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埃克替尼对非小细胞肺癌*EGFR* 20外显子突变的临床疗效分析

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[摘　要] **目的：**探讨埃克替尼对非小细胞肺癌(non-small cell lung cancer，NSCLC)*EGFR* 20外显子S768I/20-ins/T790M/V769M突变的临床疗效。**方法：**回顾性分析58例埃克替尼治疗*EGFR* 20外显子少见突变的NSCLC，服用至病情进展或出现不可耐受的毒副反应，并观察疗效。**结果：**58例S768I/20-ins/T790M/V769M突变患者中S768I突变20例，中位生存时间3.2个月，20-ins突变18例，中位生存时间1.6个月，T790M突变21例，中位生存时间1.6个月，V769M突变1例，生存时间3.2个月。S768I突变和V769M突变患者生存时间稍长。单纯突变与复合突变相比，复合突变中位生存时间更长(S768I突变2.2个月 vs. 3.3个月，P=0.174；T790M突变2.45个月 vs. 2.9个月，P=0.845)。**结论：**埃克替尼在EGFR基因20外显子少见突变的疗效上比传统敏感突变未见明显优势，但复合突变比单纯突变临床获益更多。

[关键词] 非小细胞肺癌；埃克替尼；20外显子

Clinical efficacy of icotinib in patients with advanced non-small cell lung cancer harboring *EGFR* exon 20 mutations

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Abstract **Objective:** To investigate the efficacy of icotinib in patients with non-small cell lung cancer (NSCLC) that carrying S768I/20 insertions/T790M/V769M in *EGFR* exon 20. **Methods:** Fifty eight cases of *EGFR* 20 exon

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rare mutation NSCLC patients were retrospectively analyzed until the progress of the disease or the emergence of the side effects and clinical efficacy was observed after months of followed-up. **Results:** Fifty eight patients with S768I/20 insertion/T790M/V769M mutations were enrolled. Mutations including S768I, exon 20 insertions, T790M and V769M mutations were observed in 20, 18, 21 and 1 patients, respectively. Patients with S768I mutation or V769M mutation manifested the longest median PFS (3.2 months), followed by those with T790M (1.6 months) and exon 20 insertions (1.9 months). Patients with complex mutations showed a better PFS than those with single mutations (S768I mutations 2.2 vs. 3.3 months, *P*=0.174; T790M 2.45 vs. 2.9 months, *P*=0.845). **Conclusion:** Icotinib is less effective in patients with exon 20 uncommon mutations than in those with common mutations. Patients with complex mutations benefited more from icotinib than those with single mutations.

Keywords non-small cell lung cancer; icotinib; exon 20

在世界范围内，肺癌的发病率和病死率逐年升高，已成为恶性肿瘤之首，其中非小细胞肺癌(non-small cell lung cancer，NSCLC)占80%~85%[1-3]。其中体系突变的EGFR基因突变是东亚人种NSCLC的最常见突变形式[4-7]。目前针对*EGFR*基因突变的一代EGFR TKIs(吉非替尼、厄洛替尼和埃克替尼)能明显提高*EGFR*基因敏感性突变患者的疗效，其中位生存时间在*EGFR*基因常规突变患者(19del和L858R)中已经超过2年[8]，并在国内广泛应用。埃克替尼是我国第一个具有知识产权的小分子靶向抗癌新药，对晚期NSCLC的治疗效果与国外抗药物的疗效相仿，并且安全性更好[9-11]。目前对埃克替尼仍缺乏对*EGFR*基因少见突变的系统研究。

1 对象与方法

1.1 对象

1.1.1 一般资料

选取福建省肿瘤医院、浙江省肿瘤医院、武警浙江总队医院2013年7月至2016年11月间*EGFR* 20外显子S768I/20-ins/T790M/V769M突变的NSCLC患者58例，纳入标准：1)经组织学或细胞学检查诊断确诊为NSCLC，经ARMS方法或者NGS方法检测为*EGFR* 20外显子少见突变；2)未接受过化疗或既往接受过化疗但已从任何一次化疗的毒性反应中恢复过来；3)根据实体瘤疗效评价标准(Response Evaluation Criteria in Solid Tumors，RECIST)，至少含1个可测量病灶；4)年龄≥18岁，自愿签署知情同意书。排除标准：1)本研究前曾确诊或者治疗过其他恶性肿瘤；2)既往神经或精神病史；3)存在严重呼吸、心血管和肝肾疾病。本研究经成员单位医院学伦理委员会批准，所有患者均知情同意。

