

## ORIGINAL RESEARCH

# The positive clinical therapeutically effects of Escin on advanced thyroid cancer

Jin-Yu Mei<sup>1,2</sup>, Ming-Jun Zhang<sup>3</sup>, Yuan-Yuan Wang<sup>4</sup> & Ye-Hai Liu<sup>1</sup> <sup>1</sup>Department of Otolaryngology, The First Hospital of Anhui Medical University, Hefei 230031, China<sup>2</sup>Department of Otolaryngology, The Second Hospital of Anhui Medical University, Hefei 230601, China<sup>3</sup>Department of Oncology, The Second Hospital of Anhui Medical University, Hefei 230601, China<sup>4</sup>Department of Pharmacy, The Second Hospital of Anhui Medical University, Hefei 230601, China**Keywords**

Advanced thyroid cancer, Escin, pharmacokinetics, side effects

**Correspondence**

Ye-Hai Liu, Department of Otolaryngology, The First Hospital of Anhui Medical University, Jixi Road, Hefei 230031, Hefei, China.

Tel: +86 13345515659;

Fax: +86-13345515659;

E-mail: Liuyehai666@163.com

Received: 18 November 2016; Revised: 2 January 2017; Accepted: 16 January 2017

**Cancer Medicine 2017; 6(5):937–943**

doi: 10.1002/cam4.1031

**Abstract**

The incidences of thyroid cancer keep rising worldwide over the past few decades. Although most thyroid cancers are indolent and highly curable, the treatment for advanced thyroid cancer remains challengeable in clinical practice. We performed two separate cohorts to evaluate the safety and efficiency of Escin in patients with advanced thyroid cancer. In cohort 1, 120 patients were divided into four groups equally and were administrated with placebo or different dosages of Escin. The pharmacokinetics of Escin and the side effects were evaluated. In cohort 2, 120 patients were treated with Escin. Several biomarkers related to the progression of thyroid cancer were evaluated. Kaplan–Meier (KM) analyses were performed to evaluate progression-free survival (PFS) and overall survival (OS). The serum Escin concentrations were stable during the treatment. Escin (0.6 mg/kg/day for 9 days, intravenous injection) was tolerable for patients with thyroid cancer. Escin significantly reduced the serum levels of TSH, TgAb, Tg, and calcitonin and prolonged the PFS and OS for patients with advanced thyroid cancer. This study showed Escin is efficient and well tolerated in patients with advanced thyroid cancer. Future studies are needed to investigate the mechanism of Escin on thyroid cancer and the proper dosage of Escin clinically.

**Introduction**

The incidences of thyroid cancer keep rising worldwide over the past few decades. Nowadays, thyroid cancer is the eighth and the fifth most common cancer in women in the China [1] and USA [2], respectively. An estimated around 67,778 and 62,000 new female cases occurred in China [1] and USA [2] annually. In China, this rapid increased incidence of thyroid cancer might owe to the development of screening techniques and iodine salt supplementation [3]. The first choice of treatments in nearly all patients with thyroid cancer is surgery, with most patients undergoing total (86%) or partial (12%) thyroidectomy [4]. The following options of treatments are radioactive iodine (I-131) for papillary or follicular thyroid cancer [5] and radiation therapy for medullary thyroid cancer. The prognosis of thyroid cancer is good among

all types of cancer. A recent statistical analysis showed the overall 5-year survival rate for patients with thyroid cancer who were diagnosed during 2005 through 2011 is 98% [4]. Although most thyroid cancers are indolent and highly curable, the treatment for advanced thyroid cancer remains challengeable in clinical practice.

Many studies have shown multiply oncogenic pathways are involved with the tumor genesis, therapy resistance, and recurrence of thyroid cancer, such as the MAPK signaling pathway [6], the PI3K-AKT signaling pathway [7], the NF- $\kappa$ B signaling pathway [8], the WNT- $\beta$ -catenin signaling pathway [9], and the thyroid-stimulating hormone receptor signaling pathway [10]. Utilizing the kinase inhibitors related to these signaling pathways for advanced thyroid cancer was carefully examined in the past few years. FDA has already approved many kinase inhibitors for advanced thyroid cancer treatment, such as sorafenib

[11] and lenvatinib [12] for advanced differentiated thyroid cancer; vandetanib [13] and cabozantinib [14] for advanced medullary thyroid cancer; and vemurafenib [15] and lenvatinib [16] for anaplastic thyroid cancer. Although many targeted therapy drugs are developed and applied for advanced thyroid cancer treatment, the 5-year relative survival rates of anaplastic thyroid cancer most of whom are advanced stage are low to 9% [4]. Thus, more agents for advanced thyroid cancer treatment are still needed to be investigated.

