ABSTRACT

Molecular target anticancer drugs are commonly used in various forms of cancers. It is a concern that the risk of serious adverse events (SAEs) and fatal adverse events (FAEs) of molecular target drugs are increasing. An up-to-date meta-analysis of all Phase II/III/IV randomized trials of molecular target anticancer drugs was conducted to calculate the increased risk of SAEs and FAEs. A systematic search of PubMed, Web of Science, and Cochrane Library up to April 6, 2017, was conducted. The study enrolled Phase II/III/IV randomized trials of cancer that compared molecular target drugs alone versus placebo or performed single-arm analysis of molecular target drugs. Data on SAEs and FAEs were extracted from the included studies and pooled to compute risk ratio (RR), the overall incidence, and 95% confidence interval (CI). In this meta-analysis, a total of 19,965 and 26,642 patients in randomized Phase II/III/III trials were included in the analysis of SAEs and FAEs associated with molecular target anticancer drug, respectively. There were significant differences in the relationship of molecular target anticancer drugs with SAEs (RR = 1.57, 95% CI = 1.35–1.82, P < 0.01) and FAEs (RR = 1.51, 95% CI = 1.19–1.91, P < 0.01, I² = 0%) compared to placebo. The overall incidence of SAEs and FAEs was 0.269 (95% CI = 0.262–0.276, P < 0.01) and 0.023 (95% CI = 0.020–0.025, P < 0.01), respectively. Molecular target anticancer drugs significantly increased the risk of SAEs and FAEs. For patients taking molecular target drugs, efforts are needed to prevent the occurrence of SAEs and FAEs.

KEY WORDS: Cancer, fatal adverse event, molecular target anticancer therapy, serious adverse event

INTRODUCTION

During the past two decades, the pharmacological approaches used in cancer therapy have changed extensively. Various deregulations within tumors and tumor microenvironments have helped to steer the direction of drug development in cancer.[1–3] The classical target of antineoplastic chemotherapy are the various steps of cell proliferation (DNA formation and function or the mitosis spindle).[4] Target therapy acts through several modalities that modulate or interact with cell membrane receptors (monoclonal antibodies), intracellular cascade pathways and signaling (small molecule tyrosine kinase inhibitors [TKIs]), or micro-environment factors associated with tumor vasculature or hypoxia.[5,6]

The monoclonal antibodies, rituximab or obinutuzumab, target the CD20 protein in malignant lymphoma,[7] and cetuximab targets epidermal growth factor receptor (EGFR) in colorectal cancer.[8,9] Another antibody, bevacizumab, which neutralizes vascular endothelial growth factor (VEGF) can suppress the blood supply and nutrition of growing tumor in several cancers such as breast cancer, colorectal cancer, and so on.[10,11] Imatinib, a TKI, was adopted to treat chronic myeloid leukemia[11] and acute lymphoblastic leukemia.[12] In addition, cancer cells could also be attacked by bispecific antibodies[13] and checkpoint inhibitors[14,15] through the activation of immune effectors and/or the reduction of their tolerance.

Molecular target therapies could substantially improve the outcome of patients with cancer in
daily practice. However, they could inevitably result in adverse effects such as nausea, emesis, and hair loss as well as serious adverse event (SAE) and fatal adverse event (FAE) such as thromboembolic events, bowel bleeding or perforation, and so on. SAE is defined as an adverse event that can result in death, life-threatening condition, hospitalization (short or prolonged), disability or permanent damage, and congenital anomaly or birth defect. Furthermore, it is an event that requires an intervention to prevent permanent impairment or damage, or any other adverse event that may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. FAE is defined as death caused in all likelihood by a drug.

To better understand, the overall risk of both SAEs and FAEs with molecularly target therapy, a meta-analysis of published Phase II/III trials was conducted to analyze if molecularly target anticancer therapy is connected with an increased incidence of SAEs and FAEs in patients with cancer.

**METHODS**

**Literature search strategy**

Cochrane Library, PubMed, and Web of Science were searched up to April 6, 2017. The search strategy was “afatinib or bevacizumab or brentuximab or bosutinib or cabozantinib or dabrafenib or dasatinib or docetaxel or erlotinib or everolimus or exemestane or gemcitabine or imatinib or ipilimumab or lapatinib or letrozole or methotrexate or mitumprotimut-T or neratinib or nilotinib or octreotide or pazopanib or ramucirumab or regorafenib or sorafenib or sunitinib or temsirolimus or trametinib or vandetanib or vorinostat.” We retrieved all eligible studies and checked their reference lists for additional relevant publications.