1.2 方法

58例患者获取血或肿瘤组织标本经ARMS方法或NGS方法确诊为*EGFR* 20外显子少见突变的NSCLC后给予埃克替尼125 mg tid，直至不能耐受而终止治疗。治疗期间定期检测患者血常规、肝肾功能、肿瘤标志物、心电图及影像学，评估疗效及研究其耐药机制。

1.3 研究因素与评价标准

研究因素包含年龄、性别、吸烟史、ECOG评分、TNM分期等。不吸烟定义是一生吸烟<100支。疗效评价标准使用WHO实体瘤疗效评价标准(RECIST)，包括完全缓解(complete response，CR)，部分缓解(partial response，PR)，疾病稳定(stable disease，SD)，疾病进展(progressive disease，PD)。疾病控制率(disease control rate，DCR)为CR+PR+SD。颅内病灶评估采用脑MRI，颅外病灶评估采用CT。

1.4 统计学处理

无进展生存期(progression-free survival，PFS)用Kaplan-Meier法进行分析，使用Log-rank法进行单因素预后分析，PFS指从埃克替尼治疗至第一次发生疾病进展或任何原因死亡的时间。所有统计使用SPSS 19.0统计软件进行分析。

2 结果

2.1 临床病理特征

总计3279例NSCLC通过ARMS方法或NGS方法进行*EGFR*基因检测，其中EGFR阳性患者1 347例(1 347/3 279，41.08%)，其中92例患者为*EGFR*基因20外显子突变，其中58例服用埃克替尼，临床病理特征见表1，其中男性女比例接近1∶1，年龄

以65岁以下居多，有吸烟史患者略少于未吸烟患者，PS评分以0~1为主，组织亚型以腺癌为主，突变类型：S768I 20例，20-ins 18例，T790M 21例，V769M 1例，埃克替尼治疗在三线以上占绝大多数，分期以IV期为主(表1~2)。

表1 58例埃克替尼治疗的*EGFR*基因20外显子突变的非小细胞肺癌临床病理特征

Table 1 Clinicopathologic characteristics of 58 cases of patients with *EGFR* exon 20 mutations whom were therapy by icotinib

临床病理特征	例数
性别	
男	27
女	31
年龄/岁	
<65	43
≥65	15
吸烟史	
是	24
否	34
PS	
0~1	41
2~3	17
组织亚型	
腺癌	56
非腺癌	2
突变类型	
S768I	20
20-ins	18
T790M	21
V769M	1
埃克替尼治疗	
一线	2
二线	13
三线及以上	43
分期	
ⅢB	3
Ⅳ	55

表2 58例埃克替尼治疗*EGFR*基因20外显子突变的非小细胞肺癌具体亚型

Table 2 The specific subtype of 58 cases of patients with *EGFR* exon 20 mutations whom were therapy by icotinib

突变类型	例数 (%)
S768I	20 (35.71)
单纯型	6 (10.71)
S768I+19del	1 (1.79)
S768I+L858R	2 (3.57)
S768I+G719X	8 (14.29)
S768I+G724S	1 (1.79)
S768I+L858R+20-ins	1 (1.79)
S768I+G724S+V769M	1 (1.79)
20-ins	18 (32.14)
单纯型	17 (30.36)
20-ins+S768I+L858R	1 (1.79)
T790M	21 (37.50)
单纯型	4 (7.14)
T790M+19del	9 (16.07)
T790M+L858R	7 (12.50)
T790M+19del+L858R	1 (1.79)
V769M	1 (1.79)
V769M+ S768I+G724S	1 (1.79)

2.2 20 外显子疗效分析

埃克替尼对*EGFR*基因20外显子数据显示：客观缓解率(objective response rate，ORR)和DCR分别为13.79%和60.34%，在这些患者中，未见CR患者，PR共计8例，SD共计27例，中位PFS为2.3个月。亚组分析中埃克替尼对*EGFR* 20外显子S768I单纯突变与复合突变的PFS(2.2个月 vs. 3.3个月，P=0.174)；对*EGFR* 20外显子20-ins单纯突变与复合突变的PFS(1.7个月 vs. 0.5个月，P=0.025)，其中对A763_Y764insFQEA与非A763_Y764insFQEA的PFS(9.0个月 vs. 1.2个月，P=0.000)；对*EGFR* 20外显子T790M单纯突变与复合突变的PFS(2.5个月 vs. 2.9个月，P=0.845)，其中对T790M+19del与T790M+L858R的PFS(3.0个月 vs. 1.6个月，P=0.571)(表3，图1~9)。