Escin is a natural mixture of pentacyclic triterpenoid which is isolated from the seeds of *Aesculus hippocastanum* [17]. Escin has shown multiply pharmacological effects including anti-inflammatory, vascular protection, and a venotonic effect [18]. In traditional Chinese medicine, Escin is widely used for the treatment of cerebral edema, and chronic venous insufficiency, among other conditions [19], while recent studies showed Escin might have antitumor effects as well. Ciftci and his colleagues [20] found Escin reduced cell proliferation and induces apoptosis on glioma and lung adenocarcinoma cell lines; Wang et al. [21] found Escin suppressed the metastasis of triple-negative breast cancer cells through inhibiting epithelial–mesenchymal transition. Furthermore, study also showed Escin can reverse multidrug resistance through inhibition of the GSK3 $\beta$ / $\beta$ -catenin pathway in cholangiocarcinoma cells [22]. Clinically, Escin has been proved to be well tolerated and efficiency on improving the gastrointestinal motility in patients with colorectal cancer as well [19].

As Escin showed significant antitumor effects in many types of cancer cells and is well tolerated in patients with colorectal cancer, we hypothesize that Escin may have some effects on patients with advanced thyroid cancer. Here, we conducted two cohorts of clinical studies to investigate the safety and efficiency of Escin on patients with advanced thyroid cancer.

## Methods

### Patients and healthy volunteers

Eligible patients of our studies were  $\geq 18$  years old with histologically confirmed advanced thyroid carcinoma (including papillary, follicular, Hürthle cell, and poorly differentiated). All patients have already received standard surgery with or without radioactive iodine treatment or radiation therapy following NCCN guideline. The Eastern Cooperative Oncology Group performance statuses of our patients are between 0 and 2. The previous chemotherapy or biologic treatment (kinase inhibitor or vaccine) was allowed but not within a month of treatment. The exclusion criteria included significant cardiac, hematopoietic, hepatic, or renal dysfunction. Hundred healthy volunteers

were recruited from The First Hospital of Anhui Medical University. All the volunteers were 18–50 years old and have no history or evidence of clinically chronic systemic disease. Pregnant or lactating women were excluded as well. All patients and volunteers were needed to sign the consent forms, and this study was approved by medical ethics committee of The First Hospital of Anhui Medical University.

### Study design

We performed two separate cohorts to evaluate the safety and efficiency of Escin in patients with advanced thyroid cancer. In cohort 1, 120 patients were divided into four groups equally; patients in each group were administrated with placebo, Escin 0.2 mg/kg/day (Shandong Luye Pharmaceutical Company, China), 0.4 mg/kg/day, or 0.6 mg/kg/day, respectively, for 9 days. Escin was diluted in 5% dextrose. One hour right after the Escin injection, the blood samples were taken from the patients and Escin concentrations in plasma were tested. Treatment-related adverse effects (AE) and laboratory values were recorded and assessed according to the Common Terminology Criteria for Adverse Events, version 3.0 in all the patients as well.

In cohort 2, 120 patients were treated with Escin 0.6 mg/kg/day for 9 days. Thyroid function of all the patients (such as TSH, TBG, and TgAb) was evaluated before and after the Escin treatment and compared with that of 100 healthy volunteers. The recurrence time and death time of each patient were recorded, and the Kaplan–Meier (KM) analysis was performed to compare the progression-free survival (PFS) and overall survival (OS) between the 120 patients from cohort 2 and 30 patients from cohort 1 who received placebo treatment.

### Evaluations and assessments

Serum thyroid-stimulating hormone (TSH), total or free triiodothyronine (T3), total or free thyroxine (T4), thyroglobulin (Tg), antithyroglobulin antibody (TgAb), thyroid binding globulin (TBG), and calcitonin levels are measured before and after Escin treatment in patients with cancer from cohort 2 and healthy volunteers. Standard computed tomography/magnetic resonance imaging of neck for tumor assessment was performed at baseline, approximately every 3 month after Escin treatment. Scans of other organs for metastasis were performed only when clinically indicated.

