

# Signal Detection Report: Mistletoe Therapy in Oncology

---

## Signal Detection Report date

April, 2017

## Key Findings

- Expert opinion: Both experts stated the original reviews' recommendations are still valid. Both experts were aware of new evidence that would strengthen the findings of the original review.
- Literature evidence: No signal was identified.

### Summary Decision:

The Cochrane review "Mistletoe Therapy in Oncology" does not require updating at this time.

## Authors

Investigators: Misty Pratt, Brian Hutton, Susan Wieland, Nadera Ahmadzai, Becky Skidmore, David Moher

Technical support: Raymond Daniel

Oversight: Roxanne Ward

## **Introduction**

Previous research evaluating a cohort of published systematic reviews demonstrated that 7% of reviews were out of date by the time of publication, while as many as 23% went out of date within two years of being completed[1]. The utility of systematic review-based evidence depends on their remaining up-to-date. As such, the Cochrane Complementary Medicine Field and the Knowledge Synthesis group at the Ottawa Hospital Research Institute (OHRI) have determined a set of existing reviews of interest for which signal detection work using the Ottawa Method's qualitative/quantitative signal detection approach has been performed [1].

The Ottawa method involves identification of qualitative and quantitative signals/triggers indicating the need of updating of a systematic review. [1]. The Ottawa method has been used to assess the need for updating systematic reviews in the past. [1; 2] A graphical overview of our approach and application of the Ottawa signal detection method is provided in Appendix A of this report. This work assessed potential triggers signifying the need for updating of six past Cochrane Complementary Medicine reviews. The conclusion as to whether or not each of the reviews is in need of updating was made based on the identification of qualitative and quantitative signals.

## **Methods**

We contacted content experts to provide input on whether conclusions from the review were still valid, and if they were aware of any new evidence that could potentially signal the need for a review update. This process included the authors from the original review, and also reached out to the lead authors on the included studies of the review. If we did not find sufficient number of experts we then reached out to those who had responded and asked whether they could suggest possible content experts.

Summaries and conclusions were collected for each key question (or possibly key endpoint) within each review; this summary was shared with consulting experts when seeking their input regarding the findings, as well as when establishing the presence of updating triggers. See Appendix B for the survey sent to content experts.

Experts were asked their perspectives on the following features of each review: a) whether the conclusion is still valid in their own opinion (to be answered as yes/no/don't know); b) whether he/she is aware of new evidence published since the publication date of the review being assessed (with details if yes); and c) any additional information or perspectives to be shared. If an expert indicated an opinion that one or more conclusions of the review was out of date and/or provided specific evidence they felt was critical to the decision regarding updating, we verified it by assessing the evidence brought forward by the expert(s).

Experts were given 10 business days to respond. Two reminders were sent, and a conflict of interest disclosure statement was also sent to all experts that participated. The survey was kept open until a minimum of two clinical experts responded.

One reviewer screened the evidence provided by the content experts, and determined whether the studies met the inclusion criteria of the original review. Data was extracted by one reviewer. The

identification of qualitative signals was carried out using the Ottawa method qualitative signals. The definition and categories of qualitative signals are presented in Appendix C.

An information specialist provided modified PRESS evaluations of the original review's search strategy, commenting on databases, search dates and terminology. This information is provided in Appendix D in order to inform any future updating for the original review.

### **Expert Opinion**

Of the eight experts contacted, two responded to our questions on mistletoe therapy in oncology. Both experts thought that the original reviews conclusions were still valid, although one expert believed that there were "possibly stronger conclusions [to be] made about survival." Both experts indicated that they were aware of new evidence that may strengthen the findings of the original review.

### **Flow**

17 references were put forth by the content experts. Approximately half of these publications did not meet the original review's inclusion criteria, due to a lack of comparator, cohort study design or language (Appendix E.) In total, 7 studies met the inclusion criteria and were assessed for qualitative signals.

## **Signal Detection Results:**

### **Findings of the original review**

Overall Conclusion of the Review: "The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QOL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trials".[3]

Further Details: "Of the 13 trials investigating survival, 6 showed some evidence of a benefit, but none of them were of high methodological quality. The results of two trials in patients with melanoma and head and neck cancer gave some evidence that the used mistletoe extracts are not effective for improving survival. Of the 16 trials investigating the efficacy of mistletoe extracts for either improving QOL, psychological measures, performance index, symptom scales or the reduction of adverse effects of chemotherapy, 14 showed some evidence of a benefit, but only 2 of them including breast cancer patients during chemotherapy were of higher methodological quality. Data on side effects indicated that, depending on the dose, mistletoe extracts were usually well tolerated and had few side effects". [3]

### **New findings:**

**Troger et al., 2013** reports findings from a randomized phase III study of patients with locally advanced or metastatic cancer of the pancreas. 220 patients were randomized to subcutaneous injections of mistletoe therapy (VaL extracts) or no antineoplastic therapy (control) for a period of 12 months. The authors reported that “median OS [overall survival] was 4.8 months for VaL and 2.7 months for control patients (prognosis-adjusted hazard ratio, HR = 0.49;  $p < 0.0001$ ). Within the ‘good’ prognosis subgroup, median OS was 6.6 versus 3.2 months (HR = 0.43;  $p < 0.0001$ ), within the ‘poor’ prognosis subgroup, it was 3.4 versus 2.0 months respectively (HR = 0.55;  $p = 0.0031$ ). No VaL-related adverse events were observed.” The authors concluded that “VaL therapy showed a significant and clinically relevant prolongation of OS. The study findings suggest VaL to be a non-toxic and effective second-line therapy that offers a prolongation of OS as well as less disease-related symptoms for patients with locally advanced or metastatic pancreatic cancer.” [4]

