. doi:10.1136/gutjnl-2017-315402

Duan, A., Li, H., Yu, W., Zhang, Y., and Yin, L. (2022). Long noncoding RNA XIST promotes resistance to lenvatinib in hepatocellular carcinoma cells via epigenetic inhibition of NOD2. *J. Oncol.* 2022, 4537343. doi:10.1155/2022/4537343

Dudgeon, C., Peng, R., Wang, P., Sebastiani, A., Yu, J., and Zhang, L. (2012). Inhibiting oncogenic signaling by sorafenib activates PUMA via GSK3β and NF-κB to suppress tumor cell growth. *Oncogene* 31 (46), 4848–4858. doi:10.1038/onc.2011.644

Duffy, A. G., and Greten, T. F. (2017). Liver cancer: Regorafenib as second-line therapy in hepatocellular carcinoma. *Nat. Rev. Gastroenterol. Hepatol.* 14 (3), 141–142. doi:10.1038/nrgastro.2017.7

Fan, L., Huang, X., Chen, J., Zhang, K., Gu, Y. H., Sun, J., et al. (2020). Long noncoding RNAMALAT1 contributes to sorafenib resistance by targeting miR-140-5p/aurora-A signaling in hepatocellular carcinoma. *Mol. Cancer Ther.* 19 (5), 1197–1209. doi:10.1158/1535-7163.MCT-19-0203

Fu, X., Liu, M., Qu, S., Ma, J., Zhang, Y., Shi, T., et al. (2018). Exosomal microRNA-32-5p induces multidrug resistance in hepatocellular carcinoma via the PI3K/Akt pathway. *J. Exp. Clin. Cancer Res.* 37 (1), 52. doi:10.1186/s13046-018-0677-7

Gao, C., Wang, S., Shao, W., Zhang, Y., Lu, L., Jia, H., et al. (2021). Rapamycin enhances the anti-tumor activity of cabozantinib in cMet inhibitor-resistant hepatocellular carcinoma. *Front. Med.*

Gluck, C., Glathar, A., Tsompana, M., Nowak, N., Garrett-Sinha, L. A., Buck, M. J., et al. (2019). Molecular dissection of the oncogenic role of ETS1 in the mesenchymal subtypes of head and neck squamous cell carcinoma. *PLoS Genet.* 15, e1008250. doi:10.1371/journal.pgen.1008250

Han, P., Li, H., Jiang, X., Zhai, B., Tan, G., Zhao, D., et al. (2017). Dual inhibition of Akt and c-Met as a second-line therapy following acquired resistance to sorafenib in hepatocellular carcinoma cells. *Mol. Oncol.* 11 (3), 320–334. doi:10.1002/1878-0261.12039

Hsieh, S. Y., He, J. R., Hsu, C. Y., Chen, W. J., Bera, R., Lin, K. Y., et al. (2111). Neuregulin/erythroblastic leukemia viral oncogene homolog 3 autocrine loop contributes to invasion and early recurrence of human hepatoma. *Hepatology* 53 (2), 504–516. doi:10.1002/hep.24083

Hsu, C., Lin, L. I., Cheng, Y. C., Feng, Z. R., Shao, Y. Y., Cheng, A. L., et al. (2016). Cyclin E1 inhibition can overcome sorafenib resistance in hepatocellular carcinoma cells through mcl-1 suppression. *Clin. Cancer Res.* 22 (10), 2555–2564. doi:10.1158/1078-0432.CCR-15-0499

Huang, M., Chen, C., Geng, J., Han, D., Wang, T., Xie, T., et al. (2017). Targeting KDM1A attenuates Wnt/β-catenin signaling pathway to eliminate sorafenib-resistant stem-like cells in hepatocellular carcinoma. *Cancer Lett.* 398, 12–21. doi:10.1016/j.canlet.2017.03.038

Ippolito, M. R., Martis, V., Martin, S., Tijhuis, A. E., Hong, C., Wardenaar, R., et al. (2021). Gene copy-number changes and chromosomal instability induced by aneuploidy confer resistance to chemotherapy. *Dev. Cell* 56 (17), 2440–2454. doi:10.1016/j.devcel.2021.07.006

Ito, Y., Takeda, T., Sakon, M., Tsujimoto, M., Higashiyama, S., Noda, K., et al. (2001). Expression and clinical significance of erb-B receptor family in hepatocellular carcinoma. *Br. J. Cancer* 84 (10), 1377–1383. doi:10.1054/bjoc.2000.1580

Ji, L., Lin, Z., Wan, Z., Xia, S., Jiang, S., Cen, D., et al. (2020). miR-486-3p mediates hepatocellular carcinoma sorafenib resistance by targeting FGFR4 and EGFR. *Cell Death Dis.* 11 (4), 250. doi:10.1038/s41419-020-2413-4

Jin, H., Shi, Y., Lv, Y., Yuan, S., Ramirez, C. F. A., Lieftink, C., et al. (2021). EGFR activation limits the response of liver cancer to lenvatinib. *Nature* 595 (7869), 730–734. doi:10.1038/s41586-021-03741-7