### Statistical analysis

Results are presented as mean  $\pm$  SD. Student's *t*-test was used to compare the results related to thyroid function

between the patients with thyroid cancer and healthy volunteers. KM analysis was used to compare the PFS and OS between patients with or without Escin treatment. All the analyses were performed according to the intention-to-treat principle. The commercial SPSS (version 16.0, SPSS Inc, Chicago, IL) for Windows was used for all the analysis.  $P < 0.05$  were considered as statistically significant.

## Results

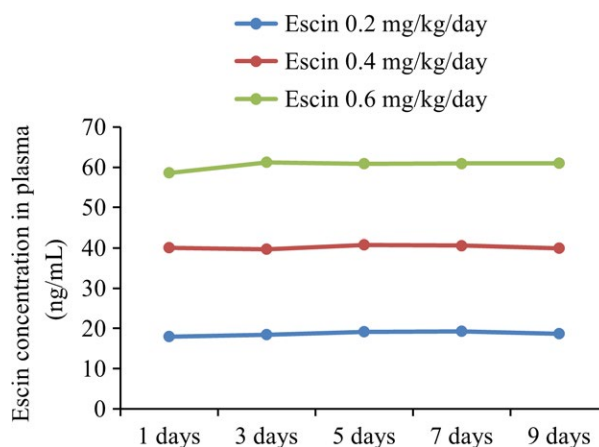
### Patients' characteristics

We performed two separate cohorts to evaluate the safety and efficiency of Escin in patients with advanced thyroid cancer. Between September 2013 and October 2015, 240 patients with advanced thyroid cancer and 100 healthy volunteers were recruited from The First Hospital of Anhui Medical University. In the first part of the study, 120 patients were enrolled and received Escin 0.2 mg/kg/day (intravenous injection, i.v.) (cohort 1;  $n = 30$ ), Escin 0.4 mg/kg/day i.v. (cohort 1;  $n = 30$ ), Escin 0.6 mg/kg/day i.v. (cohort 1;  $n = 30$ ), or placebo (cohort 1;  $n = 30$ ) for 9 days. In cohort 2, 120 patients were treated with Escin 0.6 mg/kg/day i.v. (cohort 2;  $n = 120$ ) for 9 days. The characteristics of the 240 patients and 100 healthy volunteers are shown in Table 1. As shown in Table 1, there are no differences among the patients from different Escin dosage groups of cohort 1, and there is no difference between the patients from cohort 1 and cohort 2. Although the age and sex fraction are the same between the healthy

volunteers and patients with cancer, most of patients had the symptoms of diarrhea, dyspnea, dysphagia, or corestenoma which related to pervious cancer treatments, while no healthy volunteers showed these kinds of symptoms.

### Pharmacokinetics of Escin

To investigate the pharmacokinetics of Escin, blood samples were taken one hour after Escin treatment from the patients of different Escin dosage treatment groups of cohort 1. Serum Escin concentrations were determined from each samples. As shown in Figure 1, the serum



**Figure 1.** Escin had stable blood concentration during cohort 1. Mean Escin plasma concentration vs. time profiles from patients dosed with Escin 0.2 mg/kg/day ( $n = 30$ ), Escin 0.4 mg/kg/day ( $n = 30$ ), and 0.6 mg/kg/day ( $n = 30$ ). Each value represents the mean  $\pm$  SD.

**Table 1.** Patient characteristics.

Variable	First study of patient ( $n = 120$ )	Second study of patient ( $n = 120$ )	Control ( $n = 100$ )	Significant difference (1 <sup>st</sup> vs 2 <sup>nd</sup> study; Yes/No)	Significant difference (1 <sup>st</sup> /2 <sup>nd</sup> study vs control; Yes/No)
Age: year	69.6 $\pm$ 4.3	64.8 $\pm$ 4.9	68.2 $\pm$ 2.3	No	No
Sex: no. (%)					
Male	72 (60)	66 (55)	50 (50)	No	No
Female	48 (40)	54 (45)	50 (50)	No	No
Hyperlipidemia ( $n$ , %)	108 (90)	102 (85)	0 (0)	No	Yes
Coronary artery disease ( $n$ , %)	96 (80)	108 (90)	0 (0)	No	Yes
Diabetes mellitus ( $n$ , %)	120 (100)	120 (100)	0 (0)	No	Yes
Atrial fibrillation ( $n$ , %)	108 (90)	114 (95)	0 (0)	No	Yes
Palpitation ( $n$ , %)	120 (100)	120 (100)	0 (0)	No	Yes
Face flushing ( $n$ , %)	108 (90)	114 (100)	0 (0)	No	Yes
Diarrhea ( $n$ , %)	114 (95)	120 (100)	3 (3)	No	Yes
Hoarseness ( $n$ , %)	120 (100)	114 (95)	0 (0)	No	Yes
Bucking ( $n$ , %)	102 (85)	102 (85)	0 (0)	No	Yes
Dyspnea ( $n$ , %)	108 (90)	102 (85)	0 (0)	No	Yes
Dysphagia ( $n$ , %)	120 (100)	120 (100)	0 (0)	No	Yes
Lymphadenectasis ( $n$ , %)	120 (100)	120 (100)	0 (0)	No	Yes
Corestenoma ( $n$ , %)	120 (100)	120 (100)	0 (0)	No	Yes

