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文献综述 REVIEW

Linifanib治疗肝癌的临床研究进展

胡凤蓉, 高 帆, 祁兴顺

背景资料
Linifanib已在不同部位的肿瘤患者中进行临床试验评估, 包括急性髓细胞样白血病、肾癌、肺癌等. 本文回顾有关linifanib治疗肝癌的临床试验结果.

胡凤蓉, 西安市第二医院消化内科 陕西省西安市 710003
高帆, 中国人民解放军第202医院医务处 辽宁省沈阳市 110003
祁兴顺, 中国人民解放军沈阳军区总医院消化内科 辽宁省沈阳市 110840
胡凤蓉, 主治医师, 主要从事消化系统疾病诊断与治疗的研究.
作者贡献分布: 此课题为胡凤蓉、高帆及祁兴顺共同设计; 胡凤蓉与祁兴顺收集文献; 论文写作由胡凤蓉与祁兴顺共同完成.
通讯作者: 祁兴顺, 主治医师, 医学博士, 110840, 辽宁省沈阳市文化路83号, 中国人民解放军沈阳军区总医院消化内科.
xingshunqi@126.com
电话: 024-28851113
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Linifanib for treatment of hepatocellular carcinoma: An overview of clinical trials

Feng-Rong Hu, Fan Gao, Xing-Shun Qi

Feng-Rong Hu, Department of Digestive Diseases, the 2nd Hospital of Xi'an, Xi'an 710003, Shaanxi Province, China
Fan Gao, Medical Department, the 202nd Hospital of Chinese PLA, Shenyang 110003, Liaoning Province, China
Xing-Shun Qi, Department of Gastroenterology, General Hospital of Shenyang Military Area, Shenyang 110840, Liaoning Province, China
Correspondence to: Xing-Shun Qi, Attending Physician, Department of Gastroenterology, General Hospital of Shenyang Military Area, 83 Wenhua Road, Shenyang 110840, Liaoning Province, China. xingshunqi@126.com
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Abstract
Linifanib achieves the antitumor activity by inhibiting all vascular endothelial growth factor receptors and platelet-derived growth factor receptors. We aim to review the findings of clinical trials of linifanib for the treatment of hepatocellular carcinoma (HCC). Several phase I clinical trials have confirmed the safety of linifanib in patients with solid malignancy. One phase II clinical trial has shown the clinical efficacy of linifanib alone for the treatment of HCC. Recently, a phase III randomized controlled trial showed that, compared with sorafenib, linifanib cannot significantly improve the overall survival of HCC patients. Thus, linifanib is not recommended as the first-line therapy for advanced HCC. However, because linifanib could significantly prolong the time-to-progression and progression-free survival time and increase the objective response rate, future studies might be necessary to explore the clinical utility of linifanib as a second-line therapy for advanced HCC.

Key Words: Linifanib; Sorafenib; Hepatocellular carcinoma; Clinical trial; Review

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摘要
Linifanib可以抑制所有血管内皮生长因子受体和血小板生长因子受体, 以发挥抗肿瘤活性. 本文旨在回顾linifanib治疗肝癌的临床试验结果. 多项Ⅰ期临床试验已证实了linifanib在实体肿瘤患者中的安全性. 一项Ⅱ期临床试验发现linifanib单药治疗肝癌具

同行评议者
芙卫东, 教授, 安徽省立院肝脏外科

有较好的临床疗效. 一项III期随机对照试验中, linifanib较索拉非尼并未能显著改善肝癌患者的总体生存. 因此, linifanib尚不能推荐作为晚期肝癌的一线治疗手段. 然而, 考虑到linifanib较索拉非尼可以显著延缓肿瘤进展、延长无肿瘤进展生存时间、提高客观肿瘤应答率, 未来研究也许应该探索linifanib作为晚期肝癌的二线治疗手段的临床价值.

关键词: Linifanib; 索拉菲尼; 肝癌; 临床试验; 综述

核心提示: Linifanib可以有效地延缓晚期肝癌的肿瘤进展、延长无肿瘤进展生存时间、提高客观肿瘤应答率, 但并未显著改善总体生存.

