

## Erlotinib for advanced hepatocellular carcinoma

### *A systematic review of phase III/III clinical trials*

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#### ABSTRACT

**الأهداف:** تقييم فعالية وسلامة الدواء Erlotinib في علاج سرطان الكبد المتقدم.

**الطريقة:** أجري بحث أدبي منهجي في يونيو 2015 يضم المرحلة الثانية/الثالثة من تجارب Erlotinib لعلاج سرطان الكبد المتقدم. حيث تم استخدام التحليل الوصفي. وقد أجريت الدراسة في مستشفى هونغهوي، جامعة شيان جياوتونغ، كلية الطب، كزيان، الصين، بين يونيو 2015 ويناير 2016.

**النتائج:** أدرجت في المراجعة المنهجية 10 تجارب، التي تضم 9 تجارب للمرحلة الثانية وتجربة واحدة للمرحلة الثالثة، وكان معدل استجابة الورم 0% في 4 تجارب للمرحلة الثانية، <10% في 3 تجارب للمرحلة الثانية والمرحلة الثالثة، و>20% في 2 من تجارب المرحلة الثانية وكان معدل مكافحة الأمراض 42.5-79.6% في معظم الدراسات. كما أنه ذكرت 3 دراسات بقاء متوسط بدون تقدم يذكر (PFS) من 6.5-9.0 أشهر، على الرغم من أن PFS كان <3.5 أشهر في معظم الدراسات. وأفادت غالبية التجارب متوسط بقاء إجمالي من 6.25-15.65 شهر. حيث التسممات الأكثر شيوعاً كانت 3/4 منها بسبب التعب (11.9%)، الإسهال (10%)، زيادة الألبان والترانساميناسات الاسباراتي (7.3%)، والطفح الجلدي/التقشر (6.9%).

**الخلاصة:** يتبين أن Erlotinib يوفر علاج فعال وتحمل جيد لسرطان الكبد المتقدم. ومع ذلك، هناك حاجة إلى إجراء تحقيقات أكثر تفصيلاً حول أمراض سرطان الكبد وتقييم مجموعات فرعية للمرضى الذين يظهرون حساسية لسرطان الكبد المتقدم. كما أنه من الضروري إجراء دراسات أكثر دقة ومنهجية، لتقييم فعالية وسلامة Erlotinib كعلاج وحيد أو بالاشتراك مع أدوية أخرى لمكافحة سرطان الكبد المتقدم.

**Objectives:** To evaluate the efficacy and safety of erlotinib for the treatment of advanced hepatocellular carcinoma (HCC).

**Methods:** A systematic literature search was undertaken in June 2015. Phase II/III trials of erlotinib for the treatment of advanced HCC were included. A descriptive analysis was applied. The study was conducted in College of Medicine, Honghui Hospital, Xi'an Jiaotong University, Xi'an, China, between June 2015 and January 2016.

**Results:** Ten trials, comprising 9 phase II and one phase III trial, were included in the systematic review. The tumor response rate was 0% in 4 of the phase II trials, <10% in 3 of the phase II trials and the phase III trial, and >20% in 2 of the phase II trials. The disease control rate was 42.5-79.6% in most studies. Three studies reported a median progression-free survival (PFS) of 6.5-9.0 months, although PFS was <3.5 months in most studies. Most trials reported a median overall survival of 6.25-15.65 months. The most frequent grade 3/4 toxicities were fatigue (11.9%), diarrhea (10%), increased alanine and aspartate transaminases (7.3%), and rash/desquamation (6.9%).

**Conclusion:** Erlotinib provides efficacious and well-tolerated treatment for advanced HCC. However, more detailed investigations of HCC pathogenesis and evaluation of sensitive patient subsets are needed to improve outcomes of patients with advanced HCC. Additional well-designed, randomized, controlled trials are needed to evaluate the efficacy and safety of erlotinib as monotherapy or combination with other drugs for advanced HCC.

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Globally, hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor in adults and the third-most frequent cause of cancer-induced mortality.<sup>1,2</sup> Because early-stage HCC typically has no symptoms and monitoring is infrequently performed, most patients with HCC are diagnosed at an advanced or unresectable stage.<sup>3</sup> For advanced or unresectable HCC, the treatment options are few, and therapeutic outcome is poor.<sup>4</sup> Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is orally bioavailable. Erlotinib can inhibit proliferation, invasion, metastasis, and angiogenesis in tumor cells.<sup>5,6</sup> Some clinical trials have evaluated erlotinib for the management for advanced HCC,<sup>7-11</sup> but these studies are compromised by having small and underpowered sample sizes. There is no comprehensive summary of these trials; therefore, the true impact of erlotinib on advanced HCC is unknown. We conducted a systematic literature review of the currently available data to obtain a full overview of the efficacy and safety of erlotinib for the treatment of advanced HCC.