Student's  $t$ -test was used to compare the results.

Escin concentrations are quite stable among each group during the treatment. The average of Escin serum concentration was around 20 ng/mL in the 0.2 mg/kg/day group ( $n = 30$ ), 40 ng/mL in 0.4 mg/kg/day group ( $n = 30$ ), and 60 ng/mL in 0.6 mg/kg/day group ( $n = 30$ ), suggesting a dose-dependent increase in Escin serum concentration.

### Safety and tolerability

To investigate the tolerability of Escin, common adverse events (any grade 3 or higher) from the cohort 1 are summarized in Table 2. There are no adverse events reported in 0.2 mg/kg/day and 0.4 mg/kg/day groups; while in Escin 0.6 mg/kg/day group, one patient (3%) occurred grade 3 Anemia, another patient (3%) occurred grade 3 ALT elevations. After symptomatic treatment, these two patients accomplished 9-day Escin treatment.

### Efficacy

In cohort 2, we tried to investigate whether Escin has therapeutic effects on patients with advanced thyroid cancer. Firstly, we measured several indexes of thyroid function before and after Escin treatment to see whether Escin can improve thyroid function in patients with cancer. Indeed, as shown in Table 3, after 9-day Escin treatments TSH level dropped from  $1.87 \pm 0.64$  IU/L to  $1.1 \pm 0.34$  IU/L, TgAb level dropped from  $54.9 \pm 8.14$  IU/mL to  $44.77 \pm 4.28$  IU/mL, TBG level dropped from  $78.19 \pm 7.23$   $\mu$ g/L to  $54.1 \pm 6.87$   $\mu$ g/L, and calcitonin level dropped from  $198.32 \pm 35.98$  ng/L to  $124.32 \pm 28.32$  ng/L, respectively, suggesting Escin

treatment might regulate the thyroid function in patients with thyroid cancer. As TSH, TgAb, Tg, and calcitonin increasing are well-known indicators for thyroid cancer recurrence and Escin is shown to be able to decrease these indexes simultaneously, it became very interesting to see whether the effects Escin on these indicators would lead to benefits on long-term survive rate of patients with advanced thyroid cancer.

We then evaluated the response rate of Escin treatment as shown in Table 4. Among the 120 patients in cohort 2, 12 (10%) had a partial response, 90 (75%) had stable disease, 18 (15%) had progressive disease, and the disease control rate was 102 (85%). After low term follow-up, we compared the progression-free survival (PFS) and overall survival (OS) between the 120 patients from cohort 2 who have received the Escin treatment and the 30 patients from cohort 1 who have received placebo. As shown in Figure 2, significant prolongation of PFS and OS was observed for patients receiving Escin compared with placebo. The median PFS was 2.44 years in the Escin-treated group comparing with 1.04 years in placebo group. The median OS was also significantly improved from 3.73 years (placebo group) to 7.6 years (Escin-treated group).

### Discussion

In our current study treating advanced thyroid cancer patients with Escin, we found Escin was well tolerated and significantly improved the progression-free survival and overall survival of patients with advanced thyroid cancer.