**Inclusion criteria**

Studies on the comparison between molecularly target anticancer drugs in combination with chemotherapy or biological therapy and chemotherapy or biological alone were eligible for inclusion. Studies that met all the following criteria were included: (i) prospective phase II, III or IV trials involving cancer patients; (ii) random assignment of participants to molecularly target anticancer therapy or control; and (iii) available data regarding SAEs or FAEs.

**Exclusion criteria**

The exclusion criteria were as follows: (i) not Phase II/III/IV randomized controlled trials; (ii) ongoing studies; (iii) review articles; and (iv) studies not within drug combination.

**Data extraction**

As for each study, the following information was extracted: year of publication, the first author’s surname, molecular target drug, the events of FAEs and SAEs, number of subjects, tumor type, and journal. Data extraction and information on study design and outcomes were performed by two independent reviewers. Any disagreements between reviewers were resolved by discussion and consensus with a third reviewer.

**Statistical analysis**

Effect estimates were analyzed with Review Manager 5.3 (Cochrane, Northern Europe), and single-arm analysis was performed with Comprehensive meta-analysis V2 (Biostat, Inc., USA and UK). The risk ratio (RR) was calculated with molecular target drug as baseline subtype, and their 95% confidence interval (CI) for each result was computed. Forest plots were generated for graphical presentations and heterogeneity was appraised by Q statistics and I² estimates. When effects were heterogeneous (I² > 50%), randomized effects model was carried out; otherwise, the fixed-effects model was used. Publication/reporting bias was visually evaluated by funnel plot. The difference was statistically significant when P < 0.05.

**RESULTS**

**Literature search**

As presented in Figure 1, 785 articles containing our search terms were obtained after the duplicates were removed. In these studies, based on titles or abstracts screening, 382 were excluded for nonrandom studies and 27 were excluded for reviews. The rest 221 studies were retrieved for full-text review, from which 89 articles were excluded for not reporting FAEs.
or SAEs and 30 were excluded for drug combination. Finally, 102 studies met the inclusion criteria and were included in the meta-analysis.

**Characteristics of included studies**
In this meta-analysis, few studies (9%) reported only adverse events above severity, 7% did not specify the criteria that was used to select which adverse events were reported. The brief description of included monoclonal antibodies was listed in Supplementary Table 1. The detailed characteristics of included studies for SAE and FAE were listed in Supplementary Table 2 and Supplementary Table 3, respectively. A total of 19,965 and 26,642 patients in randomized 53 and 65 Phase II/II/IV trials were included in the analysis of SAEs and FAEs in this meta-analysis, respectively. There were 4192 total SAEs and 330 total FAEs among the included patients. For SAEs, there were lung cancer (15 studies), head and neck carcinoma (1 study), renal cell carcinoma (4 studies), leukemia (2 studies), thyroid cancer (2 studies), prostate cancer (1 study), breast cancer (7 studies), angioimmunoblastic (1 study), pancreatic neuroendocrine tumor (2 studies), astrocytoma (1 study), pancreatic cancer (1 study), gastrointestinal tumor (6 studies), neuroendocrine tumor (1 study), soft-tissue sarcoma (1 study), hepatocellular carcinoma (7 studies), and myeloma (1 study).

The underlying malignancies involved in FAEs were lung cancer (20 studies), renal cell carcinoma (8 studies), myeloma (1 study), lymphoma (7 studies), melanoma (7 studies), prostate cancer (3 studies), leukemia (7 studies), neuroendocrine tumors (1 study), breast cancer (3 studies), astrocytomas (1 study), pancreatic neuroendocrine tumor (3 studies), gastrointestinal cancer (4 studies), hepatocellular cancer (6 studies), and thyroid cancer (3 studies).

**Study quality**
The quality of each enrolled study was graded by the Newcastle-Ottawa scale that provides a score from 0 to 9 for each study (a score of 6–9 indicated a good quality study). As presented in Supplementary Table 4, all the studies enrolled in this study were of good quality with scores of 6, 7, or 8.

**Risk ratio of serious adverse events**
Twenty-eight randomized trials were enrolled to analyze the SAEs of molecular target anticancer drugs compared with placebo [Table 1]. As shown in Figure 2, there was significant difference between molecular target anticancer drugs and placebo in terms of SAEs (RR = 1.57, 95% CI = 1.35–1.82, \( P < 0.01, \ P = 81\% \)) without bias [Supplementary Figure 1]. The results indicated that there was an increased risk of SAEs related to molecular target drugs compared with placebo. There was a significant difference in the incidence of SAEs with sorafenib (RR = 1.68, 95% CI = 1.21–2.35, \( P < 0.01, \ P = 85\% \)), erlotinib (RR = 2.13, 95% CI = 1.63–2.77, \( P < 0.01, \ P = 0\% \)), and everolimus (RR = 2.70, 95% CI = 1.05–6.94, \( P = 0.04, \ P = 95\% \)) compared to placebo, respectively, without bias [Supplementary Figure 2]. However, no significant difference was observed between regorafenib and placebo (RR = 1.15, 95% CI = 0.98–1.34, \( P = 0.08, \ P = 0\% \)) [Figure 3].