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0 引言

目前, 索拉菲尼是唯一被美国食品药品管理局(Food and Drug Administration, FDA)批准用于治疗晚期肝癌(本文涉及肝癌均指肝细胞癌)的药物[1-10]. 尽管多项随机对照试验已经尝试探讨其他分子靶向药物作为晚期肝癌的一线、二线或辅助治疗手段的疗效, 但研究结果均不理想[11-24]. Linifanib, 又称为ABT-869, 是由美国Abbott公司研发的一种三磷酸腺苷竞争性酪氨酸激酶抑制剂, 其可以选择性抑制所有血管内皮生长因子受体(vascular endothelial growth factor receptor, VEGFR)和血小板生长因子受体(platelet-derived growth factor receptor, PDGFR)家族酪氨酸激酶活性, 以达到抗肿瘤活性[25-36]. 目前, linifanib已在不同部位的肿瘤患者中进行临床试验评估, 包括急性髓细胞样白血病、肾癌、肺癌等[35,37-44]. 我们在此着重回顾有关linifanib治疗肝癌的临床试验结果, 并综合这些研究结果以展望linifanib在肝癌患者未来的应用前景.

1 Ⅰ期试验

Wong等[45]完成了首项Ⅰ期临床试验以评估linifanib在实体肿瘤患者中的安全性及耐受性. 33例患者参加研究并接受linifanib. 肿瘤部位包括非小细胞肺癌(n = 8)、结直肠癌(n = 7)、肝癌(n = 4)、卵巢癌(n = 3)、乳腺癌(n = 2)、神经内分泌瘤(n = 2)、子宫内膜肉瘤(n = 2)、脐尿管癌(n = 1)、软组织肉瘤(n = 1)、肾癌(n = 1)、鼻咽癌(n = 1)、原始神经外胚层肿瘤(n = 1). 药物剂量包括10 mg/d, 0.1, 0.25, 0.3 mg/(kg•d). 服药21 d内, 剂量限制性毒性包括10 mg/d组中1例患者发生3级疲劳; 0.25 mg/(kg•d)组中1例患者发生3级蛋白尿, 1例患者发生3级高血压; 0.3 mg/(kg•d)组中1例患者发生3级蛋白尿, 1例患者发生3级高血压. 2例肺癌患者和1例结肠癌患者达到了肿瘤部分应答. 16例患者维持肿瘤稳定超过3个治疗周期. 另外, 在linifanib治疗的第15天时, 内皮细胞数量显著降低(P = 0.007), 血管内皮生长因子显著升高(P = 0.004).

Asahina等[46]进行了一项开放、剂量递增、Ⅰ期临床试验以观察linifanib在日本实体肿瘤患者中的药物代谢动力学、安全性以及耐受性. 2008-09/2009-09 18例患者参加研究并接受linifanib治疗. 肿瘤部位包括肺癌(n = 8)、肉瘤(n = 5)、乳腺癌(n = 3)、胸腺肿瘤(n = 1)、结肠肿瘤(n = 1). 药物剂量包括0.05 mg/kg(n = 3)、0.10 mg/kg(n = 6)、0.20 mg/kg(n = 3)以及0.25 mg/kg(n = 6). 常见的药物不良反应包括高血压、谷草转氨酶升高、皮疹、中性粒细胞减少、甘油三酯升高. 在0.05 mg/kg组中, 无任何患者发生3级不良反应; 在0.10 mg/kg组中, 3例患者发生3级不良反应; 在0.20 mg/kg组中, 2例患者发生3级不良反应; 在0.25 mg/kg组中, 4例患者发生3级不良反应. 常见的3级药物不良反应包括蛋白尿(n = 4)、中性粒细胞减少(n = 2)、谷丙转氨酶升高(n = 2). 在所有剂量组中, 无任何患者发生4级不良反应. 2例患者达到部分肿瘤应答, 12例患者维持肿瘤稳定, 另有4例患者因缺乏相关数据而未能评估肿瘤进展/改善情况.