**Longhi et al., 2014** described findings from a randomized open-label study, with patients over 10 years of age diagnosed with osteosarcoma or spindle cell sarcoma of the bone after a second relapse. 20 patients were randomized to receive either mistletoe therapy (Viscum) or Etoposide for a period of months. Follow-up was a median of 38.5 months. The authors report that “The median PRDSF [post-relapse disease-free survival] is currently 4 months (1–47) in the Etoposide group and 39 months (2–73) in the Viscum group. Patients getting Viscum reported a higher quality of life due to lower toxicity.” The authors conclude that “Viscum shows promise as adjuvant treatment in prolonging PRDFS after second relapse in osteosarcoma patients. A larger study is required to conclusively determine efficacy and immunomodulatory mechanisms of Viscum therapy in osteosarcoma patients.” [5]

**Troger et al. 2012** reported findings from a long-term follow-up of patients participating in a randomized clinical trial. Breast cancer patients in stages  $T_1-3N_0-2M_0$  who received six consecutive cycles of CAF (chemotherapy) after surgery were enrolled. The study analyzed 28 patients in the mistletoe therapy plus chemotherapy group, and 29 patients in chemotherapy only group for 5-year disease-free survival. Treatment was 18 weeks in total, with mistletoe injections three times per week. The authors report that “six of 28 patients in one of the VaL groups and eight of 29 patients in the control group developed relapse or metastasis within 5 years. Subgroup analysis for hormone- and radiotherapy also showed no difference between groups.” The authors conclude that “additional VaL therapy during chemotherapy of early stage breast cancer patients appears not to influence the frequency of relapse or metastasis within 5 years.” [6]

**Bar-Sela et al., 2013** described findings from a randomized phase II study including patients with advanced non-small-cell lung cancer (NSCLC) treated with gemcitabine/carboplatin (GC) or pemetrexed/carboplatin (PC) chemotherapy combination. 72 patients were randomized to receive either chemotherapy alone or chemotherapy plus iscador (mistletoe.) Patients were followed until tumour progression. The authors report that “median overall survival in both groups was 11 months. Median TTP was 4.8 months for the controls and 6 months in the iscador arm ( $p = NS$ ). Differences in grade 3–4 haematological toxicity were not significant but more control patients had chemotherapy dose reductions (44% versus 13%,  $p = .005$ ), grade 3–4 non-haematological toxicities (41% versus 16%,  $p = 0.043$ ) and hospitalisations (54% versus 24%,  $p = 0.016$ ).” The authors conclude that “no effect of iscador could be found on quality of life or total adverse events. Nevertheless, chemotherapy dose

reductions, severe non-haematological side-effects and hospitalizations were less frequent in patients treated with iscador, warranting further investigation of iscador as a modifier of chemotherapy-related toxicity.” [7]

**Troger et al., 2014a** described a randomized open-label pilot study of breast cancer patients in stages T<sub>1</sub>–3N<sub>0</sub>–2M<sub>0</sub> who received six consecutive cycles of CAF (chemotherapy) after surgery. 95 patients were randomized to CAF and mistletoe (Helixor A) (n = 34), CAF and another mistletoe product (n = 30), and CAF alone (n = 31). This report only compares the Helixor A and CAF alone groups. Patients were treated over six cycles of chemotherapy, but follow-up time is unclear. The authors report that “in the explorative analysis ten of 15 scores of the EORTC QLQ-C30 showed a better quality of life in the HxA group compared to the control group ( $P < 0.001$  to  $P = 0.038$  in Dunnett-T3 test). The difference was clinically relevant (difference of at least 5 points, range 5.4–12.2) in eight of the ten scores. Neutropenia occurred in 7/34 HxA patients and in 8/31 control patients ( $P = 0.628$ ).” The authors conclude that “this pilot study showed an improvement of quality of life by treating breast cancer patients with HxA additionally to CAF. Although the open design may be a limitation, the findings show the feasibility of a confirmatory study using the methods described here.” [8]

**Troger et al., 2014b** reported findings from an RCT of patients with inoperable locally advanced or metastatic pancreatic cancer. All patients received supportive care, and were randomly assigned to receive subcutaneous injections of 1ml mistletoe extract three times per week for one year (n=110) or no treatment (n=110) The authors reported that “data on quality of life and body weight were obtained from 96 patients treated with mistletoe and 72 control patients. Those treated with mistletoe did better on all 6 functional scales and on 7 of 9 symptom scales, including pain (95% confidence interval [CI] –29 to –17), fatigue (95% CI –36.1 to –25.0), appetite loss (95% CI –51 to –36.7), and insomnia (95% CI –45.8 to –28.6). This is reflected by the trend in body weight during the trial.” The authors conclude that “In patients with locally advanced or metastatic pancreatic carcinoma, mistletoe treatment significantly improves the quality of life in comparison to best supportive care alone. Mistletoe is an effective second-line treatment for this disease.” [9]

**Kim et al., 2012** reported results from an RCT of gastric cancer patients waiting for chemotherapy. 32 patients were randomized to receive a standardized mistletoe extract bnoBaVISCUMW Q (aVQ) (n=16) or no additional therapy (n=16.) Subcutaneous aVQ was administered three times per week in increasing doses from day 7 post-surgery to week 24. The authors reported that “Global health status ( $p < 0.01$ ), leukocyte- and eosinophil counts ( $p \leq 0.01$ ) increased significantly in the treatment group compared to the control group. Diarrhea was less frequently reported (7% vs. 50%,  $p=0.014$ ) in the intervention group. There was no significant treatment effect on levels of TNF-alpha, IL-2, CD16+/CD56+ and CD 19+ lymphocytes and liver function tests measured by ANOVA.” The authors conclude that “Additional treatment with aVQ is safe and was associated with improved QoL of gastric cancer patients.” [10]

**Adverse effects:** There were no safety alerts found from the key sources identified in the methods section. The studies identified by the experts showed no new adverse effects than what was already covered in the original review.