**Methods. Search strategy.** In June 2015, we systematically searched the Cochrane Library database, the World Health Organization trial registry, clinicaltrials.gov, MEDLINE, and EMBASE without language or year restrictions. We used the following search terms: “Erlotinib”, “Tarceva”, “OSI-774”, “hepatocellular carcinoma OR hepatoma OR liver cell carcinoma OR hepatocellular cancer”, and “unresectable OR advanced”. The bibliographies of all eligible articles and related reviews were searched manually to retrieve any additional relevant articles not discovered by electronic searches.

**Inclusion and exclusion criteria.** We included any articles that reported phase II/III trials of erlotinib for the treatment of unresectable or advanced HCC. The exclusion criteria were animal studies and meeting abstracts that did not report data for the outcomes of interest. Two independent reviewers initially screened and excluded studies based on the titles and abstracts. The remaining publications were scrutinized for relevant outcomes of interest.

**Study design.** A systematic literature review of phase II/III trials of erlotinib for the treatment of unresectable or advanced HCC was performed.

**Outcome measures.** Based on the National Cancer Institute Common Terminology Criteria (version 2.0) and Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) criteria, tumor responses and toxicities were assessed.

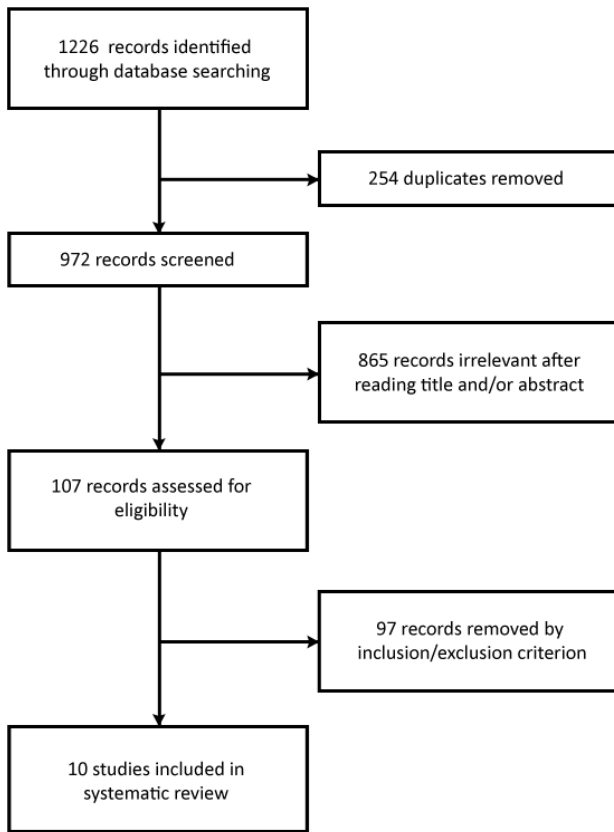
**Data extraction.** Data extraction was performed and cross-checked independently by 2 reviewers using a standard data extraction form. Any discrepancies were determined by consensus with involvement of the third investigator if necessary. The following data were extracted when available: detailed information regarding erlotinib, including dosages, treatment regimen, number of cycles, and line of treatment; response evaluation, including complete response rate (CR), partial response rate (PR), progressive disease rate (PD), stable disease rate (SD), in addition to 2 indirect index: response rate (RR, CR + PR), and disease control rate (DCR, CR + PR + SD); prognosis, including progression-free survival (PFS), time-to-progression (TTP), overall survival (OS); and the incidence of toxicities.

**Statistical analysis.** We planned to combine suitable data to calculate the risk ratios with 95% confidence intervals for dichotomized variables and the weighted mean difference for continuous variables. A meta-analysis was planned using Review Manager (The Cochrane Collaboration, Version 5.2). If it proved impossible to combine the data for analysis, as an alternative, a descriptive analysis would be employed.