Chiu等[47]完成的一项开放、随机、Ⅰ期临床试验也探讨了linifanib在晚期实体肿瘤患者中对心脏去极化的影响. 在最大耐受剂量(0.25 mg/kg)的情况下, linifanib并未显著延长QT间期. 这一发现说明linifanib并未影响心脏去极化.

2 Ⅱ期试验

Toh等[48]进行了一项单臂、多中心、Ⅱ期临

研发前沿

分子靶向治疗是目前晚期肝细胞癌的治疗的热点, 尽管索拉非尼开辟了晚期肝细胞癌治疗的新纪元, 但疗效依然有限. Linifanib较索拉非尼可以显著延缓肿瘤进展、延长无肿瘤进展生存时间、提高客观肿瘤应答率, 今后可探讨linifanib作为晚期肝癌二线治疗手段的临床价值.

应用要点

Ⅰ期及Ⅱ期临床试验初步证实了linifanib的安全性和有效性, 未来研究也许应该尝试探讨在索拉菲尼无效的情况下linifanib的疗效.

床试验以明确linifanib治疗不可切除或已发生转移的肝癌的疗效及安全性. 2007-09/2008-08研究者在6所医院招募了44例受试者. 给药剂量根据肝功能情况而不同. 对于Child-Pugh A和B级患者, linifanib剂量分别为每日0.25 mg/kg和每隔1 d 0.25 mg/kg. 82%的患者为男性; 89%为亚洲人; 61%伴有乙型肝炎; 86%为Child-Pugh A级; 52%为美国东部肿瘤协作组(Eastern Cooperative Oncology Group, ECOG)评分0分, 39%为ECOG评分1分; 82%从未接受过全身治疗. 31.8%的患者达到主要观察终点, 即16 wk内无肿瘤进展生存. 中位肿瘤进展时间为3.7 mo(95%CI: 1.9-5.5 mo), 中位总体生存时间为9.7 mo(95%CI: 6.0-12.2 mo), 客观肿瘤应答率为9.1%. 常见的3-4级药物不良反应包括高血压(25.0%)和疲劳(13.6%). 1例患者因脑出血死亡, 这也许与linifanib有关. 这项研究提示linifanib治疗肝癌较好的临床有效性以及可靠的药物安全性.

3 III期试验

Cainap等[49]完成的一项全球多中心、随机、开放、III期临床试验比较了linifanib与索拉菲尼治疗晚期肝癌的有效性及安全性. 主要研究终点是总体生存, 次要研究终点包括肿瘤进展时间以及肿瘤客观应答率. 根据预先的研究设计, 研究者首先采用非劣效性检验比较linifanib与索拉菲尼的疗效, 预计总体生存终点的风险比上限需<1.0491; 此后, 研究者将进一步采用优效性检验比较组间差异. 研究者在28个国家的186所医院中招募了1035例受试者. 其中, 514例受试者随机分配到linifanib(17.5 mg/d)组, 519例分配到索拉菲尼(400 mg, *bid*)组. 84.6%的患者为男性; 66.6%为亚洲人; 53.2%伴有乙型肝炎; 94.4%为Child-Pugh A级; 64.4%为ECOG评分0分; 82.3%为BCLC C期. Linifanib与索拉菲尼组, 中位总体生存时间分别为9.1 mo(95%CI: 8.1-10.2 mo)以及9.8 mo(95%CI: 8.3-11.0 mo), 组间差异并无统计学意义(风险比 = 1.046, 95%CI: 0.896-1.221); 中位肿瘤进展时间分别为5.4 mo(95% CI: 4.2-5.6 mo)以及4.0 mo(95% CI: 2.8-4.2 mo), 组间差异有统计学意义; 无肿瘤进展生存时间分别为4.2 mo(95%CI: 4.1-5.4 mo)以及2.9 mo(95%CI: 2.8-4.0 mo), 组间差异有统计学意义; 客观肿瘤应答率分别为10.1%以及6.1%, 组间差异有统计学意义. 另外, linifanib组的严重不良反应发病率均较索拉菲尼组显著更高(52.4% *vs* 38.5%, $P<0.001$). 这也许间接反映了linifanib较索拉菲尼对肝癌更加敏感. Linifanib组比索拉菲尼组更频繁出现的3-4级不良反应包括高血压(20.8% *vs* 10.6%)、疲劳(9.6% *vs* 4.8%)、肝性脑病(7.3% *vs* 3.3%)、乏力(7.1% *vs* 2.1%)、腹水(6.1% *vs* 3.3%)、血小板减少(5.3% *vs* 2.1%)、低血钾(4.7% *vs* 2.3%)、呕吐(4.3% *vs* 0.8%)、低钙(3.1% *vs* 0.8%). 索拉菲尼组比linifanib组更频繁出现的3-4级不良反应为谷丙转氨酶升高(4.8% *vs* 2.2%). 总体上, 这项头对头比较linifanib与索拉菲尼的随机对照试验发现, linifanib较索拉菲尼可以显著延缓肿瘤进展、延长无肿瘤进展生存时间、提高客观肿瘤应答率, 但并未显著改善总体生存. 考虑研究并未满足主要观察终点, 我们仍无法推荐linifanib作为晚期肝癌的一线治疗手段.