### **Qualitative Signal: No signal was identified**

The results from expert opinion and recent publications show that the original review's findings are still valid. Of the seven identified primary studies with small samples (ranged 20-220 patients), five reported some benefit in survival and/or quality of life [4, 5, 8, 9, 10] and two [7, 6] showed no significant difference in disease free survival, and quality of life between the intervention and control groups. The new evidence remains consistent with the original review's findings. However, new evidence provides some indication of a beneficial effect of the intervention in cancer types that were not captured in the original review for the survival and quality of life outcomes. For example, two smaller randomized trials show some evidence on survival for pancreatic cancer [4] and osteosarcoma. [5] There is also some evidence that mistletoe may offer benefits on QOL measures, not only for breast cancer [8] but also pancreatic [9] and gastric cancers. [10]. Consistent with the original review, no significant survival difference was found in patients with lung cancer [7]. In breast cancer patients, the original review reported a significant mean survival difference (4.79 years in treatment arm versus 2.41 years in control arm); however, a new study demonstrated no significant difference in survival, and quality of life between the intervention and control groups. [7]

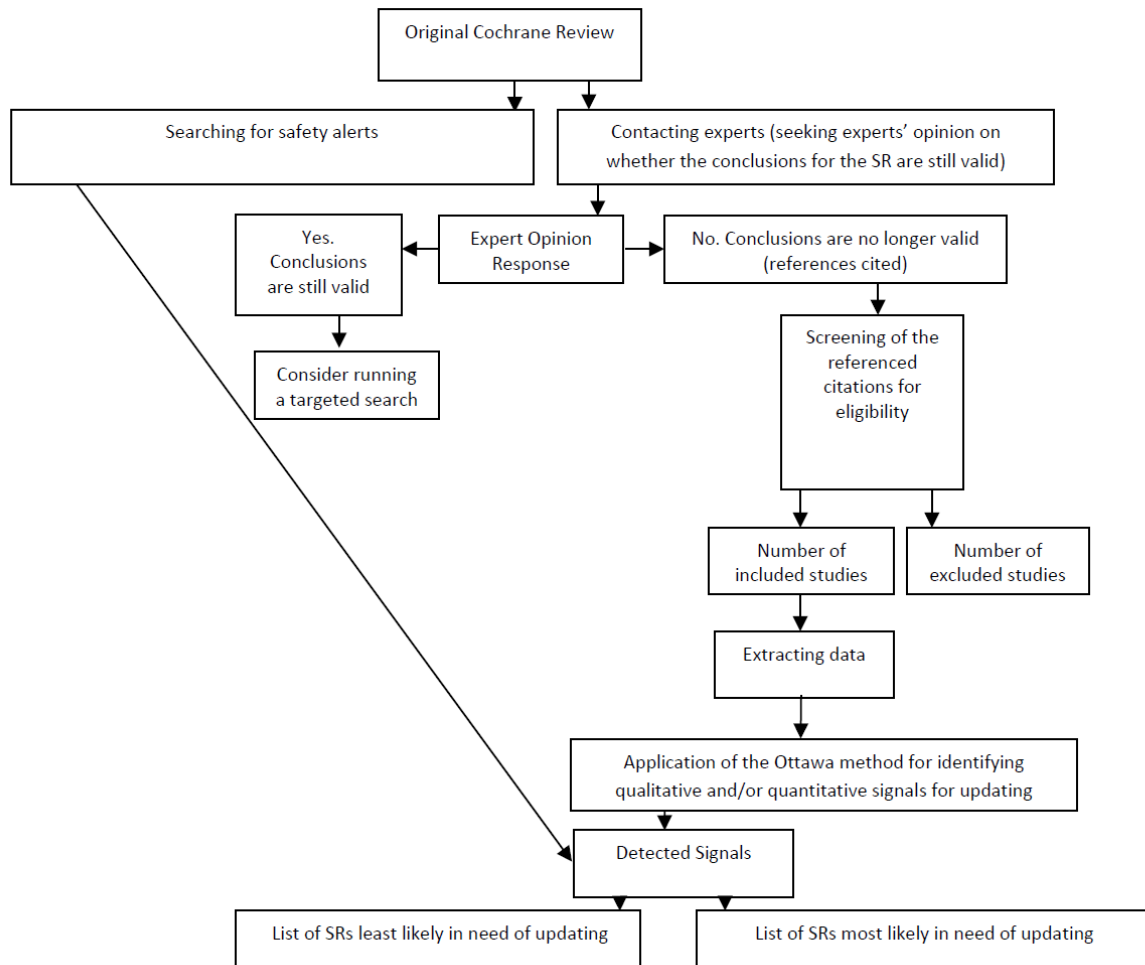
**Conclusion:** No signal was identified. As such, the original review does not require updating at this time.

### **References:**

1. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med* 2007 Aug 21;147(4):224-33. [PMID: 17638714]
2. Ahmadzai N, Newberry SJ, Maglione MA, Tsertsvadze A, Ansari MT, Hempel S, et al. A surveillance system to assess the need for updating systematic reviews. *Syst Rev* 2013 Nov 14;2:104. [PMID: 24225065]
3. Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology. *Cochrane Database Syst Rev* 2008 Apr 16;(2):CD003297. [PMID: 18425885]
4. Troger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M. *Viscum album* [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: a randomised clinical trial on overall survival. *Eur J Cancer* 2013 Dec;49(18):3788-97. [PMID: 23890767]
5. Longhi A, Reif M, Mariani E, Ferrari S. A Randomized Study on Postrelapse Disease-Free Survival with Adjuvant Mistletoe versus Oral Etoposide in Osteosarcoma Patients. *Evid Based Complement Alternat Med* 2014;2014:210198. [PMID: 24803944]
6. Troger W, Zdravle Z, Stankovic N, Matijasevic M. Five-year follow-up of patients with early stage breast cancer after a randomized study comparing additional treatment with *viscum album* (L.) extract to chemotherapy alone. *Breast Cancer (Auckl)* 2012;6:173-80. [PMID: 23150723]
7. Bar-Sela G, Wollner M, Hammer L, Agbarya A, Dudnik E, Haim N. Mistletoe as complementary treatment in patients with advanced non-small-cell lung cancer treated with carboplatin-based combinations: a randomised phase II study. *Eur J Cancer* 2013 Mar;49(5):1058-64. [PMID: 23218588]