**Results. Study characteristics.** The process of study selection is shown in Figure 1. Ultimately, 10 trials were included in the present systematic review.<sup>7-16</sup> The basic characteristics of the included trials are shown in Table 1. Inter-study heterogeneity in the different inclusion and exclusion criteria, the differences in drug combinations, and dosages and treatment regimens precluded a meta-analysis to compare the efficacy and safety of erlotinib versus control treatment. Furthermore, most trials were single-arm and phase II trials without a control arm, except one phase III randomized controlled trial (RCT), preventing us from conducting a meta-analysis. Therefore, the findings of this study are reported using a descriptive analysis.

**Tumor response.** Tumor RR and PR rates were 0-25.0%. Four of the phase II trials reported a 0% tumor RR,<sup>8,12,13,15</sup> while <10% was reported in 3 of the phase II trials and the phase III trial,<sup>7,11,14,16</sup> and >20% in 2 of the phase II trials (Table 2).<sup>9,10</sup> There were no CRs in the phase II trials, but 2 (0.6%) patients showed a CR in the phase III RCT.<sup>16</sup> In most trials, 40-50% of patients had SD after erlotinib treatment.<sup>7,11,14,15</sup>

**Disease control rate.** The DCR was 42.5-79.6% in most studies. The DCR in 4 phase II trials was 50-80%,<sup>7,9,10,14</sup> and the DCR in 3 phase II trials and the phase III RCT was 40-50% (Table 2).<sup>8,11,15,16</sup> For the remaining phase II trials, one reported a DCR of 28%,<sup>13</sup> whereas the other reported a DCR of 0%.<sup>12</sup>



**Figure 1** - Study selection process for the systematic review of phase II/III trials of erlotinib for the treatment of unresectable or advanced hepatocellular carcinoma.

**Progression-free survival/time-to-progression.** The median PFS or TTP in all studies was 1.81-9.0 months. Three of the included studies reported a median PFS of 6.5-9.0 months,<sup>8-10</sup> but most reported a PFS of <3.5 months (Table 2).<sup>7,11-16</sup>

**Overall survival.** The median OS in all studies was 4.37-15.65 months. Nine of the 10 trials reported a median OS of 6.25-15.65 months,<sup>7-11,13-16</sup> except one phase II trial that reported an OS of 4.37 months (Table 2).<sup>12</sup>

**Toxicities.** The phase II trials of Thomas et al<sup>9</sup> and Kaseb et al<sup>10</sup> were performed in the same institution, and the latter sample (n=59) included that of the former (n=40). Therefore, we included only the study of Kaseb et al<sup>10</sup> during toxicity analysis. In addition, due to the differences in the study types, we did not combine the phase III RCT data with the phase II study data. Eventually, the toxicity was assessed using the data combined from 8 phase II trials (n=260).<sup>7,8,10-15</sup>

The most typical reported toxicities, experienced by ≥20% of patients, regardless of grade, were diarrhea (57.3%), rash/desquamation (55.4%), fatigue (46.2%), nausea (26.9%), dry skin (26.9%), acne (26.9%), anorexia (26.5%), increased alanine and aspartate transaminases (22.7%), and epistaxis (21.5%). Grade 1 and grade 2 toxicities were most frequently reported. Within grade 3/4 toxicities, those that occurred in more than 5% of patients were fatigue (11.9%), diarrhea (10%), increased alanine and aspartate transaminases

**Table 1** - Basic characteristics of included studies in systematic review of phase II/III trials of erlotinib for the treatment of unresectable or advanced hepatocellular carcinoma.

Study	Country	Line	Sample size	Design of parent study/ phase	Treatment regimen	Cycles of erlotinib median (range)
Philip 2005 <sup>7</sup>	USA	first or second line	38	Single-arm/II	E 150 mg po qd	5 (1-26)
Thomas 2007 <sup>8</sup>	USA	first line	40	Single-arm/II	E 150 mg po qd	2 (1-16)
Thomas 2009 <sup>9</sup>	USA	first or second line	40	Single-arm/II	E 150 mg po qd + B 10 mg/kg iv q2w	6 (1-13)
Kaseb 2012 <sup>10</sup>	USA	first or second line	59	Single-arm/II	E 150 mg po qd + B 10 mg/kg iv q2w	86% of patients completed ≥8 cycles
Philip 2012 <sup>11</sup>	USA	second line	27	Single-arm/II	E 150 mg po qd + B 10 mg/kg iv q2w	2 (1-12)
Yau 2012 <sup>12</sup>	China	≥second line	10	Single-arm/II	E 150 mg po qd + B 10 mg/kg iv q2w	3 (2-3)
Govindarajan 2013 <sup>13</sup>	USA	first line	21	Single-arm/II	E 150 mg po qd + B 15 mg/kg iv q3w	E:3(1-21); B:3(1,22)
Hsu 2013 <sup>14</sup>	Korea, Philippines, and Taiwan	first line	51	Single-arm/II	E 150 mg po qd + B 5 mg/kg iv q2w	Unclear
Chiorean 2012 <sup>15</sup>	USA	first line	14	Single-arm/II	E 150 mg po on days 2-7, 9-14, 16-28, D 30 mg/m <sup>2</sup> IV on days 1, 8, 15 of each 28-day cycle	Unclear
Zhu 2015 <sup>16</sup>	Europe, North and South America, and the Asia-Pacific region	first line	720	RCT/ III	S 400 mg po bid + E 150 mg po qd vs S 400 mg po bid + P 150 mg po qd	S + E:3 S + P:4