表3 埃克替尼对非小细胞肺癌*EGFR*基因20外显子的疗效分析

Table 3 Clinical efficacy of icotinib with advanced non-small-cell lung cancer harboring *EGFR* exon 20 mutations

突变类型	*n*	CR	PR	SD	PD	ORR/%	DCR/%	PFS/月
S768I	20	0	5	11	4	25.00	80.00	3.2
20-ins	18	0	2	6	10	11.11	44.44	1.6
T790M	21	0	1	9	11	4.76	47.62	2.3
V769M	1	0	0	1	0	0	100	3.2

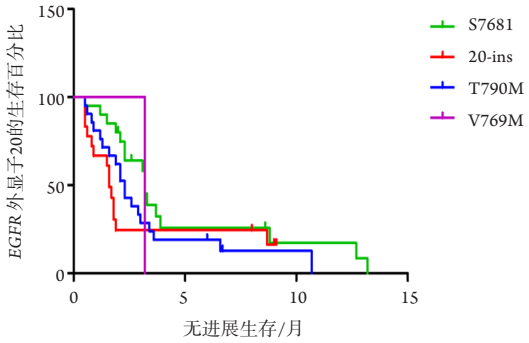

图1 埃克替尼对*EGFR* 20外显子PFS(*P*=0.181)

Figure 1 PFS of *EGFR* 20 exon by icotinib (*P*=0.181)

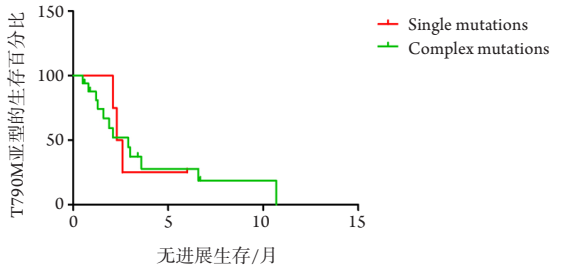

图4 埃克替尼对*EGFR* 20外显子T790M单纯突变与复合突变的PFS(*P*=0.845)

Figure 4 PFS comparison between patients harboring *EGFR* exon 20 T790M single mutations and complex mutations (*P*=0.845)

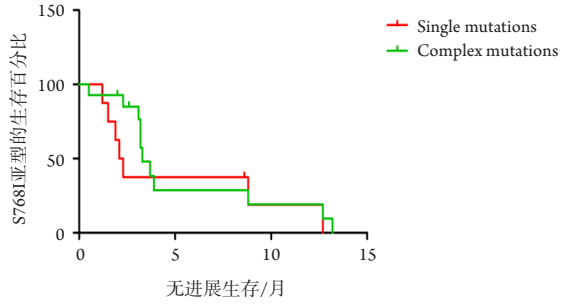

图2 埃克替尼对*EGFR* 20外显子S768I单纯突变与复合突变的PFS(*P*=0.174)

Figure 2 PFS comparison between patients harboring *EGFR* exon 20 S768I single mutations and complex mutations (*P*=0.174)

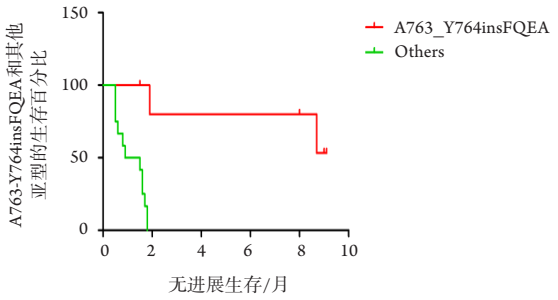

图5 A763_Y764insFQEA与非A763_Y764insFQEA的PFS(*P*<0.001)

Figure 5 PFS comparison between patients harboring A763_Y764insFQEA and non-A763_Y764insFQEA (*P*<0.001)

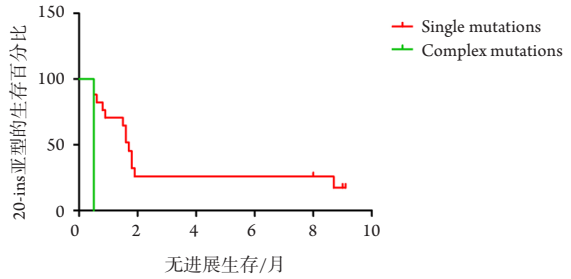

图3 埃克替尼对*EGFR* 20外显子20-ins单纯突变与复合突变的PFS(*P*=0.025)