8. Troger W, Zdrale Z, Tisma N, Matijasevic M. Additional Therapy with a Mistletoe Product during Adjuvant Chemotherapy of Breast Cancer Patients Improves Quality of Life: An Open Randomized Clinical Pilot Trial. *Evid Based Complement Alternat Med* 2014;2014:430518. [PMID: 24701238]
9. Troger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M. Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe: a randomized controlled trial. *Dtsch Arztebl Int* 2014 Jul 21;111(29-30):493-502, 33. [PMID: 25142075]
10. Kim KC, Yook JH, Eisenbraun J, Kim BS, Huber R. Quality of life, immunomodulation and safety of adjuvant mistletoe treatment in patients with gastric carcinoma - a randomized, controlled pilot study. *BMC Complement Altern Med* 2012 Oct 3;12:172. [PMID: 23033982]

## Appendix A: Overview of the Modified Ottawa Method



**Figure 1:** The process of signal detection methods for Cochrane reviews

**Appendix B: Expert Opinion Survey**

<p align="center"><b>Conclusions from systematic review</b></p>	<p align="center"><b>Is the conclusion(s) in this review still valid? (Yes/No/Don't know)</b></p>	<p align="center"><b>Are you aware of any new evidence that is sufficient to invalidate the finding(s) in this review? (Yes/No/Don't know) If yes, please provide references</b></p>	<p align="center"><b>Comments</b></p>
<p><b>Review Objective:</b></p>			
<p><b>Overall Conclusion of the Review:</b>                      The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QOL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trails.</p> <p><u>Further Details:</u>                      Of the 13 trials investigating survival, 6 showed some evidence of a benefit, but none of them was of high methodological quality. The results of two trials in patients with melanoma and head and neck cancer gave some evidence that the used mistletoe extracts are not effective for improving survival. Of the 16 trials investigating the efficacy of mistletoe extracts for either improving QOL, psychological measures, performance index, symptom scales or the reduction of adverse effects of chemotherapy, 14 showed some evidence of a benefit, but only 2 of them including breast cancer patients during chemotherapy were of higher methodological quality. Data on side effects indicated that, depending on the dose, mistletoe extracts were usually well tolerated and had few side effects.</p>			
<p><b>Survival:</b>                      Of the 21 included studies 13 provided data on survival. Results suggesting a benefit were</p>			

<p>found in six trials (Cazacu 2003; Douwes 1986a; Grossarth 2001a; Grossarth 2001b; Lenartz 2000; Salzer 1983) and results that do not in seven (Dold 1991, Goebell 2002; Heiny 1997; Kleeberg 2004; Luemmen 2001; Salzer 1991; Steuer-Vogt 2001). Four of those 13 trials were considered to be of high methodological quality and belong to the group in which no evidence for a benefit was reported (Dold 1991; Goebell 2002; Kleeberg 2004; Steuer-Vogt 2001).</p> <p><b>Breast cancer:</b> In Grossarth 2001b, women with different stages of breast cancer had a mean survival of 4.79 years compared to 2.41 years in women who were in the control group (SD not reported; <math>p = 0.02</math>, log rank test) . Median survival data (extracted from a plot) was 6.2 years for patients of the mistletoe group and 2.3 for controls.</p> <p><b>Colorectal Cancer:</b> In Cazacu 2003, patients with Dukes C stage who were treated with 6 cycles of chemotherapy and additional mistletoe extracts survived a median of 757 days, those who received chemotherapy alone survived 547 days, and those without a postoperative adjuvant treatment 502 days (no confidence intervals (CIs) presented; <math>p &lt; 0.05</math>). Patients with Dukes D colorectal cancer who received chemotherapy and mistletoe extracts survived a median of 505 days, those who were treated with chemotherapy alone survived 214 days, and those without a postoperative antineoplastic treatment 451 days (no CIs; <math>p &lt; 0.05</math>). In Heiny 1997, patients with metastatic diseases received chemotherapy and lived a mean of 53 weeks when additionally treated with mistletoe extracts compared with 50 weeks in the control group. The mean progression-free survival (PFS) was 30.8 weeks and 31.2 weeks respectively. Authors performed no statistical analysis. In Douwes 1986a, patients with metastatic diseases were treated with chemotherapy and survival data were reported for responders (patients with a complete, partial or minimal response) and non-responders (patients with a no-change or progression of the disease). On average, responders of the mistletoe group lived 26.7 months (standard deviation (SD) 11.9), non-responders of this group 11.9 months (SD 4.7), responders of the group which was only treated with chemotherapy lived on average 13.6 (SD 4.4), and non-responders of this group 4.8 months (SD 4.1). A statistical analysis was not performed.</p> <p><b>Head and Neck Cancer:</b> In Steuer-Vogt 2001, participants with operable diseases were stratified into one group that underwent surgery (stratum A) and a second one with surgery followed by</p>			
---	--	--	--