As shown in Figure 4, in single-arm analysis, there was a significant difference with molecular target drugs (event rate [ER] = 0.269, 95% CI = 0.262–0.276, \( P < 0.01 \)) with bias [Supplementary Figure 3]. Significant difference was observed in afatinib (ER = 0.241, 95% CI = 0.216–0.269, \( P < 0.01 \)), axitinib (ER = 0.339, 95% CI = 0.275–0.409, \( P < 0.01 \)), bosutinib (ER = 0.327, 95% CI = 0.271–0.387, \( P < 0.01 \)), cabozantinib (ER = 0.421, 95% CI = 0.366–0.488, \( P < 0.01 \)), dacotinib (ER = 0.118, 95% CI = 0.091–0.152, \( P < 0.01 \)), dasatinib (ER = 0.493, 95% CI = 0.458–0.529, \( P < 0.01 \)), docetaxel (ER = 0.070, 95% CI = 0.053–0.092, \( P < 0.01 \)), erlotinib (ER = 0.263, 95% CI = 0.245–0.282, \( P < 0.01 \)), everolimus (ER = 0.382, 95% CI = 0.351–0.415, \( P < 0.01 \)), exemestane (ER = 0.121, 95% CI = 0.086–0.169, \( P < 0.01 \)), gemcitabine (ER = 0.455, 95% CI = 0.383–0.549, \( P < 0.01 \), imatinib (ER = 0.187, 95% CI = 0.145–0.238, \( P < 0.01 \), lapatinib (ER = 0.074, 95% CI = 0.062–0.088, \( P < 0.01 \), letrozole (ER = 0.004, 95% CI = 0.000–0.057, \( P < 0.01 \), mohetrexate (ER = 0.113, 95% CI = 0.072–0.171, \( P < 0.01 \), neratinib (ER = 0.073, 95% CI = 0.060–0.087, \( P < 0.01 \), nilotinib (ER = 0.046, 95% CI = 0.034–0.061, \( P < 0.01 \), octreotide (ER = 0.042, 95% CI = 0.022–0.079, \( P < 0.01 \), pazopanib (ER = 0.402, 95% CI = 0.346–0.460, \( P = 0.01 \), ramucirumab (ER = 0.440, 95% CI = 0.383–0.499, \( P < 0.01 \), regorafenib (ER = 0.327, 95% CI = 0.299–0.355, \( P < 0.01 \), sorafenib (ER = 0.271, 95% CI = 0.254–0.288, \( P < 0.01 \), temsirolimus (ER = 0.410, 95% CI = 0.350–0.472, \( P < 0.01 \), trametinib (ER = 0.372, 95% CI = 0.277–0.479, \( P < 0.01 \), vandetanib (ER = 0.258, 95% CI = 0.225–0.294, \( P < 0.01 \), or vorinostat (ER = 0.413, 95% CI = 0.360–0.468, \( P < 0.01 \), compared to placebo [Figure 5].

**Risk ratio of fatal adverse events**
Thirty-seven randomized trials were included in the analysis of molecular target anticancer drugs compared to placebo [Table 2]. Among the 37 studies, there was a significant difference in the relationship of molecular target anticancer drug with FAEs (RR = 1.51, 95% CI = 1.19–1.91, \( P < 0.01, \ P = 0\% \)) compared to that with placebo [Figure 6]. The results suggested that there was an increased risk of FAEs related to molecular target drug compared with placebo. No bias was presented in funnel plot in Supplementary Figure 4. As presented in Figure 7, significant difference was observed between ipilimumab (RR = 4.41, 95% CI = 1.19–16.33, \( P = 0.03, \ P = 0\% \)) and erlotinib (RR = 2.25, 95% CI = 1.46–3.47, \( P < 0.01, \ P = 57\% \)) and placebo. No significant difference was observed between sunitinib (RR = 1.46, 95% CI = 0.34–6.28, \( P = 0.62, \ P = 0\% \)), vandetanib (RR = 1.04, 95% CI = 0.57–1.90, \( P = 0.90, \ P = 0\% \)), everolimus (RR = 1.01, 95% CI = 0.64–1.59, \( P = 0.97, \ P = 5\% \)), or sorafenib (RR = 1.80, 95% CI = 0.88–3.69, \( P = 0.11, \ P = 0\% \)) and placebo. However, there was a bias between ipilimumab or erlotinib and placebo while no bias was observed between other molecular target drugs and placebo [Supplementary Figure 5].
In single-arm analysis, there was a significant difference in molecular target anticancer drugs (ER = 0.023, 95% CI = 0.020–0.025, P < 0.01) [Figure 8] with bias [Supplementary Figure 6]. As shown in Figure 9, there was statistical significance in afatinib (ER = 0.005, 95% CI = 0.002–0.005, P < 0.001), bexacizimab (ER = 0.012, 95% CI = 0.003–0.045, P < 0.01), brentuximab (ER = 0.012, 95% CI = 0.003–0.045, P < 0.01), dabrafenib (ER = 0.003, 95% CI = 0.001–0.013, P < 0.01), dasatinib (ER = 0.014, 95% CI = 0.009–0.020, P < 0.01), erlotinib (ER = 0.048, 95% CI = 0.039–0.060, P < 0.01), everolimus (ER = 0.062, 95% CI = 0.039–0.068, P < 0.01), imatinib (ER = 0.011, 95% CI = 0.007–0.015, P < 0.01), ipilimumab (ER = 0.009, 95% CI = 0.006–0.015, P < 0.01).
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Figure 2: Forest plot of relative risk of serious adverse events associated with molecular target anticancer drugs versus control