4 结论

虽然Ⅰ期及Ⅱ期临床试验初步证实了linifanib的安全性和有效性, 但大规模随机对照试验无法证实linifanib作为晚期肝癌的一线治疗手段的生存优势. 此外, 尚无研究探讨linifanib作为晚期肝癌二线治疗手段的临床价值. 考虑到linifanib也许对肝癌患者更加敏感, 未来研究也许应该尝试探讨在索拉菲尼无效的情况下linifanib的疗效.

5 参考文献

1 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

2 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

3 Abdel-Rahman O, Fouad M. Sorafenib-based combination as a first line treatment for advanced hepatocellular carcinoma: a systematic review of

the literature. *Crit Rev Oncol Hematol* 2014; 91: 1-8 [PMID: 24457121 DOI: 10.1016/j.critrevonc.2013.12.013]
4 Zhang X, Yang XR, Huang XW, Wang WM, Shi RY, Xu Y, Wang Z, Qiu SJ, Fan J, Zhou J. Sorafenib in treatment of patients with advanced hepatocellular carcinoma: a systematic review. *Hepatobiliary Pancreat Dis Int* 2012; 11: 458-466 [PMID: 23060390 DOI: 10.1016/S1499-3872(12)60209-4]
5 Xie B, Wang DH, Spechler SJ. Sorafenib for treatment of hepatocellular carcinoma: a systematic review. *Dig Dis Sci* 2012; 57: 1122-1129 [PMID: 22451120 DOI: 10.1007/s10620-012-2136-1]
6 Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, Cammà C, Colombo M. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. *Hepatology* 2011; 54: 2055-2063 [PMID: 21898496 DOI: 10.1002/hep.24644]
7 Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; 57: 821-829 [PMID: 22727733 DOI: 10.1016/j.jhep.2012.06.014]
8 Wörns MA, Weinmann A, Pfingst K, Schulte-Sasse C, Messow CM, Schulze-Bergkamen H, Teufel A, Schuchmann M, Kanzler S, Düber C, Otto G, Galle PR. Safety and efficacy of sorafenib in patients with advanced hepatocellular carcinoma in consideration of concomitant stage of liver cirrhosis. *J Clin Gastroenterol* 2009; 43: 489-495 [PMID: 19247201 DOI: 10.1097/MCG.0b013e31818ddfc6]
9 Galle PR. Sorafenib in advanced hepatocellular carcinoma - We have won a battle not the war. *J Hepatol* 2008; 49: 871-873 [PMID: 18817997 DOI: 10.1016/j.jhep.2008.09.001]
10 Roberts LR. Sorafenib in liver cancer--just the beginning. *N Engl J Med* 2008; 359: 420-422 [PMID: 18650519 DOI: 10.1056/NEJMe0802241]
11 Villanueva A. Rethinking future development of molecular therapies in hepatocellular carcinoma: a bottom-up approach. *J Hepatol* 2013; 59: 392-395 [PMID: 23548196 DOI: 10.1016/j.jhep.2013.03.025]
12 祁兴顺, 贾佳, 韩国宏, 樊代明. 舒尼替尼治疗肝细胞癌的临床研究现状. 胃肠病学 2014; 19: 169-172
13 祁兴顺, 贾佳, 刘雷, 陈辉, 樊代明, 韩国宏. Regorafenib治疗肝癌的临床研究进展. 临床肝胆病杂志 2014; 30: 225-227
14 祁兴顺, 杨曼, 白苇, 任维榕, 樊代明, 韩国宏. Brivanib治疗肝癌的临床研究进展. 临床肝胆病杂志 2014; 30: 222-224
15 Shin JW, Chung YH. Molecular targeted therapy for hepatocellular carcinoma: current and future. *World J Gastroenterol* 2013; 19: 6144-6155 [PMID: 24115810 DOI: 10.3748/wjg.v19.i37.6144]