<p>radiotherapy (stratum B). The five-year Kaplan estimates of the disease-specific survival and DFS were not significantly different between a) the groups both in the main analysis and b) in that of the two strata. Also, no significant differences were found in the five year survival rates, the relapse incidence, the development of distant metastases and second primaries.</p> <p><b>Lung Cancer:</b> In Dold 1991, participants with previously untreated, inoperable non-small cell lung cancer had a median survival time of 9.1 months (95%CI 6.8 to 10.7) when treated with mistletoe extracts compared to 7.6months (95%CI 6.0 to 8.9) in the placebo group (<math>p = 0.24</math> [log rank]). The rate of patients in the mistletoe group surviving 6 months was 62.7% (SD 4.6), one year 36.0% (SD 4.6) and two years 11.5% (SD 3.2). The respective rates for patients in the control group were 59.0% (SD 4.7), 32.2% (SD 4.4) and 10.1% (SD 3.0). In Salzer 1991, patients with all stages of lung cancer after surgery were included and the median survival time in the mistletoe group was 33 months compared with 31 months in the control group (n.s., log-rank test). A post-hoc analysis of subgroups revealed no difference in median survival for patients with stage IV(16.5 versus 17months) and stage I/II without positive lymph nodes (44 versus 43 months). There was, however, a difference for the subgroup of patients with stage II or III with positive lymph nodes (T1-3, N1-2): Patients in this subgroup who had received mistletoe extracts experienced a median survival of 31 months compared to 24 months without treatment and 38% of the mistletoe group survived 5 years compared to 20% of the control group (n.s., logrank test).</p> <p><b>Malignant Glioma:</b> Lenartz 2000 reported the OS and relapse-free survival of patients with malignant glioma after a follow-up of 50 weeks. Though stated in the 1996 publication that only patients with stage III/IV were included, in the 2000 publication of the trial, survival data were separately analysed for all stages and for stage III/IV without reporting the numbers of patients in each group. The mean OS of patients from the all stages group who had received mistletoe extracts was 21.71 (SD 3.7) months and for the controls 17.32 (SD 3.9). Patients with stage III or IV of the disease were reported as having survived a mean of 20.05 (SD 3.5) months if they had received mistletoe extracts, and 9.90 (SD 2.1) months if they did not (<math>p = 0.035</math>, Breslow test). The DFS of patients from the all stages group who had received mistletoe extracts was 14.41 (SD2.7) months and for the controls 14.76 (SD3.6). Patients with stage III or IV of the disease survived a mean of 17.43 (SD 8.2) months if they had received mistletoe extracts, and 10.45 (SD 3.9) months if they did not.</p>			
--	--	--	--

<p><b>Melanoma:</b> In the DKG 80-1 part of Kleeberg 2004, patients with melanoma either received mistletoe extracts for one year or no treatment after all had curative surgery. The univariate analysis of the Cox Proportional Hazards model revealed an estimate for the disease-free interval of 1.32 (95% CI 0.93 to 1.87; <math>p = 0.12</math>, [Wald test]) and 1.21 (95%CI 0.84 to 1.75; <math>p = 0.31</math>) for the OS. The multivariate analysis was adjusted for stage, number of positive lymph nodes, localisation of primary and Breslow thickness. The hazard ratio (HR) estimate for the disease-free interval was 1.34 (95% CI 0.95 to 1.91; <math>p = 0.10</math>) and 1.27 (95% CI 0.87 to 1.84; <math>p = 0.21</math>) for the OS.</p> <p><b>Renal Cell Carcinoma:</b> In Salzer 1983, patients with all stages of gastric cancer after surgery either received chemotherapy, mistletoe extracts or no treatment. In 1979 data from the interim analyses after three years and four years of follow-up were published. Survival data had to be extracted from two Kaplan-Meier diagrams: After three years of follow-up more than 50% of patients of both the mistletoe and chemotherapy group were alive and the median survival of the control group was 1.9 years. After four years of follow-up, more than 50% of patients of the mistletoe group were still alive, the median survival time of patients in the chemotherapy group was 3.1 yrs. and 1.1 years for patients of the control group respectively. The final publication in 1983 reported only data from patients of the mistletoe and the control group and of those with stage II and III. Furthermore, for the comparison of survival times, patients of both stages were grouped into those with or without affected lymph-nodes: Patients with stage II or III and affected lymph-nodes who had received mistletoe extracts lived a median of 660 days on average whereas the same subgroup of patients of the control group lived 324 days (<math>p &lt; 0.05</math>, Breslow test). For lymph-node negative stage II-III patients no difference in terms of survival was found.</p> <p><b>Urinary Bladder Cancer:</b> After transurethral surgery and an eighteen-months treatment with subcutaneous mistletoe extracts, the number of recurrences were assessed. Thirty-one were found in the mistletoe group, and 30 in the control group with a mean time to recurrence of 6.3 and 6.4 months, respectively (Goebell 2002). Nine patients in each group of this study remained without evidence of disease during follow-up. Patients receiving mistletoe extracts had a median disease-free interval of 9 months and patients of the control group one of 10.5 months. None of these estimates showed statistical significance.</p> <p><b>Various cancer:</b> In Grossarth 2001a, for patients with mixed cancer who had been treated with</p>			
---	--	--	--

<p>mistletoe extracts a mean survival of 3.49 years was reported compared to 2.45 years for patients of the control group (<math>p = 0.04</math>, log-rank test). Median survival data had to be extracted from a plot and showed similar results for both groups: 2.5 years for patients of the mistletoe group and 2.4 for controls.</p>			
<p><b>Effects of intervention by tumour response:</b>  Of the 21 included studies 7 provided data on tumour response. Results suggesting a benefit were found in 2 trials (Borrelli 1999; Lange 1993) and results that did not in 5 (Dold 1991; Douwes 1986a; Heiny 1997; Luemmen 2001; Piao 2004). Only one trial was judged as being of high methodological quality (Dold 1991) and pertained to the latter group.</p> <p><b>Breast cancer:</b> Borrelli 1999 reported on tumour response after three months treatment with mistletoe extracts. Assessment revealed 4 patients showing a partial remission (20%), 10 with a stable disease (50%) and 6 with progressive disease (30%) in the mistletoe group compared with 4 stable diseases (40%) and 6 progressive diseases (60%) in the control group.</p> <p><b>Colorectal Cancer:</b> In Douwes 1986a assessment of treatment response found 13 tumour responses in the mistletoe group (3 complete and 6 partial remissions) and 12 in the group without a concomitant treatment (3 complete and 5 partial remissions). Heiny 1997 found complete and partial remissions in 21.4% of the group treated with mistletoe extracts and chemotherapy and in 22.6% of patients in the control group (only chemotherapy).</p> <p><b>Lung Cancer:</b> In Dold 1991, 30 patients in the mistletoe group experienced a tumor response compared to 22 in the placebo group (<math>p = 0.10</math>, Chi2 test). Remissions, were reported in four patients of the mistletoe group and three patients of the control group.</p> <p><b>Renal Cell cancer:</b> Luemmen 2001 reported a response rate of 2% in the mistletoe group (no complete and 2 partial remissions) compared with 25% in the chemoimmunotherapy group (7 complete and 15 partial remissions).</p>			