| Study or Subgroup | Molecular target medicine | Placebo | Risk Ratio |
|-------------------|---------------------------|---------|-----------|
|                   | Events | Total | Events | Total | Weight | M.H. Random. 95% CI | M.H. Random. 95% CI |
| Akira Kawai 2016  | 110    | 271   | 32    | 139   | 4.7%   | 1.78 [1.26, 2.47] |
| Andrew X 2013     | 122    | 277   | 89    | 276   | 5.4%   | 1.37 [1.10, 1.70] |
| Ann-Li Cheng 2013 | 13     | 149   | 1     | 75    | 0.5%   | 6.04 [0.87, 40.00] |
| Arlene Chan 2016  | 193    | 1420  | 85    | 1420  | 5.1%   | 1.21 [0.92, 1.60] |
| Axel Grotzky 2013 | 219    | 500   | 100   | 253   | 5.6%   | 1.13 [0.92, 1.33] |
| Brose MS 2014     | 77     | 207   | 55    | 209   | 5.0%   | 1.41 [1.06, 1.88] |
| Camillo Porto 2015| 83     | 227   | 66    | 139   | 5.3%   | 0.77 [0.60, 0.98] |
| Catherine Lombard-Bahs 2015 | 48 | 207  | 4    | 203  | 1.7% | 11.77 [4.32, 32.04] |
| David Neal Franz 2013 | 60 | 78   | 4    | 82   | 1.8% | 4.75 [1.63, 12.35] |
| Escudier B 2009   | 154    | 451   | 110   | 451   | 5.5%   | 1.40 [1.14, 1.72] |
| Fabrice André 2014 | 117   | 284   | 55    | 285   | 5.1%   | 2.13 [1.62, 2.81] |
| George D Demetri 2012 | 38 | 132   | 14   | 146   | 3.5% | 1.36 [0.78, 2.32] |
| Jin Li 2015       | 43     | 136   | 18    | 154   | 3.9%   | 1.19 [0.75, 1.91] |
| Jin Soo Lee 2012  | 180    | 620   | 63    | 603   | 5.2%   | 1.24 [0.96, 1.61] |
| John C Araujo 2013| 376    | 762   | 317   | 760   | 5.9%   | 1.19 [0.96, 1.43] |
| Jordi Bruix 2015  | 52     | 559   | 14    | 549   | 3.2%   | 3.65 [2.05, 6.50] |
| Josep M Llovet 2008 | 153  | 297   | 184   | 302   | 5.0%   | 0.95 [0.82, 1.10] |
| Jun Yao 2015      | 30     | 44    | 7     | 35    | 2.7%   | 3.88 [2.02, 7.85] |
| Karen Kelly 2013  | 15     | 612   | 5     | 617   | 1.7%   | 1.88 [0.81, 4.57] |
| Katrin Hoffmann 2015 | 3   | 24    | 3     | 25    | 0.9%   | 1.04 [0.23, 4.66] |
| Masatoshi Kudo 2011 | 41   | 229   | 20    | 249   | 3.7%   | 2.03 [1.23, 3.36] |
| Paul E Goss 2013  | 99     | 1573  | 77    | 1574  | 5.0%   | 1.29 [0.96, 1.72] |
| Rossella Elisei 2013 | 90 | 214   | 25    | 189   | 4.4% | 1.83 [1.26, 2.68] |
| Scagliotti G 2010 | 78     | 436   | 39    | 459   | 4.5%   | 2.11 [1.47, 3.02] |
| Vincent A Miller 2012 | 30 | 390   | 195   | 505   | 0.5% | 15.00 [9.06, 109.18] |
| Yi-Long Wu 2014   | 4      | 59    | 0     | 63    | 0.3%   | 9.80 [0.53, 174.55] |
| Yoshito Komatsu 2014 | 33  | 132   | 13    | 145   | 3.3% | 1.27 [0.72, 2.24] |
| Total (95% CI)    | 10290  | 8632  | 100%  | 16320 | 1.57 [1.35, 1.82] |
| Total events      | 2334   | 1381  |       |       |        |