16 Villanueva A, Llovet JM. Targeted therapies for hepatocellular carcinoma. *Gastroenterology* 2011; 140: 1410-1426 [PMID: 21406195 DOI: 10.1053/j.gastro.2011.03.006]
17 Qi X, Jia J, Fan D, Han G. Brivanib for hepatocellular carcinoma trials: selection bias from barcelona clinic liver cancer stage? *J Clin Oncol* 2014; 32: 968 [PMID: 24516020 DOI: 10.1200/JCO.2013.53.8199]
18 Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013; 31: 3509-3516 [PMID: 23980090 DOI: 10.1200/JCO.2012.47.3009]
19 Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Aviña J, Kudo M, Yan L, Sobhonslidsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine R, Walters I, Cheng AL. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; 31: 3517-3524 [PMID: 23980084 DOI: 10.1200/JCO.2012.48.4410]
20 Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. *Clin Cancer Res* 2014; 20: 2072-2079 [PMID: 24589894 DOI: 10.1158/1078-0432.CCR-13-0547]
21 Finn RS. Emerging targeted strategies in advanced hepatocellular carcinoma. *Semin Liver Dis* 2013; 33 Suppl 1: S11-S19 [PMID: 23457035 DOI: 10.1055/s-0033-1333632]
22 Lord R, Suddle A, Ross PJ. Emerging strategies in the treatment of advanced hepatocellular carcinoma: the role of targeted therapies. *Int J Clin Pract* 2011; 65: 182-188 [PMID: 21235699 DOI: 10.1111/j.1742-1241.2010.02545.x]
23 Zhu AX. New agents on the horizon in hepatocellular carcinoma. *Ther Adv Med Oncol* 2013; 5: 41-50 [PMID: 23323146 DOI: 10.1177/1758834012458480]
24 Linifanib. *Drugs R D* 2010; 10: 111-122 [PMID: 20698720 DOI: 10.2165/11584520-000000000-00000]
25 Zhou J, Goh BC, Albert DH, Chen CS. ABT-869, a promising multi-targeted tyrosine kinase inhibitor: from bench to bedside. *J Hematol Oncol* 2009; 2: 33 [PMID: 19642998 DOI: 10.1186/1756-8722-2-33]
26 Marlow M, Al-Ameedee M, Smith T, Wheeler S, Stocks MJ. Linifanib--a multi-targeted receptor tyrosine kinase inhibitor and a low molecular weight gelator. *Chem Commun* (Camb) 2015; 51: 6384-6387 [PMID: 25761611 DOI: 10.1039/C5CC00454C]
27 Iqbal M, Ezzeldin E, Wani TA, Khalil NY. Simple, sensitive and rapid determination of linifanib (ABT-869), a novel tyrosine kinase inhibitor in rat plasma by UHPLC-MS/MS. *Chem Cent J* 2014; 8: 13 [PMID: 24533632 DOI: 10.1186/1752-153X-8-13]
28 Pan H, Wang Z, Jiang L, Sui X, You L, Shou J, Jing Z, Xie J, Ge W, Cai X, Huang W, Han W. Autophagy inhibition sensitizes hepatocellular carcinoma to the multikinase inhibitor linifanib. *Sci Rep* 2014; 4: 6683 [PMID: 25327881 DOI: 10.1038/srep06683]
29 Jiang F, Albert DH, Luo Y, Tapang P, Zhang K,