E - erlotinib, B - bevacizumab, S - sorafenib, P - placebo, D - docetaxel, RCT - randomized controlled trial

**Table 2** - Efficacy of studies included in systemic review of phase II/III trials of erlotinib for the treatment of unresectable or advanced hepatocellular carcinoma.

Study	Treatment	CR	PR	SD n (%)	RR	DCR	Median PFS/ TTP (mo)	Median OS
Philip 2005 <sup>7</sup>	E	0 (0.0)	3 (9.0)	17 (50.0)	3 (9.0)	20 (59.0)	3.2	13
Thomas 2007 <sup>8</sup>	E	0 (0.0)	0 (0.0)	17 (42.5)	0 (0.0)	17 (42.5)	6.5	6.25
Thomas 2009 <sup>9</sup>	E+B	0 (0.0)	10 (25.0)	17 (42.5)	10 (25.0)	27 (67.5)	9.0	15.65
Kaseb 2012 <sup>10</sup>	E+B	0 (0.0)	14 (23.7)	33 (55.9)	14 (23.7)	47 (79.6)	7.2	13.7
Philip 2012 <sup>11</sup>	E+B	0 (0.0)	1 (2.1)	11 (40.7)	1 (2.1)	12 (44.4)	3.0	9.5
Yau 2012 <sup>12</sup>	E+B	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.81	4.37
Govindarajan 2013 <sup>13</sup>	E+B	0 (0.0)	0 (0.0)	5 (28.0)	0 (0.0)	5 (28.0)	2.57	8.33
Hsu 2013 <sup>14</sup>	E+B	0 (0.0)	3 (6.0)	24 (47.0)	3 (6.0)	27 (53.0)	2.9	10.7
Chiorean 2012 <sup>15</sup>	E+D	0 (0.0)	0 (0.0)	6 (46.0)	0 (0.0)	6 (46.0)	3.5	6.7
Zhu 2015 <sup>16</sup>	E+S	2 (0.6)	22 (6.1)	135 (37.3)	24 (6.6)	159 (43.9)	3.2	9.5
	P+S	1 (0.3)	13 (3.6)	174 (48.6)	14 (3.9)	188 (52.5)	4.0	8.5

CR - complete response, PR - partial response, SD - stable disease, RR - response rate (CR+PR), DCR - disease control rate (CR+PR+SD), PFS - progression-free survival, TTP - time-to-progression, OS - overall survival, mo - months, E - erlotinib, B - bevacizumab, S - sorafenib, P - placebo, D - docetaxel

(7.3%), and rash/desquamation (6.9%). For the phase III trial,<sup>16</sup> the overall rates of emergent adverse events (AEs) (100% versus 99.2%) and drug-related AEs (95.0% versus 95.2%) were similar between the sorafenib plus erlotinib and sorafenib plus placebo groups.

In the phase II studies, 2 patients died: one due to complications after experiencing gastrointestinal hemorrhage,<sup>9</sup> and one due to acute respiratory failure caused by pneumonia that was deemed unrelated to the study drugs.<sup>11</sup> In the phase III RCT, the frequency of emergent AEs leading to death was similar between the arms; 72 (20.3%) patients in the sorafenib plus placebo group and 80 (22.1%) patients in the sorafenib plus erlotinib group died of grade 5 emergent AEs.<sup>16</sup>

Adverse reactions led to 5 (13%) patients withdrawing from a phase II trial, but the details of their adverse reactions were unclear.<sup>7</sup> In another phase II study,<sup>9</sup> 7 (17.5%) patients withdrew due to fatigue, proteinuria, delayed wound healing, and gastrointestinal hemorrhage. One phase II study<sup>10</sup> reported that 6 (10%) patients were excluded owing to grade 3-4 gastrointestinal hemorrhage. In the remaining phase II studies,<sup>8,11-15</sup> there were no toxicity-related withdrawals. In the phase III RCT,<sup>16</sup> the incidence of emergent AEs resulting in withdrawal was similar in the sorafenib plus erlotinib (45.0%) and sorafenib plus placebo (45.6%) groups.