Heterogeneity: Tau² = 0.10; Chi² = 136.06, df = 26 (P < 0.0001); I² = 81%

Test for overall effect: Z = 5.82 (P < 0.0001)

P < 0.01), lapatinib (ER = 0.000, 95% CI = 0.000–0.005, P < 0.01), mitumprotimut-T (ER = 0.003, 95% CI = 0.000–0.004, P < 0.01), neratinib (ER = 0.003, 95% CI = 0.001–0.007, P < 0.01), nilotinib (ER = 0.013, 95% CI = 0.007–0.022, P < 0.01), pazopanib (ER = 0.006, 95% CI = 0.002–0.015, P < 0.01), sorafenib (ER = 0.013, 95% CI = 0.009–0.018, P < 0.01), sunitinib (ER = 0.018, 95% CI = 0.013–0.024, P < 0.01), vandetanib (ER = 0.035, 95% CI = 0.024–0.049, P < 0.01), and vorinostat (ER = 0.013, 95% CI = 0.005–0.033, P < 0.01).

DISCUSSION

The development of molecular target anticancer therapy, which was accelerated by the development of cancer biology, has presented impressive clinical advances with regards to efficacy and prognosis. However, although it seems that the actions of molecular target drugs on the preoncogenic pathways or molecules associated with tumor growth and survival may not always cause therapy-related SAEs and FAEs, the therapy-related SAEs and FAEs increased in recent studies. The risk of therapy-related SAEs and FAEs among cancer patients in Phase II/III/IV randomized trials of molecular target anticancer drugs were increased by 49% and 82%, respectively, with sorafenib in a study by Llovet et al.\[19\] and Porta et al.\[20\]. Moreover, the study by Porta et al.\[20\] indicated that a molecular target drug was effective and tolerable in elderly patients with metastatic renal cell carcinoma. For SAEs, significant difference was only observed between erlotinib or everolimus and placebo. Previous studies showed that everolimus was associated with a significantly risk of mucocutaneous toxicities (all-grade stomatitis, skin rash, and pruritus and mouth ulceration),\[21\] metabolic complications (all-grade and high-grade hyperglycemia, hypertriglyceridemia, and hypercholesterolemia),\[22\] and FAEs,\[23\] which was consistent with the outcome of our study. Furthermore, significant differences in the incidence of FAEs were only observed with ipilimumab and erlotinib when compared to placebo. Consistent with our meta-analysis, the previous study by Zhu et al.\[24\] indicated that ipilimumab is more associated with an increased risk of FAEs in cancer patients compared to control or placebo.\[24\] Interestingly, only erlotinib, one of the EGFR inhibitors, showed a significant difference in the incidence of both FAEs and SAEs compared to placebo.\[24\]
Figure 3: Forest plot of relative risk of serious adverse events associated with molecular target anticancer drugs versus control in subgroup analysis.

Studies by Llovet et al.\textsuperscript{[19]} and Hoffmann et al.\textsuperscript{[28]} indicated that the safety profile of the sorafenib group was similar to that of the placebo group, which was different from the outcome of our result. The heterogeneity in the subgroup analysis of everolimus was addressed in a study conducted by Porta et al. which showed that everolimus was generally well tolerated in elderly patients with metastatic renal cell carcinoma, and most adverse events were grade 1 or 2 in severity rather than SAEs.\textsuperscript{[20]} Although no heterogeneity was observed in the analysis of the included molecular target drugs and the subgroup analysis of ipilimumab for FAEs, there was heterogeneity in the subgroup analysis of erlotinib compared to placebo, from the study by Kelly et al.\textsuperscript{[29]} Interestingly, no heterogeneity was observed in the subgroup analysis of SAEs in erlotinib compared to placebo. In a single-arm analysis, for both SAEs and FAEs, there was a significant difference in molecular target drug, which suggested that molecular target could increase the
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Figure 4: Forest plot of relative risk of serious adverse events associated with molecular target anticancer drugs versus control in single-arm analysis
### Figure 5: Forest plot of relative risk of serious adverse events associated with molecular target anticancer drugs versus control in single-arm subgroup analysis
**Table 2: Characteristics of 27 random trials enrolled to analyze FAEs of molecular target anticancer drug compared with placebo**