名词解释

Linifanib: 又称为ABT-869, 是由美国Abbott公司研发的一种三磷酸腺苷竞争性酪氨酸激酶抑制剂, 其可以选择性抑制所有血管内皮生长因子受体(vascular endothelial growth factor receptor, VEGFR)和血小板生长因子受体(platelet-derived growth factor receptor, PDGFR)家族酪氨酸激酶活性, 以达到抗肿瘤活性.

同行评价

本文从安全性和有效性等方面综述了linifanib治疗肝细胞癌的Ⅰ期、Ⅱ期和Ⅲ期临床研究进展, 作者提出linifanib未来在肝细胞癌研究的可能方向. 帮助临床医生了解linifanib在晚期肝细胞癌治疗中的可能价值.

Davidsen SK, Fox GB, Lesniewski R, McKeegan EM. ABT-869, a multitargeted receptor tyrosine kinase inhibitor, reduces tumor microvascularity and improves vascular wall integrity in preclinical tumor models. *J Pharmacol Exp Ther* 2011; 338: 134-142 [PMID: 21505059 DOI: 10.1124/jpet.110.178061]

30 Luo Y, Jiang F, Cole TB, Hradil VP, Reuter D, Chakravartty A, Albert DH, Davidsen SK, Cox BF, McKeegan EM, Fox GB. A novel multi-targeted tyrosine kinase inhibitor, linifanib (ABT-869), produces functional and structural changes in tumor vasculature in an orthotopic rat glioma model. *Cancer Chemother Pharmacol* 2012; 69: 911-921 [PMID: 22080168 DOI: 10.1007/s00280-011-1740-7]

31 Ikeda AK, Judelson DR, Federman N, Glaser KB, Landaw EM, Denny CT, Sakamoto KM. ABT-869 inhibits the proliferation of Ewing Sarcoma cells and suppresses platelet-derived growth factor receptor beta and c-KIT signaling pathways. *Mol Cancer Ther* 2010; 9: 653-660 [PMID: 20197394 DOI: 10.1158/1535-7163.MCT-09-0812]

32 Jasinghe VJ, Xie Z, Zhou J, Khng J, Poon LF, Senthilnathan P, Glaser KB, Albert DH, Davidsen SK, Chen CS. ABT-869, a multi-targeted tyrosine kinase inhibitor, in combination with rapamycin is effective for subcutaneous hepatocellular carcinoma xenograft. *J Hepatol* 2008; 49: 985-997 [PMID: 18930332 DOI: 10.1016/j.jhep.2008.08.010]

33 Zhou J, Khng J, Jasinghe VJ, Bi C, Neo CH, Pan M, Poon LF, Xie Z, Yu H, Yeoh AE, Lu Y, Glaser KB, Albert DH, Davidsen SK, Chen CS. In vivo activity of ABT-869, a multi-target kinase inhibitor, against acute myeloid leukemia with wild-type FLT3 receptor. *Leuk Res* 2008; 32: 1091-1100 [PMID: 18160102 DOI: 10.1016/j.leukres.2007.11.025]

34 Dai Y, Hartandi K, Ji Z, Ahmed AA, Albert DH, Bauch JL, Bouska JJ, Bousquet PF, Cunha GA, Glaser KB, Harris CM, Hickman D, Guo J, Li J, Marcotte PA, Marsh KC, Moskey MD, Martin RL, Olson AM, Osterling DJ, Pease LJ, Soni NB, Stewart KD, Stoll VS, Tapang P, Reuter DR, Davidsen SK, Michaelides MR. Discovery of N-(4-(3-amino-1H-indazol-4-yl)phenyl)-N'-(2-fluoro-5-methylphenyl)urea (ABT-869), a 3-aminoindazole-based orally active multitargeted receptor tyrosine kinase inhibitor. *J Med Chem* 2007; 50: 1584-1597 [PMID: 17343372 DOI: 10.1021/jm061280h]