**Discussion.** This systematic review provides a comprehensive overview of the current evidence of the efficacy and safety of erlotinib for the treatment of advanced HCC. Although it was impossible to perform an overall meta-analysis for several reasons, in general,

the results reported in these studies demonstrate that erlotinib is efficacious and well-tolerated in the treatment of advanced HCC.

When used as monotherapy, the DCR of erlotinib for advanced HCC was good, but the RR was poor,<sup>7,8</sup> suggesting that erlotinib alone exhibited modest antitumor activity. However, the promising DCR, TTP, and OS rates in these studies encouraged clinicians to explore the use of erlotinib in conjunction with other anticancer therapies. For example, erlotinib was administered in combination with bevacizumab in 6 phase II trials;<sup>9-14</sup> among these 6 trials, 4 phase II trials were included in another systematic review on bevacizumab performed by Fang et al.<sup>17</sup> Erlotinib has also been combined with docetaxel in another study,<sup>15</sup> and with sorafenib in a phase III RCT.<sup>16</sup> Only 2 studies,<sup>9,10</sup> with overlapping study populations, showed superior RRs for the combination of bevacizumab with erlotinib when compared with erlotinib monotherapy.<sup>7,8</sup> However, other drug combinations did not show any significant benefits for RR.<sup>11-16</sup> Most of the drug combinations<sup>9-11,14-16</sup> showed similar or slightly better DCRs compared with erlotinib monotherapy,<sup>7,8</sup> except for the combinations used in the study by Govindarajan et al<sup>12</sup> and Yau et al,<sup>13</sup> both of which utilized bevacizumab. All combined therapy studies, except one with bevacizumab,<sup>12</sup> demonstrated similar or slightly improved PFS/TTP and OS rates compared with erlotinib monotherapy.<sup>7,8</sup>

None of the trials reported any unexpected toxicities, and most were grade 1 or 2 in severity. In the phase II studies, there were only 2 patient deaths; one was due to pneumonia<sup>11</sup> and deemed unrelated to treatment, and the other was due to gastrointestinal bleeding that

occurred during study, but whether it was treatment-related was not disclosed.<sup>9</sup> Overall, the number of withdrawals due to AEs was low. In the phase III RCT, the difference in the death or withdrawal rates between the 2 study groups was not significant, suggesting that most were related to sorafenib rather than erlotinib.<sup>16</sup> Therefore, the safety analysis in these reports suggested that erlotinib was safe and well-tolerated.

Although sorafenib is the only approved standard treatment for advanced HCC, the survival benefit is relatively modest according to 2 studies.<sup>18,19</sup> In the SHARP trial,<sup>18</sup> the DCR and median OS rates were 43% and 10.7 months, and in the Asia-Pacific region phase III RCT, they were 35.3% and 6.5 months.<sup>19</sup> Overall, the effect of erlotinib for the treatment of advanced HCC in all the trials evaluated in this present study, except for that of Yau et al,<sup>12</sup> is comparable with that of sorafenib.<sup>18,19</sup> Yau et al<sup>12</sup> reported that none of their enrolled 10 patients, who were resistant to sorafenib, responded to the therapeutic combination of erlotinib and bevacizumab. This conclusion suggested that patients who were resistant to sorafenib would not obtain any clinical benefit from treatment with erlotinib or bevacizumab, and the trial was terminated early due to poor patient response. For this reason, the data from that study should be interpreted with caution. However, Kaseb et al<sup>10</sup> indicated that PFS and OS in response to erlotinib plus bevacizumab were shorter in those previously treated with sorafenib (PFS of 6.7 months and OS of 9.6 months) when compared with treatment-naïve patients (PFS of 7.4 months and OS of 15.0 months). This might suggest further that in sorafenib non-responders, erlotinib plus bevacizumab may not be an appropriate treatment regimen.