| Author                  | Molecular target medicine | FAE | Overall | Tumor type                      | Journal                      | Serial number* |
|-------------------------|---------------------------|-----|---------|----------------------------------|------------------------------|----------------|
| Vincent A Miller 2012   | Apatinib                  | 395 | 2       | Lung adenocarcinoma              | The lancet oncology          | 4              |
|                          | Placebo                   | 195 | 0       | Lung adenocarcinoma              | The lancet oncology          | 4              |
| Craig H Moskowitz 2015  | Brentuximab               | 165 | 1       | Hodgkin’s lymphoma               | The lancet oncology          | 44             |
|                          | Placebo                   | 164 | 0       | Hodgkin’s lymphoma               | The lancet oncology          | 44             |
| John C Araujo 2013      | Dasatinib                 | 762 | 6       | Prostate cancer                  | The lancet oncology          | 9              |
|                          | Placebo                   | 760 | 4       | Prostate cancer                  | The lancet oncology          | 9              |
| Ronald P DeMatteo 2009  | Imatinib                  | 359 | 5       | Gastrointestinal stromal tumour  | The lancet oncology          | 45             |
|                          | Placebo                   | 354 | 0       | Gastrointestinal stromal tumour  | The lancet oncology          | 45             |
| Jin Li 2015             | Regorafenib               | 136 | 2       | Colorectal cancer                | The lancet oncology          | 26             |
|                          | Placebo                   | 68  | 0       | Colorectal cancer                | The lancet oncology          | 26             |
| M. Dror Michaelson 2013 | Sunitinib                 | 584 | 4       | Prostate Cancer                  | J Clin oncol                 | 46             |
|                          | Placebo                   | 289 | 2       | Prostate Cancer                  | J Clin oncol                 | 46             |
| George D. Demetri 2012  | Sunitinib                 | 228 | 4       | Gastrointestinal Stromal Tumor   | Clin Cancer Res              | 47             |
|                          | Placebo                   | 114 | 0       | Gastrointestinal Stromal Tumor   | Clin Cancer Res              | 47             |
| Sophie Leboulleux 2012  | Vandetanib                | 72  | 2       | Thyroid cancer                   | The lancet oncology          | 48             |
|                          | Placebo                   | 73  | 1       | Thyroid cancer                   | The lancet oncology          | 48             |
| Jin Soo Lee 2012         | Vandetanib                | 619 | 24      | Non small cell lung cancer       | J Clin oncol                 | 36             |
|                          | Placebo                   | 303 | 12      | Non small cell lung cancer       | J Clin oncol                 | 36             |
| Samuel A. Wells Jr 2011 | Vandetanib                | 231 | 5       | Medullary Thyroid Cancer         | J Clin oncol                 | 58             |
|                          | Placebo                   | 99  | 2       | Medullary Thyroid Cancer         | J Clin oncol                 | 58             |
| Katrin Hoffmann 2015     | Sorafenib                 | 24  | 0       | Hepatocellular carcinoma         | BMC Cancer                   | 32             |
|                          | Placebo                   | 25  | 0       | Hepatocellular carcinoma         | BMC Cancer                   | 32             |
| Jordi Bruix 2015         | Sorafenib                 | 559 | 4       | Hepatocellular carcinoma         | The lancet oncology          | 30             |
|                          | Placebo                   | 548 | 2       | Hepatocellular carcinoma         | The lancet oncology          | 30             |
| Marcia S Brose 2014      | Sorafenib                 | 207 | 1       | Thyroid cancer                   | The lancet oncology          | 91             |
|                          | Placebo                   | 209 | 1       | Thyroid cancer                   | The lancet oncology          | 91             |
| Masatoshi Kudo 2011      | Sorafenib                 | 229 | 0       | Hepatocellular carcinoma         | Eur J Cancer                 | 33             |
|                          | Placebo                   | 227 | 0       | Hepatocellular carcinoma         | Eur J Cancer                 | 33             |
| Giorgio Scagliotti 2015  | Sorafenib                 | 436 | 13      | Non small cell lung cancer       | J Clin oncol                 | 92             |
|                          | Placebo                   | 459 | 4       | Non small cell lung cancer       | J Clin oncol                 | 92             |
| Ann-Lii Cheng 2009       | Sorafenib                 | 149 | 0       | Hepatocellular carcinoma         | The lancet oncology          | 40             |
|                          | Placebo                   | 75  | 0       | Hepatocellular carcinoma         | The lancet oncology          | 40             |