Kabir, T. D., Ganda, C., Brown, R. M., Beveridge, D. J., Richardson, K. L., Chaturvedi, V., et al. (2018). A microRNA-7/growth arrest specific 6/TYRO3 axis regulates the growth and invasiveness of sorafenib-resistant cells in human hepatocellular carcinoma. *Hepatology* 67 (1), 216–231. doi:10.1002/hep.29478

Karabicici, M., Azbazdar, Y., Ozhan, G., Senturk, S., Firtina Karagonlar, Z., and Erdal, E. (2021). Changes in wnt and TGF-β signaling mediate the development of regorafenib resistance in hepatocellular carcinoma cell line HuH7. *Front. Cell Dev. Biol.* 9, 639779. doi:10.3389/fcell.2021.639779

Lei, Z. J., Wang, J., Xiao, H. L., Guo, Y., Wang, T., Li, Q., et al. (2015). Lysine-specific demethylase 1 promotes the stemness and chemoresistance of Lgr5 + liver cancer initiating cells by suppressing negative regulators of β-catenin signaling. *Oncogene* 34 (24), 3188–3198. doi:10.1038/onc.2015.182

Leung, H. W., Leung, C. O. N., Lau, E. Y., Chung, K. P. S., Mok, E. H., Lei, M. M. L., et al. (2021). EPHB2 activates β-catenin to enhance cancer stem cell properties and drive sorafenib resistance in hepatocellular carcinoma. *Cancer Res.* 81 (12), 3229–3240. doi:10.1158/0008-5472.CAN-21-0184

Li, S., Dai, W., Mo, W., Li, J., Feng, J., Wu, L., et al. (2017). By inhibiting PFKFB3, aspirin overcomes sorafenib resistance in hepatocellular carcinoma. *Int. J. Cancer* 141 (12), 2571–2584. doi:10.1002/ijc.31022

Li, W., Dong, X., He, C., Tan, G., Li, Z., Zhai, B., et al. (2019). LncRNA SNHG1 contributes to sorafenib resistance by activating the Akt pathway and is positively regulated by miR-21 in hepatocellular carcinoma cells. *J. Exp. Clin. Cancer Res.* 38 (1), 183. doi:10.1186/s13046-019-1177-0

Li, T. T., Mou, J., Pan, Y. J., Huo, F. C., Du, W. Q., Liang, J., et al. (2021). MicroRNA-138-1-3p sensitizes sorafenib to hepatocellular carcinoma by targeting PAK5 mediated β-catenin/ABCB1 signaling pathway. *J. Biomed. Sci.* 28 (1), 56. doi:10.1186/s12929-021-00752-4

Lin, Z., Xia, S., Liang, Y., Ji, L., Pan, Y., Jiang, S., et al. (2020a). LXR activation potentiates sorafenib sensitivity in HCC by activating microRNA-378a transcription. *Theranostics* 10 (19), 8834–8850. doi:10.7150/thno.45158

Lin, Z., Niu, Y., Wan, A., Chen, D., Liang, H., Chen, X., et al. (2020b). RNA m6 A methylation regulates sorafenib resistance in liver cancer through FOXO3-mediated autophagy. *EMBO J.* 39 (12), e103181. doi:10.15252/embj.2019103181

Lu, S., Yao, Y., Xu, G., Zhou, C., Zhang, Y., Sun, J., et al. (2018). CD24 regulates sorafenib resistance via activating autophagy in hepatocellular carcinoma. *Cell Death Dis.* 9 (6), 646. doi:10.1038/s41419-018-0681-z

Lu, Y., Shen, H., Huang, W., He, S., Chen, J., Zhang, D., et al. (2021). Genome-scale CRISPR-Cas9 knockout screening in hepatocellular carcinoma with lenvatinib resistance. *Cell Death Discov.* 7 (1), 359. doi:10.1038/s41420-021-00747-y

Ma, X. L., Hu, B., Tang, W. G., Xie, S. H., Ren, N., Guo, L., et al. (2020). CD73 sustained cancer-stem-cell traits by promoting SOX9 expression and stability in hepatocellular carcinoma. *J. Hematol. Oncol.* 13 (1), 11. doi:10.1186/s13045-020-0845-z

McGranahan, N., and Swanton, C. (2017). Clonal heterogeneity and tumor evolution: Past, present, and the future. *Cell* 168 (4), 613–628. doi:10.1016/j.cell.2017.01.018

Negrini, S., Gorgoulis, V. G., and Halazonetis, T. D. (2010a). Genomic instability-an evolving hallmark of cancer. *Nat. Rev. Mol. Cell Biol.* 11 (3), 220–228. doi:10.1038/nrm2858

Negrini, S., Gorgoulis, V. G., and Halazonetis, T. D. (2010b). Clonal heterogeneity and tumor evolution: Past, present, and the future. *Nat. Rev. Mol. Cell Biol.* 11 (3), 220–228. doi:10.1038/nrm2858.14.McGranahan