<p><b>Various types of cancer:</b> Lange 1993 evaluated tumour responses after 2 cycles of chemotherapy and found 8 complete and 10 partial remissions (78%) in patients of the mistletoe group, 10 and 3 respectively (62%) in the control group. Application of the combination chemotherapy with cisplatin and ifosfamide was possible in the first cycle in 17 out of 23 patients of the mistletoe group compared to 14 out of 21 of the control group and in the second cycle in 14 out of 23 patients of the mistletoe group compared to 9 out of 21 of the control group. In the remaining patients, cisplatin was omitted. Combination chemotherapy could be given at full dose (defined as equal to 85% of the scheduled dose) in the first cycle in 12 out of 17 patients of the mistletoe group compared to 9 out of 14 of the control group and in the second cycle the numbers were 11 out of 14 and 6 out of 9 respectively.</p> <p>Piao 2004 reported complete and partial remissions in 21.4% of patients in the mistletoe group and 20.5% in the control group.</p>			
<p><b><u>Studies reporting on health related QOL, psychological measures, performance index, symptom scales or adverse effects of chemotherapy:</u></b></p> <p>Of the 21 included studies 16 provided data on QOL, psychological outcomes, symptom scales, performance index and 11 on chemotherapy-related side effects.</p> <p><b>Assessment during chemotherapy:</b> Results suggesting a benefit for at least one of these outcomes during a treatment with chemotherapy were found in all nine trials (Auerbach 2005, Cazacu 2003; Douwes 1986a; Heiny 1991; Heiny 1997; Lange 1993; Piao 2004; Semiglasov 2004; Semiglasov 2006). Two of these trials were of high methodological quality (Semiglasov 2004; Semiglasov 2006).</p> <p><b>Breast Cancer:</b> In Auerbach 2005, health-related QOL was assessed in patients with early stage breast cancer with the QLQ-C30 and a visual analogue scale. Authors stated that there had been no difference in QOL between the mistletoe and the placebo group, but presented no data of the assessment. No episodes of leukopenia were found in patients who had received mistletoe extracts.</p> <p>In Heiny 1999 well-being and anxiety during chemotherapy were measured. For the assessment of well-being, four instruments were distributed (Befindlichkeitsskala, Beschwerdeliste, Eigenschaftswörterliste, FLIC) and the results of these instruments were merged into a 5-point scale named Index of well-being (Befindlichkeitsindex). Anxiety was measured with two</p>			

<p>instruments (Therapieangstskala and Catell-Angstskala) and the results were merged into a 10-point scale named the Index of anxiety (Angstindex). The authors did not report the methods of how the patient-reported outcomes were merged into the physician rated indices. In patients receiving additional mistletoe extracts the physician-assessed index of well-being decreased from a mean of 4 (out of 5) at baseline to 2.8 after 6 cycles of chemotherapy, whereas in patients of the placebo group the mean index fell from 4 to 2 (measures of variability not reported; <math>p &lt; 0.01</math>, t-test). The mean values of the physician-assessed index of anxiety showed the following course in patients of the mistletoe group: 5 (out of 10) at baseline, 6 before second cycle of chemotherapy, 6 before 3rd, 5 before 4th, 4 before 5th, 4 before 6th and 4 at 10 days after completion of chemotherapy. The corresponding estimates in patients of the control group were: 5 at baseline, 6 before 2nd cycle: 6 before 3rd, 7 before 4th and 5th, and 7.5 before 6th and 7.5 at 10 days after completion of chemotherapy (no measures of variability; <math>p \leq 0.01</math>, unclear which estimates were tested).</p> <p>In Semiglasov 2004, QOL was assessed during chemotherapy. The changes of the GLQ-8 sum score were combined with those of Spitzer's Uniscale (QLU) score by means of a nonparametric ranksum (O'Brien) and tested for statistical significance. The changes from baseline to week 15 were found to be significantly different in patients from the medium and high dose mistletoe group compared with those who were treated with low dose mistletoe or placebo (<math>p = 0.0035</math>, O'Brien rank sum test). Pair-wise comparisons between placebo and each single mistletoe group revealed significance only for the medium dose mistletoe group (<math>p = 0.007</math>). For the medium dose mistletoe group, all changes in the 8 items of the GLQ-8 were larger than those in the placebo group. Significance was reached for changes in tiredness, sexual interest and anxiety related to treatment. For the results of the QLQ-C30 assessment, the authors reported no relevant difference without presenting data. An analysis of covariance, which had been carried out due to baseline in homogeneities in the GLQ-8 and QLU score, revealed significant differences in week 15 between the medium dose mistletoe group and the placebo group for both measures (<math>p = 0.012</math> and <math>p = 0.0021</math> respectively). Concerning the incidence of chemotherapy-induced adverse effects the authors reported no differences in white blood cells among the four groups. However, in red blood cells they found changes in 6% of the placebo group versus 3% in the low and medium dose mistletoe group and 12% in the high dose mistletoe group.</p> <p>Adverse effects related to the gastrointestinal tract were found in 9% of the placebo, the low</p>			
--	--	--	--