| Bernad Escudier 2009     | Sorafenib                 | 451 | 0       | Renal Cell Carcinoma             | N ENGL J MED                 | 90             |
|                          | Placebo                   | 451 | 0       | Renal Cell Carcinoma             | N ENGL J MED                 | 90             |
| Llovet JM 2008           | Sorafenib                 | 297 | 0       | Hepatocellular carcinoma         | N ENGL J MED                 | 31             |
|                          | Placebo                   | 302 | 0       | Hepatocellular carcinoma         | N ENGL J MED                 | 31             |
| James C Yao 2016         | Everolimus                | 202 | 7       | Neuroendocrine tumours           | The lancet oncology          | 79             |
|                          | Placebo                   | 98  | 3       | Neuroendocrine tumours           | The lancet oncology          | 79             |
| Robert J Motzer 2008     | Everolimus                | 272 | 26      | Renal Cell Carcinoma             | The lancet oncology          | 80             |
|                          | Placebo                   | 138 | 18      | Renal Cell Carcinoma             | The lancet oncology          | 80             |
| Fabrice André 2014       | Everolimus                | 284 | 2       | Breast cancer                    | The lancet oncology          | 82             |
|                          | Placebo                   | 285 | 2       | Breast cancer                    | The lancet oncology          | 82             |
| Jun Yao 2014             | Placebo                   | 35  | 0       | Pancreatic neuroendocrine tumors | Med Oncol                    | 63             |
|                          | Everolimus                | 44  | 0       | Pancreatic neuroendocrine tumors | Med Oncol                    | 63             |
| Catherine                | Everolimus                | 207 | 6       | Pancreatic neuroendocrine tumors | Pancreas                     | 39             |
| Lombard-Bohas 2015       | Placebo                   | 203 | 2       | Pancreatic neuroendocrine tumors | Pancreas                     | 39             |
| James C Yao 2011         | Everolimus                | 207 | 7       | Pancreatic neuroendocrine tumors | N ENGL J MED                 | 81             |
|                          | Placebo                   | 203 | 1       | Pancreatic neuroendocrine tumors | N ENGL J MED                 | 81             |
| David Neal Franz 2013    | Everolimus                | 0   | 78      | Astrocytomases                   | The lancet oncology          | 99             |
|                          | Placebo                   | 0   | 39      | Astrocytomases                   | The lancet oncology          | 99             |
| Eugene D Kwon 2014       | Ipilimumab                | 399 | 3       | Prostate cancer                  | The lancet oncology          | 83             |
|                          | Placebo                   | 400 | 0       | Prostate cancer                  | The lancet oncology          | 83             |
| Alexander M M            | Ipilimumab                | 471 | 4       | Prostate cancer                  | The lancet oncology          | 83             |
| Eggermont 2015           | Placebo                   | 474 | 0       | Prostate cancer                  | The lancet oncology          | 83             |
| Thomas J. Lynch 2012     | Ipilimumab                | 70  | 1       | Non small cell lung cancer       | J Clin oncol                 | 85             |
|                          | Placebo                   | 66  | 1       | Non small cell lung cancer       | J Clin oncol                 | 85             |
| M. Reck 2012             | Ipilimumab                | 44  | 1       | Small cell lung cancer           | Ann Oncl                     | 86             |
|                          | Placebo                   | 42  | 0       | Small cell lung cancer           | Ann Oncl                     | 86             |
| A.M.M. Eggermont 2016    | Ipilimumab                | 475 | 5       | Melanoma                        | N ENGL J MED                 | 87             |
|                          | Placebo                   | 476 | 0       | Melanoma                        | N ENGL J MED                 | 87             |
| Ulrich Gatzemeier 2015   | Ipilimumab                | 580 | 8       | Non small cell lung cancer       | J Clin oncol                 | 75             |
|                          | Placebo                   | 579 | 1       | Non small cell lung cancer       | J Clin oncol                 | 75             |
| Karen Kelly 2013         | Ipilimumab                | 612 | 7       | Non small cell lung cancer       | J Clin oncol                 | 60             |
|                          | Placebo                   | 342 | 0       | Non small cell lung cancer       | J Clin oncol                 | 60             |
| Ken Y 2016               | Ipilimumab                | 527 | 53      | Non small cell lung cancer       | Journal of thoracic oncology | 101            |
|                          | Placebo                   | 533 | 7       | Non small cell lung cancer       | Journal of thoracic oncology | 101            |