Figure 3 PFS comparison between patients harboring *EGFR* exon 20 insertions single mutations and complex mutations (*P*=0.025)

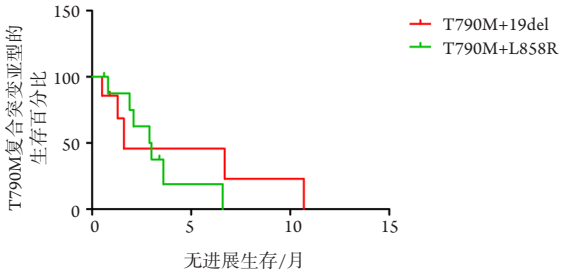

图6 埃克替尼对T790M+19del与T790M+L858R的PFS(*P*=0.571)

Figure 6 PFS comparison between patients harboring T790M+19del and T790M+L858R (*P*=0.571)

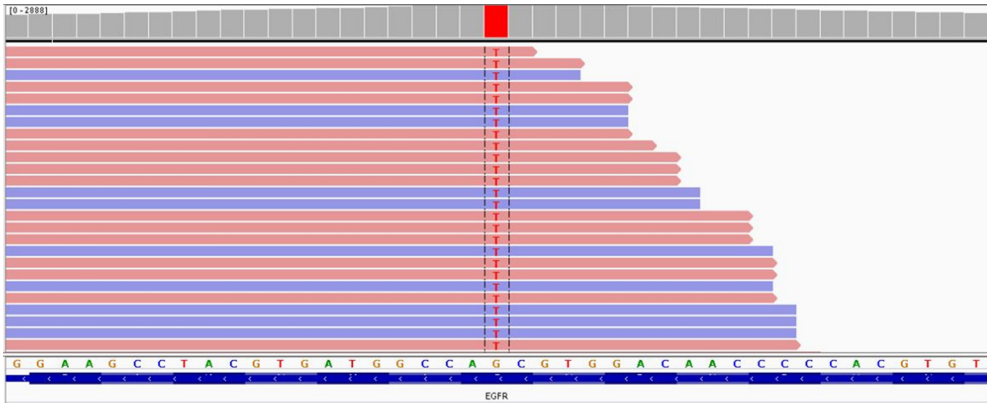

图7 *EGFR* S768I IGV图

Figure 7 IGV of *EGFR* S768I

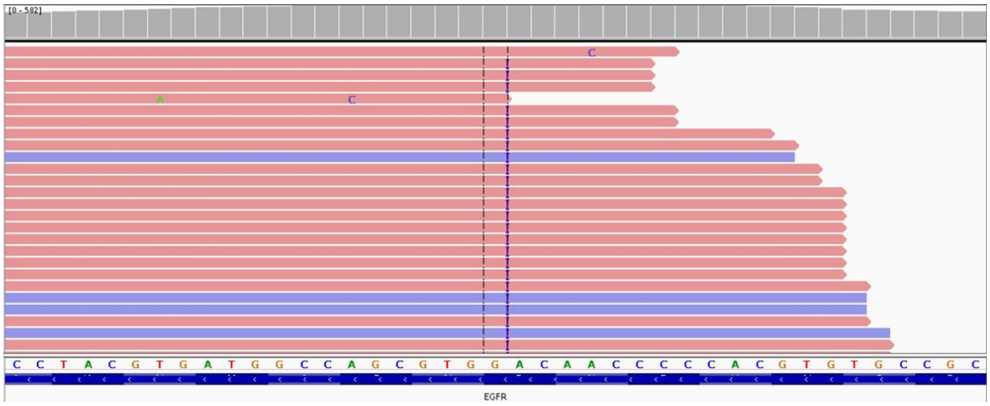

图8 *EGFR* 20-ins IGV图(D770delinsGY)

Figure 8 IGV of *EGFR* 20-ins (D770delinsGY)