Sorafenib can block vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor signaling,<sup>20,21</sup> whereas erlotinib blocks EGFR signaling;<sup>6</sup> it was hoped that the combination might have a synergistic anticancer effect. Because the combination of erlotinib and sorafenib showed promising antitumor efficacy in a phase I trial,<sup>22</sup> and erlotinib showed moderate efficacy in phase II studies,<sup>7,8</sup> phase II trials were skipped and a phase III trial was performed directly. Finally, this combination provided no synergistic benefit.<sup>16</sup> In this study, we used SEARCH trial,<sup>16</sup> erlotinib plus sorafenib as a first-line treatment in advanced HCC patients had similar OS ( $p=0.408$ ) and TTP ( $p=0.18$ ) outcomes compared with placebo plus sorafenib. Possible reasons for the failure of this trial to produce any meaningful effect in advanced HCC patients might be explained by the findings of

a study conducted by Sieghart et al<sup>23</sup> in a rat model of HCC. Sieghart et al<sup>23</sup> found that treatment with erlotinib and sorafenib was not superior to the effect of sorafenib alone in vitro or in vivo, suggesting a lack of any synergistic or additive effect between the 2 drugs. However, they also suggested that erlotinib-induced VEGF expression might have contributed to the failure of the combination therapy.<sup>23</sup> This trial demonstrates that we should perform research systematically following the study-design strategy guidelines, instead of carry out large-scale phase III trials without a clear signal of efficacy from earlier-phase studies.

HCC trials are characterized by study population heterogeneity and are, therefore, complex to interpret and dissect.<sup>18</sup> Drugs that target all HCC subtypes will need to be explored, and there is room for such drugs, especially for the second-line or third-line treatments. There is an intensive requirement for valid biomarkers to enable selection of suitable subgroups of HCC patients who would be more likely to achieve an objective response to specific anticancer agents.<sup>24</sup> For example, erlotinib efficacy is affected by the T790M mutation in the EGFR kinase in non-small-cell lung cancer.<sup>25</sup> Therefore, such cases should encourage analogous studies with biomarkers to predict erlotinib efficacy in future phase III trials.

Moreover, sample augmentation or incorporation of a control arm in phase II studies would reduce selection bias and decrease the risk of random effects to obtain an impartial comparison for outcome analysis.<sup>18,26</sup> These approaches might reduce the possibility of negative outcomes for future phase III trials.

In all of the included trials, except 2 trials,<sup>9,10</sup> the objective response rate was low, but it may be inappropriate to apply this extremely stringent parameter. As alternative endpoints in these studies, DCR, PFS/TTP, and OS have thus been adopted. However, DCR, PFS/TTP, and OS are endpoints that reflect not only treatment effect but also tumor behavior.<sup>27</sup> Perhaps it would be better to use primary endpoints to measure the treatment effect of erlotinib.

All of the previous observations remind us to optimize the design of trials, augment sample size, select sensitive subset populations, and use better primary endpoints in order to improve the therapeutic effect in patients with advanced HCC.

There are some limitations in the present systematic review. First, publication bias may affect this area of study and research. In this systematic review, data for one study<sup>15</sup> were derived from an abstract because the full-text publication could not be identified, preventing

a more in-depth analysis. Second, heterogeneity among trials could affect the validity of the present results. Only one study was an RCT, and most of phase II studies had no head-to-head comparisons. Furthermore, heterogeneity may exist owing to the differences in patients' characteristics, drug dosages, and treatment regimens, which impedes comparisons between studies. Third, there could be discrepancies in the measurement of outcome measures. For example, PFS is frequently confused with TTP,<sup>28</sup> and an unequivocal definition of PFS is seldom provided.

In conclusion, these results are encouraging, and suggest that erlotinib may be a relatively efficacious and well-tolerated treatment for advanced HCC. Owing to the small sample size and lack of controls, this conclusion is not definitive. Although the efficacy of erlotinib was not confirmed in the sole phase III trial, it should not be discarded as a possible treatment option and should be evaluated in future. Given the better overall survival observed in most phase II trials and because treatment of advanced HCC remains unstandardized and unsatisfactory, it is worth determining whether erlotinib can be of benefit to patients with advanced HCC. In future studies, further investigation of the underlying pathogenesis of HCC and exploration of sensitive subset populations are warranted to enhance the effect of erlotinib, thereby improving survival outcomes in patients with advanced HCC. Meanwhile, this systematic review has identified the need for more well-designed RCTs to evaluate the efficacy and safety of erlotinib as monotherapy and in combination with other drugs for advanced HCC.

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