Contd...
Table 2: Contd...

| Author                  | Molecular target medicine | FAE | Overall | Tumor type   | Journal               | Serial number* |
|-------------------------|----------------------------|-----|---------|--------------|-----------------------|----------------|
| Meletios Dimopoulos    | Vorinostat                 | 315 | 4       | Melanoma     | The lancet oncology   | 88             |
| 2013                    | Placebo                    | 320 | 5       | Melanoma     | The lancet oncology   | 88             |
| Arnold Freedman 2013    | Mitumprotimut-T            | 174 | 0       | B-cell lymphoma | J Clin oncol         | 89             |
|                         | Placebo                    | 175 | 0       | B-cell lymphoma | J Clin oncol         | 89             |
| Paul E Goss 2013        | Lapatinib                  | 1573| 0       | Breast cancer | The lancet oncology   | 64             |
|                         | Placebo                    | 1574| 0       | Breast cancer | The lancet oncology   | 64             |
| Arlene Chan 2016        | Neratinib                  | 1420| 4       | Breast cancer | The lancet oncology   | 65             |
|                         | Placebo                    | 1420| 3       | Breast cancer | The lancet oncology   | 65             |

*The serial number of included studies presented in Supplementary Material.

Figure 6: Forest plot of relative risk of fatal adverse events associated with molecular target anticancer drugs versus control

risk of SAEs and FAEs. Eleven and nineteen molecular target drugs were analyzed for SAEs and FAEs, respectively. Both FAEs and SAEs were estimated with EGFR inhibitors. With regards to SAEs, the incidence was much higher than that of FAEs, and letrozole had the lowest incidence (0.4%). The incidence of FAEs with the EGFR inhibitors was below 1.5% with erlotinib having the highest incidence. It was reported that EGFR-TKI was associated with the mitigation of the risk for certain types of toxicity like interstitial lung disease while afatinib was associated with a higher frequency of rash and
Figure 7: Forest plot of relative risk of fatal adverse events associated with molecular target anticancer drugs versus control in subgroup analysis.
Figure 8: Forest plot of relative risk of fatal adverse events associated with molecular target anticancer drugs versus control in single-arm analysis.
Figure 9: Forest plot of relative risk of fatal adverse events associated with molecular target anticancer drugs versus control in single-arm subgroup analysis.
diarrhea of grade ≥3 and gefitinib was associated with a higher frequency of hepatotoxicity of grade ≥3 in patients with EGFR mutation-positivity NSCLC.\textsuperscript{[25]} The molecular drugs targeting VEGF receptor (VEGFR) as inhibitors and antibodies, also presented a significant increase in the risk of FAEs and SAEs. The highest incidence of SAEs was observed in prostate cancer patients treated with dasatinib, a TKI,\textsuperscript{[20]} whereas the lowest incidence was observed in patients treated with letrozole,\textsuperscript{[31]} an oral non-steroidal aromatase inhibitor. Previous meta-analyses illustrated that both VEGFR inhibitors and antibodies resulted in increased incidence of FAEs,\textsuperscript{[18,32,33]} which was consistent with the result of this meta-analysis. The highest incidence of FAEs (n = 26) was observed in patients treated with everolimus, an mTOR inhibitor, from the study conducted by Motzer et al. on renal cell carcinoma\textsuperscript{[34]} while the lowest incidence was observed in patients treated with lapatinib, an EGFR inhibitor.

When discussing the risk-benefit of molecular target anticancer therapy, evidence strength, benefit estimate, and the possibility of the incidence of SAEs and FAEs should be taken into account. This is the first meta-analysis to link molecular target anticancer drugs with an increased risk of both SAEs and FAEs in patients with cancer. This may help in decision-making by providing correlative information with regards to incidence and increased RR. The enrollment of well-conducted, good quality, Phase II/III/IV randomized trials was the strength of this meta-analysis. Besides, a large number of patients and recent studies were enrolled in our study. Moreover, well-selected studies were presented such that no heterogeneity was observed in the RR analysis of FAEs.

However, some limitations need to be acknowledged. First, the risk estimates at trial-level and confounders at patient-level excluded the outcomes to be generalized clinically. Second, bias might have been created by different therapy duration in the evaluation of RR with molecular target drugs. Third, SAEs and FAEs were not the primary endpoints of included trials, and SAEs and FAEs extracted by investigator might result in bias. Fourth, the data extracted represented only the pooled results. Last but not the least, with regard to SAEs, only one study was enrolled for the analysis of axitinib, bosutinib, cabozantinib, dasatinib, exemestane, letrozole, methotrexate, neratinib, octreotide, ramucirumab, temsirolimus, trtametinib, vandetanib, and vorinostat, in single-arm analysis. For FAEs, in single-arm analysis, only one study was included for the analysis of vorinostat, mitumprotimut-T, lapatinib, and neratinib. Therefore, more studies should focus on the relationship between temsirolimus, trametinib, vandetanib, or vorinostat and SAEs, and the relationship between vorinostat, mitumprotimut-T, lapatinib, or neratinib and FAEs.

In conclusion, molecular target anticancer drugs significantly increased the risk of SAEs and FAEs. For patients taking molecular target drugs, more effort is needed to prevent the incidence of SAEs and FAEs. It is crucial for physicians and patients to recognize the risk-benefit balance of molecular target drugs, and identify and treat the SAEs and FAEs associated with these drugs.

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**Conflicts of interest**

There are no conflicts of interest.

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