To monitor the thyroid cancer progression and recurrence, clinicians test the levels of several biomarkers regularly as the indicators, such as TSH, TgAb, Tg, and

**Table 2.** All adverse a dose-limiting toxicity (DLT) during first study.

	30 patients with 0.2 mg/kg Escin. No. (%)	30 patients with 0.4 mg/kg Escin. No. (%)	30 patients with 0.6 mg/kg Escin. No. (%)
Hyperbilirubinemia	0 (0)	0 (0)	0 (0)
AST elevation	0 (0)	0 (0)	0 (0)
Anemia	0 (0)	0 (0)	1 (3)
Thrombocytopenia	0 (0)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)
Neutropenia	0 (0)	0 (0)	0 (0)
Rash	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)
Fever	0 (0)	0 (0)	0 (0)
Bleeding	0 (0)	0 (0)	0 (0)
Mucositis	0 (0)	0 (0)	0 (0)
Hypocalcemia	0 (0)	0 (0)	0 (0)
ALT elevation	0 (0)	0 (0)	1 (3)
Hyponatremia	0 (0)	0 (0)	0 (0)
Hypophosphatemia	0 (0)	0 (0)	0 (0)
Sudden death	0 (0)	0 (0)	0 (0)

Unless otherwise noted, all data presented as  $n$  (%).

**Table 3.** All significant adverse events for thyroid cancer during second study ( $P < 0.5$ ).

Variable	Second study of patient N = 120	Second study of patient with treatment N = 120	Control N = 100	Significant difference between second study and control ( $P < 0.5$ )
TSH (IU/L)	1.1 ± 0.34	1.87 ± 0.64	2.34 ± 0.76	$P < 0.5$
Total T3 (ng/mL)	5.81 ± 1.23	3.21 ± 0.77	1.27 ± 0.25	$P < 0.5$
Total T4 (µg/dL)	22.68 ± 3.24	2.64 ± 1.08	10.1 ± 2.09	$P < 0.5$
Free T3 (pg/mL)	5.6 ± 1.41	4.35 ± 1.07	3.21 ± 1.35	$P < 0.5$
Free T4 (ng/dL)	2.61 ± 0.13	1.60 ± 0.11	1.34 ± 0.22	$P < 0.5$
TG (ng/mL)	55.98 ± 7.41	25.78 ± 2.14	10.29 ± 2.66	$P < 0.5$
TGA(IU/mL)	54.9 ± 8.14	44.77 ± 4.28	22.57 ± 4.92	$P < 0.5$
TBG(µg/L)	78.19 ± 7.23	54.1 ± 6.87	35.44 ± 4.17	$P < 0.5$
Calcitonin (ng/L)	198.32 ± 35.98	124.32 ± 28.32	89.67 ± 11.44	$P < 0.5$

Unless otherwise noted, all data presented as  $n$  (%).

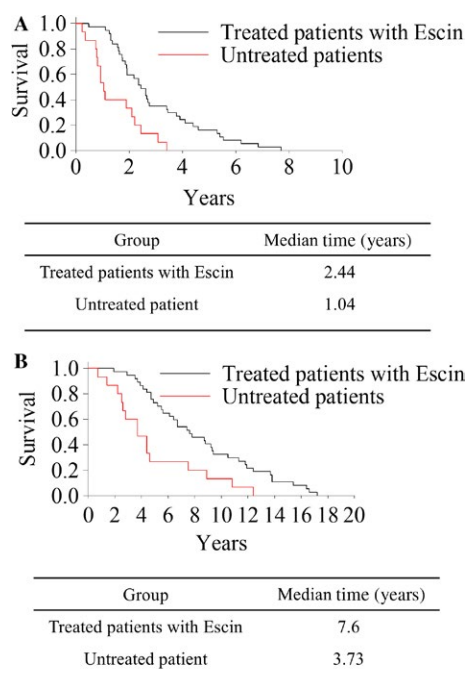
IQR, interquartile range; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.

**Table 4.** Response rates using the response evaluation criteria in patients in second study.

Response	Number of patients (%)
Complete response	0 (0)
Partial response	12 (10)
Stable disease	90 (75)
Progression disease	18 (15)
Disease control rate (DCR)	102 (85)

Unless otherwise noted, all data presented as  $n$  (%). The disease control rate was defined as the proportion of patients who had a best response rating of a complete response, partial response, or stable disease that was maintained for  $\geq 4$  weeks from the first manifestation of the rating.

calcitonin. Circulating TSH is shown to stimulate proliferation in most thyroid cancer cells [23]. Pervious study showed reducing TSH concentrations by the administration of L-T4 after routine treatments can significantly improve clinical outcomes in patients with advanced thyroid cancer [24, 25]. The trends of serum TgAb level can reflect changes of thyroid tissue mass; thus, serum TgAb concentrations also serve as a surrogate postoperative differentiated thyroid cancer tumor marker clinically. A rising level of TgAb suggests cancer recurrence, whereas a progressive decline suggests successful treatment [26]. Thyroglobulin (Tg) is another important biomarker for monitoring the progression of thyroid cancer especially papillary thyroid cancer. Achieving an undetectable serum Tg level after surgical and radioiodine treatment is associated with low recurrence rates and has been termed biochemical remission [27]. Calcitonin secreted by the thyroid C cells which give rise of the medullary thyroid carcinoma (MCT) is a sensitive biomarker for diagnosis and follow-up in medullary thyroid cancer (MTC) especially for decades [28]. In our current study, all the patients showed higher serum level of TSH, TgAb, Tg, and calcitonin after