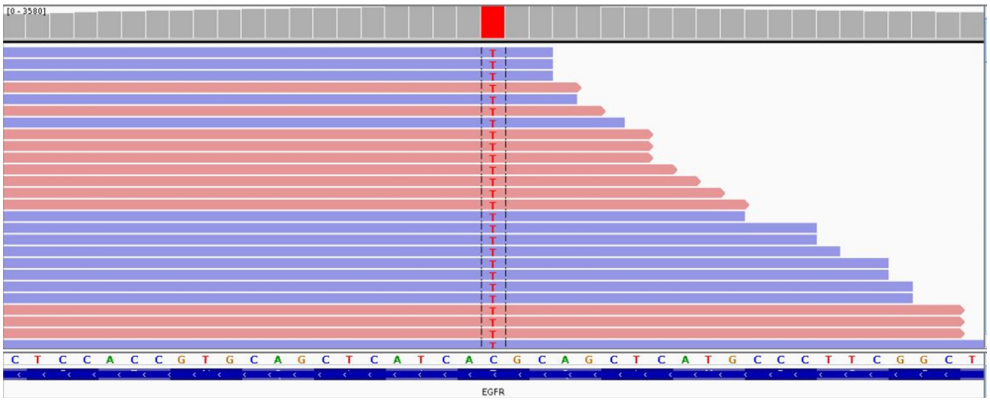

图9 *EGFR* T790M IGV图

Figure 9 IGV of *EGFR* T790M

3 讨论

既往研究[12-18]表明：*EGFR*基因突变90%为19外显子的缺失突变(19del)或者21外显子的L858R点突变的常见突变，少见突变中最常见的为18外显子G719X点突变，21外显子L861Q点突变，它们对一代EGFR TKIs相对敏感，中位生存时间超过6个月以上。20外显子突变包括S768I/N，

T790M，20-ins，V769M/L，Q787Q等，其中S768I，T790M和20-ins最常见，但略低于G719X和L861Q[19-20]。本研究中20外显子的突变占*EGFR*基因突变型6.83%(92/1347)，与以往研究类似。

目前一代EGFR-TKIs对*EGFR*基因突变型NSCLC治疗存在一定的争议[15,17-18]，Chen等[21]回顾性研究发现：S768I突变是一代EGFR-TKIs治疗的一个耐药原因，但另外有研究[22-24]发现部分S768I突变患者能从一代EGFR-TKIs治疗中获益。本研究选择具有中国特色的EGFR-TKIs-埃克替尼治疗S768I发现：18例埃克替尼对*EGFR* 20外显子S768I的PFS为3.2个月，其中单纯突变与复合突变的PFS(2.2个月 vs. 3.3个月，*P*=0.174)。

Oxnard等[25]研究发现：20外显子插入突变亚型繁多，其中V769_D770insASV占插入突变的22.22%，其中位总生存时间16个月，与*EGFR*基因野生型生存相似。Yasuda等[20]研究发现大部分20外显子插入突变很少从一代EGFR TKIs中获益，但是其中特殊亚型A763_Y764insFQEA却对厄洛替尼高度敏感。Chen等[24]研究发现一代EGFR TKIs对29例20外显子插入突变中位PFS 1.9个月，其中PFS超过6个月的有4例，均为A763_Y764insFQEA。本研究中埃克替尼治疗18例20外显子插入突变中位PFS为1.6个月，与既往研究相近，单纯突变与复合突变的PFS(1.7个月 vs. 0.5个月，*P*=0.025)，与S768I突变和T790M结果均相反，可能原因由于复合突变例数过少，仅1例，存在偏倚。20外显子插入突变中单纯突变与复合突变我们期待今后大样本验证。

T790M作为*EGFR*基因EGFR-TKIs原发性耐药的一个常见原因，经常与敏感突变19del和L858R共存，仅1%~2%的患者存在单纯性T790M[16,26]，此类患者对一代EGFR TKIs中位PFS为2.4个月，目前此类患者对三代EGFR TKIs获益显著，本研究中T790M突变的NSCLC患者对埃克替尼的中位PFS为2.3个月，T790M单纯突变与复合突变的PFS(2.45个月 vs. 2.9个月，*P*=0.845)，其中对T790M+19del与T790M+L858R的PFS(2.95个月 vs. 1.6个月，*P*=0.571)。

针对V769M少见突变位点，埃克替尼的疗效国内外并未报道，本研究中1例埃克替尼的PFS为3.2个月。

总之，本研究作为首个埃克替尼对*EGFR* 20外显子的疗效分析，虽然我们发现埃克替尼在*EGFR*基因20外显子少见突变的疗效上比传统突变未见明显优势，但复合突变比单纯突变临床获益更多，A763_Y764insFQEA对埃克替尼的临床获益显著，与传统突变临床获益接近，值得重视。