35 Albert DH, Tapang P, Magoc TJ, Pease LJ, Reuter DR, Wei RQ, Li J, Guo J, Bousquet PF, Ghoreishi-Haack NS, Wang B, Bukofzer GT, Wang YC, Stavropoulos JA, Hartandi K, Niquette AL, Soni N, Johnson EF, McCall JO, Bouska JJ, Luo Y, Donawho CK, Dai Y, Marcotte PA, Glaser KB, Michaelides MR, Davidsen SK. Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. *Mol Cancer Ther* 2006; 5: 995-1006 [PMID: 16648571 DOI: 10.1158/1535-7163.MCT-05-0410]

36 Guo J, Marcotte PA, McCall JO, Dai Y, Pease LJ, Michaelides MR, Davidsen SK, Glaser KB. Inhibition of phosphorylation of the colony-stimulating factor-1 receptor (c-Fms) tyrosine kinase in transfected cells by ABT-869 and other tyrosine kinase inhibitors. *Mol Cancer Ther* 2006; 5: 1007-1013 [PMID: 16648572 DOI: 10.1158/1535-7163.MCT-05-0359]

37 Tan EH, Goss GD, Salgia R, Besse B, Gandara DR, Hanna NH, Yang JC, Thertulien R, Wertheim M, Mazieres J, Hensing T, Lee C, Gupta N, Pradhan R, Qian J, Qin Q, Scappaticci FA, Ricker JL, Carlson DM, Soo RA. Phase 2 trial of Linifanib (ABT-869) in patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2011; 6: 1418-1425 [PMID: 21597387 DOI: 10.1097/JTO.0b013e318220c93e]

38 Tannir NM, Wong YN, Kollmannsberger CK, Ernstoff MS, Perry DJ, Appleman LJ, Posadas EM, Cho D, Choueiri TK, Coates A, Gupta N, Pradhan R, Qian J, Chen J, Scappaticci FA, Ricker JL, Carlson DM, Michaelson MD. Phase 2 trial of linifanib (ABT-869) in patients with advanced renal cell cancer after sunitinib failure. *Eur J Cancer* 2011; 47: 2706-2714 [PMID: 22078932 DOI: 10.1016/j.ejca.2011.09.002]

39 Wang ES, Yee K, Koh LP, Hogge D, Enschede S, Carlson DM, Dudley M, Glaser K, McKeegan E, Albert DH, Li X, Pradhan R, Stock W. Phase 1 trial of linifanib (ABT-869) in patients with refractory or relapsed acute myeloid leukemia. *Leuk Lymphoma* 2012; 53: 1543-1551 [PMID: 22280537 DOI: 10.3109/10428194.2012.660631]

40 Shankar DB, Li J, Tapang P, Owen McCall J, Pease LJ, Dai Y, Wei RQ, Albert DH, Bouska JJ, Osterling DJ, Guo J, Marcotte PA, Johnson EF, Soni N, Hartandi K, Michaelides MR, Davidsen SK, Priceman SJ, Chang JC, Rhodes K, Shah N, Moore TB, Sakamoto KM, Glaser KB. ABT-869, a multitargeted receptor tyrosine kinase inhibitor: inhibition of FLT3 phosphorylation and signaling in acute myeloid leukemia. *Blood* 2007; 109: 3400-3408 [PMID: 17209055 DOI: 10.1182/blood-2006-06-029579]

41 Hsu HW, de Necochea-Campion R, Williams V, Duerksen-Hughes PJ, Simental AA, Ferris RL, Chen CS, Mirshahidi S. Linifanib (ABT-869), enhances cytotoxicity with poly (ADP-ribose) polymerase inhibitor, veliparib (ABT-888), in head and neck carcinoma cells. *Oral Oncol* 2014; 50: 662-669 [PMID: 24735547 DOI: 10.1016/j.oraloncology.2014.03.006]