<p>dose and the medium dose mistletoe group compared to 15% in the high dose mistletoe group.</p> <p>In Semiglasov 2006, pre-post changes of QOL during chemotherapy were measured with FACT-G, GLQ-8 and QLU. The rank sums of changes of all three instruments from baseline to week 15 and from baseline to a follow-up of another two months after completion of chemotherapy were significant different between groups. Authors stated, that all results were confirmed in a baseline-adjusted analysis of covariance, which had been carried out due to baseline in homogeneities, but presented no data. No significant changes were found in Karnofsky's performance indices between groups after 15 weeks and after the 2 months follow-up</p> <p><b>Colorectal Cancer:</b> The authors of Cazacu 2003 stated that adverse effects of chemotherapy pertaining to the gastrointestinal tract and/or bone marrow had been found in four patients of the group exclusively treated with chemotherapy and in none of the patients who had received mistletoe extracts in addition to chemotherapy, but without reporting further details. Douwes 1986a reported inconsistently on the rates of chemotherapy-associated side effects and a referenced table was not included in the publication.</p> <p>In Heiny 1997, health related QOL during chemotherapy was assessed every 6 weeks with the FACT questionnaire. After the second cycle of chemotherapy, authors reported a significantly higher FACT sum score for patients of the mistletoe group. Concerning adverse effects of chemotherapy, a lower incidence of grade III mucositis in the mistletoe group was reported, but no differences were found for rates of nausea, vomiting, diarrhoea and hand-foot syndrome. A lower rate of leukopenia (32.1% versus 38.7%) was reported for patients of the mistletoe group without presentation of further details.</p> <p><b>Various types of cancer:</b> Lange 1993 investigated 44 participants with inoperable cancer of the ENT tract, lung or ovary. Evaluation was restricted to two cycles of chemotherapy. Application of the combination chemotherapy with cisplatin and ifosfamide at full dose (defined as equal to 85% of the scheduled dose) was possible more frequently in patients of the mistletoe group. Mean performance index (Karnofsky) rose in both groups during the first cycle of chemotherapy, but the increase was significantly higher in the mistletoe group. All symptom scores for nausea, pain and vomiting were lower in the patients who had received mistletoe extracts. The difference was statistically significant for</p>			
---	--	--	--

<p>nausea and pain during the 5 following days after the first cycle of chemotherapy. Leukocytes regenerated to significant higher values after the second cycle of chemotherapy in patients who had received mistletoe extracts (<math>p = 0.003</math>, test not stated). No differences between the mistletoe and control group were found for chemotherapy-related hepato- and renotoxicity.</p> <p>Piao et al evaluated the influence of mistletoe extracts compared to lentinan on chemotherapy-related side effects, performance index and QOL in patients with all stages of breast, ovarian or non-small cell lung cancer (Piao 2004). The authors evaluated all outcomes before start of chemotherapy and after termination. Changes in Karnofsky's performance Index during the treatment period were classified as reduced or increased in case of a difference of at least 10%, otherwise as stable. A significantly larger rate of increased or stable performance indices was found in the mistletoe group compared with the control group (96.5% versus 89%). Twenty-eight adverse events related to chemotherapy were reported for the mistletoe group compared to 77 for the control group, but were not further described. Health-related QOL was measured with the FLIC and a median improvement of the sum score of 6.0 points was reported for the mistletoe group compared with 3.0 points for the control group. Changes in the TCM score showed a median improvement for the mistletoe group of -1 compared to 0 for the control group.</p> <p><b>Assessment during radiotherapy:</b> In Lenartz 2000, a better QOL in patients with malignant glioma of the mistletoe group was reported 12 and 24 weeks after surgery. Data were not statistically analysed and the results of the five subscales of the questionnaire were not presented.</p> <p><b>Assessment during rehabilitation:</b> Schwiersch 1999 assessed measures of psychosocial distress and QOL in women with breast cancer during a 4-week oncological rehabilitation after completion of adjuvant therapy. No significant differences between the groups were found in psychosocial distress (FBK-KF), Karnofsky's performance index and overall QOL (SF-36). However, for the subscale vitality of the SF-36, significantly higher values were found in the mistletoe group. Also for the subscale energy/joie de vivre of the questionnaire on life satisfaction significantly higher values were found in the mistletoe group.</p> <p><b>Assessment during sole mistletoe treatment:</b> Borrelli 1999 assessed QOL with Spitzer's Quality of Life Index</p>			
--	--	--	--

<p>(QLI) (Spitzer 1981) in women with metastatic breast cancer who had completed chemo-/radiotherapy. QLI mean scores increased in the mistletoe group from baseline to follow-up after one and three months, whereas corresponding mean scores in the control group decreased. Differences in estimates at three-months followup were statistically significant. Dold 1991 assessed wellbeing, Karnofsky's performance index and symptom scales in patients with lung cancer. Fifty-nine percent of patients receiving mistletoe extracts perceived an improvement in their wellbeing (patient statement documented by the physician) compared to 45% in the placebo group. The difference was statistically significant (<math>p = 0.018</math>). No significant difference was found between the mistletoe and the placebo group for Karnofsky's performance index. Assessment of QOL by means of symptom scales (patient's degree of discomfort documented by the physician) including fatigue, pain, loss of appetite, dyspnea, fever and others revealed no significant differences. Steuer-Vogt 2001 assessed QOL with the QLQ-C30 over a maximum period of 156 weeks (median 95 weeks) and 399 patients completed 3611 questionnaires. Data were analysed in a repeated measurement model which differentiated between treatment effects, time effects and treatment-time interaction. Although one group of patients received mistletoe extracts during radiotherapy (stratum B) data of the comparison between the mistletoe group and the control group were presented unstratified. Authors reported no significant differences between groups for overall QOL and five subscales.</p> <p><b>Assessment in an unclear therapeutic setting:</b> In both of Grossarth et al's trials, psychosomatic self-regulation was assessed after three months of treatment with mistletoe extracts (Grossarth 2001a;Grossarth 2001b). In patients with various types of cancer, mean score for self-regulation increased significantly within three months in the mistletoe group, whereas a decrease was found in the control group. The difference in the change in self-regulation values was statistically significant (<math>p = 0.02</math>, Mann-Whitney test) (Grossarth 2001a). In patients with breast cancer, mean scores for self-regulation increased within three months from 2.92 at baseline to 3.70 in the mistletoe group (<math>p = 0.01</math>, Wilcoxon test) compared with a non significant increase from 2.87 to 2.99 in the control group. The difference in the change in self-regulation values between groups was not statistically significant (<math>p = 0.13</math>, Mann-Whitney test) (Grossarth 2001b).</p>			
<p><b>Adverse Effects:</b></p> <p>Twelve studies reported on side effects related to the treatment with mistletoe extracts</p>			