参考文献

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016[J]. CA Cancer J Clin, 2016, 66(1): 7-30.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015[J]. CA Cancer J Clin, 2016, 66(2): 115-132.
3. Sher T, Dy GK, Adjei AA. Small cell lung cancer[J]. Mayo Clin Proc, 2008, 83(3): 355-367.
4. Sun Y, Ren Y, Fang Z, et al. Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases[J]. J Clin Oncol, 2010, 28(30): 4616-4620.
5. Li H, Pan Y, Li Y, et al. Frequency of well-identified oncogenic driver mutations in lung adenocarcinoma of smokers varies with histological subtypes and graduated smoking dose[J]. Lung Cancer, 2013, 79(1): 8-13.
6. Zhang Y, Sun Y, Pan Y, et al. Frequency of driver mutations in lung adenocarcinoma from female never-smokers varies with histologic subtypes and age at diagnosis[J]. Clin Cancer Res, 2012, 18(7): 1947-1953.
7. Wu C, Zhao C, Yang Y, et al. High discrepancy of driver mutations in patients with NSCLC and synchronous multiple lung ground-glass nodules[J]. J Thorac Oncol, 2015, 10(5): 778-783.
8. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer[J]. N Engl J Med, 2005, 353(2): 123-132.
9. Shao L, Zhang B, He C, et al. Efficacy and safety of icotinib in Chinese patients with advanced non-small cell lung cancer after failure of chemotherapy[J]. Chin Med J (Engl), 2014, 127(2): 266-271.
10. 宋正波, 余新民, 蔡菊芬, 等. 埃克替尼在晚期非小细胞肺癌EGFR状态明确的患者中的疗效分析[J]. 中国肺癌杂志, 2013, 16(3): 138-143.
    SONG Zhengbo, YU Xinmin, CAI Jufen, et al. Efficacy of icotinib for advanced non-small cell lung cancer patients with EGFR status identified[J]. Chinese Journal of Lung Cancer, 2013, 16(3): 138-143.
11. 朱礼阳, 许春伟, 于忠和. 埃克替尼治疗37例晚期非小细胞肺癌疗效分析[J]. 临床与病理杂志, 2016, 36(9): 1340-1344.
    ZHU Liyang, XU Chunwei, YU Zhonghe. Analysis of icotinib on treatment of 37 cases of advanced non-small cell lung cancer[J]. Journal of Clinical and Pathological Research, 2016, 36(9): 1340-1344.
12. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma[J]. N Engl J Med, 2009, 361(10): 947-957.
13. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based

chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials[J]. Lancet Oncol, 2015, 16(2): 141-151.

14. Sharma SV, Bell DW, Settleman J, et al. Epidermal growth factor receptor mutations in lung cancer[J]. Nat Rev Cancer, 2007, 7(3): 169-181.
15. Pallan L, Taniere P, Koh P. Rare EGFR exon 20 S768I mutation predicts resistance to targeted therapy: a report of two cases[J]. J Thorac Oncol, 2014, 9(10): e75.
16. Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network[J]. Ann Oncol, 2014, 25(1): 126-131.
17. Wu JY, Yu CJ, Chang YC, et al. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer[J]. Clin Cancer Res, 2011, 17(11): 3812-3821.
18. Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial[J]. Lancet Oncol, 2012, 13(5): 539-548.
19. Lee Y, Lee GK, Hwang JA, et al. Clinical likelihood of sporadic primary EGFR T790M mutation in EGFR-mutant lung cancer[J]. Clin Lung Cancer, 2015, 16(1): 46-50.
20. Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer[J]. Sci Transl Med, 2013, 5(216): 216ra177.
21. Chen YR, Fu YN, Lin CH, et al. Distinctive activation patterns in constitutively active and gefitinib-sensitive EGFR mutants[J]. Oncogene, 2006, 25(8): 1205-1215.
22. Masago K, Fujita S, Irisa K, et al. Good clinical response to gefitinib in a non-small cell lung cancer patient harboring a rare somatic epidermal growth factor gene point mutation; codon 768 AGC > ATC in exon 20 (S768I)[J]. Jpn J Clin Oncol, 2010, 40(11): 1105-1109.
23. Hellmann MD, Reva B, Yu H, et al. Clinical and in vivo evidence that EGFR S768I mutant lung adenocarcinomas are sensitive to erlotinib[J]. J Thorac Oncol, 2014, 9(10): e73-e74.
24. Chen D, Song Z, Cheng G. Clinical efficacy of first-generation EGFR-TKIs in patients with advanced non-small-cell lung cancer harboring EGFR exon 20 mutations[J]. Onco Targets Ther, 2016, 9: 4181-4186.
25. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions[J]. J Thorac Oncol, 2013, 8(2): 179-184.
26. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6[J]. Lancet Oncol, 2015, 16(7): 830-838.

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