42 Ramalingam SS, Shtivelband M, Soo RA, Barrios CH, Makhson A, Segalla JG, Pittman KB, Kolman P, Pereira JR, Srkalovic G, Belani CP, Axelrod R, Owonikoko TK, Qin Q, Qian J, McKeegan EM, Devanarayan V, McKee MD, Ricker JL, Carlson DM, Gorbunova VA. Randomized phase II study of carboplatin and paclitaxel with either linifanib or placebo for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2015; 33: 433-441 [PMID: 25559798 DOI: 10.1200/JCO.2014.55.7173]

43 O'Neil BH, Cainap C, Van Cutsem E, Gorbunova V, Karapetis CS, Berlin J, Goldberg RM, Qin Q, Qian J, Ricker JL, Fischer J, McKee MD, Carlson DM, Kim TW. Randomized phase II open-label study of mFOLFOX6 in combination with linifanib or bevacizumab for metastatic colorectal cancer. *Clin Colorectal Cancer* 2014; 13: 156-163. e2 [PMID: 25066269 DOI: 10.1016/j.clcc.2014.04.001]

44 Hsu HW, Gridley DS, Kim PD, Hu S, de Necochea-Campion R, Ferris RL, Chen CS, Mirshahidi S. Linifanib (ABT-869) enhances

radiosensitivity of head and neck squamous cell carcinoma cells. *Oral Oncol* 2013; 49: 591-597 [PMID: 23490884 DOI: 10.1016/j.oraloncology.2013.02.009]

45 Wong CI, Koh TS, Soo R, Hartono S, Thng CH, McKeegan E, Yong WP, Chen CS, Lee SC, Wong J, Lim R, Sukri N, Lim SE, Ong AB, Steinberg J, Gupta N, Pradhan R, Humerickhouse R, Goh BC. Phase I and biomarker study of ABT-869, a multiple receptor tyrosine kinase inhibitor, in patients with refractory solid malignancies. *J Clin Oncol* 2009; 27: 4718-4726 [PMID: 19720910 DOI: 10.1200/JCO.2008.21.7125]

46 Asahina H, Tamura Y, Nokihara H, Yamamoto N, Seki Y, Shibata T, Goto Y, Tanioka M, Yamada Y, Coates A, Chiu YL, Li X, Pradhan R, Ansell PJ, McKeegan EM, McKee MD, Carlson DM, Tamura T. An open-label, phase 1 study evaluating safety, tolerability, and pharmacokinetics of linifanib (ABT-869) in Japanese patients with solid tumors. *Cancer Chemother Pharmacol* 2012; 69: 1477-1486 [PMID: 22382879 DOI: 10.1007/s00280-012-1846-6]

47 Chiu YL, Lorusso P, Hosmane B, Ricker JL, Awni W, Carlson DM. Results of a phase I, open-label, randomized, crossover study evaluating the effects of linifanib on QTc intervals in patients with solid tumors. *Cancer Chemother Pharmacol* 2014; 73: 213-217 [PMID: 24241212 DOI: 10.1007/s00280-013-2351-2]

48 Toh HC, Chen PJ, Carr BI, Knox JJ, Gill S, Ansell P, McKeegan EM, Dowell B, Pedersen M, Qin Q, Qian J, Scappaticci FA, Ricker JL, Carlson DM, Yong WP. Phase 2 trial of linifanib (ABT-869) in patients with unresectable or metastatic hepatocellular carcinoma. *Cancer* 2013; 119: 380-387 [PMID: 22833179 DOI: 10.1002/cncr.27758]

49 Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Eskens FA, Qian J, McKee MD, Ricker JL, Carlson DM, El-Nowiem S. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015; 33: 172-179 [PMID: 25488963 DOI: 10.1200/JCO.2013.54.3298]

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•消息•

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