**Figure 2.** Escin inhibited the recurrence of cancer and prolonged the survival time of patients. (A) The recurrence time was recorded of 120 patients of second study compared 30 patients of first study without Escin treatment as control from surgery and radiation therapy ( $P < 0.01$ ). (B) The survival time was recorded of 120 patients of second study compared 30 patients of first study without Escin treatment as control from surgery and radiation therapy ( $P < 0.01$ ).

surgery and radiation therapy as shown in Table 3, while 9 days of Escin treatment significantly reduced the serum levels of all these four biomarkers close to the normal level of healthy volunteers suggesting Escin might benefit all subtypes of thyroid cancer.

In traditional Chinese medicine, Escin has been widely used to promote appetite, prevent gas formation of

gastrointestinal tract, and documented as an antiseptic, anti-edematous, and anti-inflammatory agent in various disease models [29]. Studies have shown the major mechanisms for the anti-inflammatory effects of Escin are through modulation of NF- $\kappa$ B signaling pathway [29]. As chronic inflammation and the incidence or the recurrence of thyroid cancer are highly related [30] and, moreover, increased NF- $\kappa$ B activation in thyroid cancer cell lines and tissues has long been documented [8], we hypothesize that Escin would benefit the patients with thyroid cancer. Furthermore, many recent studies showed Escin might have antitumor effects in various cancer types. Thus, we conducted current clinical study to investigate the antitumor effect of Escin on patients with advanced thyroid cancer.

To our knowledge, this is the first clinic study of Escin with thyroid cancer patients. Escin showed striking effects on prolonging the progression-free survival and overall survival in our current patients. This kind of antitumor effect is consistent with other in vitro and in vivo nude mice studies showing Escin has antitumor effects on lung cancer [20], breast cancer [21], liver cancer [31], pancreas cancer [32], and colon cancer [33]. The dosage of Escin in our current was 0.6 mg/kg/day i.v. for 9 days. In our study, there are only two patients (6%) developed grade 3 side effects, one occurred Anemia, another showed ALT elevations. While after symptomatic treatment, both patients accomplished 9-day Escin treatment. Our dosage of Escin is higher than another clinical study investigating whether Escin can improve gastrointestinal motility in patients with colon cancer after surgery [19]. In that study, the highest dose of Escin was 25 mg/day i.v. for 7 days. There are no severe side effects reported in that trial either. Since at current dosage, Escin is well tolerated and shows some promising antitumor effects on patients with cancer. Further studies need to investigate the feasibility of higher dose or longer duration of Escin usage.

Escin showed different antitumor mechanisms in various types of cancer. For example, in pancreas cancer [32], Wang and his colleague found Escin potentiated the antitumor activity of gemcitabine via the inactivation of NF- $\kappa$ B. While in cholangiocarcinoma [22], Escin was found to reverse P-gp-dependent multidrug resistance via inhibition of the GSK3 $\beta$ / $\beta$ -catenin pathway. Because Escin has different antitumor mechanisms according to different cancer types, understanding via which pathway Escin affects the thyroid cancer cells become interesting and necessary. Better understanding of the mechanism of Escin on thyroid cancer will help us to find some biomarkers to identify the most suitable subgroup of patients with thyroid cancer for Escin treatment.

In conclusion, our current study showed Escin is efficient and well tolerated in patients with advanced thyroid

cancer. Based on the safety, and pharmacokinetic and efficacy profiles of our study, it was concluded that Escin 0.6 mg/kg/day i.v. for 9 days was tolerable. Furthermore, Escin significantly reduced the serum levels of TSH, TgAb, Tg, and calcitonin related to thyroid cancer progression and recurrence and prolonged the PFS and OS for patients with advanced thyroid cancer. Future studies are needed to investigate the mechanism of Escin on thyroid cancer and the proper dosage of Escin clinically.

## Acknowledgments

None.

## Funding Information

No funding information provided.

## Conflicts of Interest

The authors declare that there is no conflict of interests.

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