<p>(Auerbach 2005; Dold 1991; Goebell 2002; Heiny 1991; Heiny 1997; Kleeberg 2004; Luemmen 2001; Piao 2004; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001) All authors recorded local or systemic reactions, with the exception of one in which no patient experienced adverse effects of mistletoe extracts (Goebell 2002). Local reactions were most commonly rubor, prurigo and induration at injection site, typical systemic reactions were mild fever and flu-like symptoms. Patients in Schwiersch's trial experienced no systemic side effects. Five patients in Kleeberg 2004, 1 in Semiglasov 2006 and 43 in Steuer-Vogt 2001 discontinued mistletoe treatment due to adverse effects. In the Piao 2004 trial they described one patient with angioedema and urticaria which was related to mistletoe application and recovered two days after discontinuation of study medication. In Semiglasov 2004, mistletoe extracts evoked reactions at injection site in 9% of patients of the low dose mistletoe group, in 18% of those who were in the medium dose mistletoe group, and in 32% of those treated with high doses.</p>			
<p>Abbreviations: CI = confidence interval; DFS = disease-free survival; OS = overall survival</p>			

## Appendix C: The Ottawa Method Qualitative Signals\*

### Potentially invalidating change in evidence

This refers to a situation in which it is expected that clinicians do not act upon the results of the original systematic review (SR) and the agency/organization that supported the original production of the SR would retract the SR until it is updated. Criteria for potentially invalidating change in evidence are presented below.

This category of signals (A1-A3) specifies findings from a pivotal trial\*\*, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

### Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of “opposing findings” – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

\* Please, see Shojania et al. 2007 for further definitions and details

\*\*A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

#### **Appendix D: Modified PRESS Review for Original Review's Search Strategy**

The original searches were performed in August 2007 and updated in 2008 (no specific dates provided). Multiple databases were searched, including both the Cochrane Complementary Medicine and Gynaecological Cancer registers. The strategy is logically constructed from a PICO standpoint, with no language or date limits. However, there are some limitations both with regard to the search strategy itself and the documentation.

The search terms are available in an appendix and incorporate both English- and German-language terms. However, it is not readily apparent which database or search platform is represented. The strategy is a textual representation of the search statements and set numbers and does not show the strategy exactly as run in each database, complete with full database name and version, fields searched (including controlled vocabulary), date run, and number of hits per line. As such, the strategy is not fully transparent.

Most of the limitations pertaining to the strategy pertain to the vocabulary. There are additional terms for cancer, including but not limited to adenoma, adenocarcinoma, carcinoma, carcinosarcoma, lymphoma, malignancy, mesenchymoma and metastatic. There appear to be additional terms for mistletoe (e.g., Loranthaceae, Phoradendron) and mistletoe extract (e.g., detensyl, guipsine), although this would need to be confirmed with the clinical team as to their applicability in this context. Perhaps most limiting, is the requirement for the terms "therap\*" or "medicine\*", since this would exclude other related terms such as treatment, phytotherapy, or (disease) management.

In conclusion, the strategy has limitations both with regard to vocabulary and documentation, and relevant citations may have potentially been missed.

## Appendix D: Excluded studies

Axtner J, Steele M, Kroz M, Spahn G, Matthes H, Schad F. Health services research of integrative oncology in palliative care of patients with advanced pancreatic cancer. *BMC Cancer*. 2016; 16:579. [PMID: 27485618]

Beuth J, Schneider B, Schierholz JM. Impact of complementary treatment of breast cancer patients with standardized mistletoe extract during aftercare: a controlled multicenter comparative epidemiological cohort study. *Anticancer Res*. 2008 Jan-Feb;28(1B):523-7. [PMID:18383896]

Bock PR, Hanisch J, Matthes H, Zänker KS. Targeting inflammation in cancer-related-fatigue: a rationale for mistletoe therapy as supportive care in colorectal cancer patients. *Inflamm Allergy Drug Targets*. 2014;13(2):105-11. [PMID: 24766319]

Eisenbraun J, Scheer R, Kröz M, Schad F, Huber R. Quality of life in breast cancer patients during chemotherapy and concurrent therapy with a mistletoe extract. *Phytomedicine*. 2011 Jan 15;18(2-3):151-7. [PMID:20724129]

Friedel WE, Matthes H, Bock PR, Zänker KS. Systematic evaluation of the clinical effects of supportive mistletoe treatment within chemo- and/or radiotherapy protocols and long-term mistletoe application in nonmetastatic colorectal carcinoma: multicenter, controlled, observational cohort study. *J Soc Integr Oncol*. 2009 Fall;7(4):137-45. [PMID: 19883529]

Grossarth-Maticsek R, Ziegler R. Prospective controlled cohort studies on long-term therapy of ovarian cancer patients with mistletoe (*Viscum album L.*) extracts iscador. *Arzneimittelforschung*. 2007;57(10):665-78. [PMID:18074761]

Grossarth-Maticsek R, Ziegler R. Randomized and non-randomized prospective controlled cohort studies in matched pair design for the long-term therapy of corpus uteri cancer patients with a mistletoe preparation (Iscador). *Eur J Med Res*. 2008 Mar 31;13(3):107-20. [PMID: 18499556]

Rexer H. Therapy of untreated local advanced or metastatic renal cell carcinoma. Phase III, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, local advanced or metastatic renal cell carcinoma (CheckMate 214 - AN 36/15 of the AUO). *Urologe A*. 2015 Oct;54(10):1443-5. [PMID:26350358]

Rexer H, Geschäftsstelle der AUO. Study for the treatment of nonmuscle invasive bladder cancer : A phase III efficacy trial for intravesical instillation of mistletoe extract in superficial bladder cancer (TIM) - AB 40/11 of the AUO. *Urologe A*. 2016 Jul;55(7):963-5. [PMID:27272001]

Rose, A, El-Leithy T, vom Dorp F, Zakaria A, Eisenhardt A, Tschirdewahn S, Rübber H. Mistletoe plant extract in patients with nonmuscle invasive bladder cancer: results of a phase Ib/IIa single group dose escalation study. *J Urol*. 2015 Oct;194(4):939-43. [PMID: 25910967]