Neophytou, C. M., Trougakos, I. P., Erin, N., and Papageorgis, P. (2021). Apoptosis deregulation and the development of cancer multi-drug resistance. *Cancers (Basel)* 13 (17), 4363. doi:10.3390/cancers13174363

O'Connor, R., Clynes, M., Dowling, P., O'Donovan, N., and O'Driscoll, L. (2007). Drug resistance in cancer - searching for mechanisms, markers and therapeutic agents. *Expert Opin. Drug Metab. Toxicol.* 3 (6), 805–817. doi:10.1517/17425255.3.6.805

Pan, J., Zhang, M., Dong, L., Ji, S., Zhang, J., Zhang, S., et al. (2022). Genome-Scale CRISPR screen identifies LAPTM5 driving lenvatinib resistance in hepatocellular carcinoma. *Autophagy* 7, 1–15. doi:10.1080/15548627.2022.2117893

Repana, D., and Ross, P. (2015). Targeting FGF19/FGFR4 pathway: A novel therapeutic strategy for hepatocellular carcinoma. *Diseases* 3 (4), 294–305. doi:10.3390/diseases3040294

Shi, W., Zhang, S., Ma, D., Yan, D., Zhang, G., Cao, Y., et al. (2020). Targeting SphK2 reverses acquired resistance of regorafenib in hepatocellular carcinoma. *Front. Oncol.* 10, 694. doi:10.3389/fonc.2020.00694

Tan, W., Luo, X., Li, W., Zhong, J., Cao, J., Zhu, S., et al. (2019). TNF-α is a potential therapeutic target to overcome sorafenib resistance in hepatocellular carcinoma. *EBioMedicine* 40, 446–456. doi:10.1016/j.ebiom.2018.12.047

Tong, M., Che, N., Zhou, L., Luk, S. T., Kau, P. W., Chai, S., et al. (2018). Efficacy of annexin A3 blockade in sensitizing hepatocellular carcinoma to sorafenib and regorafenib. *J. Hepatol.* 69 (4), 826–839. doi:10.1016/j.jhep.2018.05.034

Vasan, N., Baselga, J., and Hyman, D. M. (2019). A view on drug resistance in cancer. *Nature* 575 (7782), 299–309. doi:10.1038/s41586-019-1730-1

Vishnoi, K., Ke, R., Viswakarma, N., Srivastava, P., Kumar, S., Das, S., et al. (2022). Ets1 mediates sorafenib resistance by regulating mitochondrial ROS pathway in hepatocellular carcinoma. *Cell Death Dis.* 13 (7), 581. doi:10.1038/s41419-022-05022-1

Wang, J., Zhang, N., Han, Q., Lu, W., Wang, L., Yang, D., et al. (2019). Pin1 inhibition reverses the acquired resistance of human hepatocellular carcinoma cells to Regorafenib via the Gli1/Snail/E-cadherin pathway. *Cancer Lett.* 444, 82–93. doi:10.1016/j.canlet.2018.12.010

Wang, Z., Zhu, Q., Li, X., Ren, X., Li, J., Zhang, Y., et al. (2022). TOP2A inhibition reverses drug resistance of hepatocellular carcinoma to regorafenib. *Am. J. Cancer Res.* 12 (9), 4343–4360.

Xu, Y., Huang, J., Ma, L., Shan, J., Shen, J., Yang, Z., et al. (2016). MicroRNA-122 confers sorafenib resistance to hepatocellular carcinoma cells by targeting IGF-1R to regulate RAS/RAF/ERK signaling pathways. *Cancer Lett.* 371 (2), 171–181. doi:10.1016/j.canlet.2015.11.034

Yamauchi, M., Ono, A., Ishikawa, A., Kodama, K., Uchikawa, S., Hatooka, H., et al. (2020). Tumor fibroblast growth factor receptor 4 level predicts the efficacy of lenvatinib in patients with advanced hepatocellular carcinoma. *Clin. Transl. Gastroenterol.* 11 (5), e00179. doi:10.14309/ctg.0000000000000179

Yu, T., Yu, J., Lu, L., Zhang, Y., Zhou, Y., Zhou, Y., et al. (2021). MT1JP-mediated miR-24-3p/BCL2L2 axis promotes Lenvatinib resistance in hepatocellular carcinoma cells by inhibiting apoptosis. *Cell Oncol. (Dordr).* 44 (4), 821–834. doi:10.1007/s13402-021-00605-0

Zhang, X., Wu, L., Xu, Y., Yu, H., Chen, Y., Zhao, H., et al. (2020). Microbiota-derived SSL6 enhances the sensitivity of hepatocellular carcinoma to sorafenib by down-regulating glycolysis. *Cancer Lett.* 481, 32–44. doi:10.1016/j.canlet.2020.03.027

Zhang, P., Sun, H., Wen, P., Wang, Y., Cui, Y., and Wu, J. (2021). circRNA circMED27 acts as a prognostic factor and mediator to promote lenvatinib resistance of hepatocellular carcinoma. *Mol. Ther. Nucleic Acids* 27, 293–303. doi:10.1016/j.omtn.2021.12.001