Published Helixor studies

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Combined Immune Checkpoint Blockade and Helixor® Therapy in Oncology: Real-World Tolerability and Subgroup Survival (ESMO GROW)

Thronicke A et al. Int. J. Mol. Sci. **2025**, 26(8), 3669;
https://doi.org/10.3390/ijms26083669

Trial site, country	Network Oncology registry (Hospital Havelhoehe, Berlin, Germany)
Study medication	Helixor® A/M/P (i.v./s.c.)
Concomitant oncological treatment	1. Various Checkpoint blockade therapies (ICB) 2. PD-1/PD-L1 inhibitors)
Study design	Controlled, not randomised, RWD-Study COMB group: PD-1/PD-L1 + Helixor® Control goup: PD-1/PD-L1
Cancer entities	Safety: various tumor entities Efficacy: NSCLC
No. of patients	312 (COMB: n=34; Control: n=278)
Outcome	Comparable tolerability and slightly fewer treatment discontinuations due to ir adverse events (4.9 % vs. 6.4 %; not significant) in patients receiving ICB + Helixor® (COMB group). The 3-year survival rate was significantly higher with Helixor® (34.3 % vs. 17.2 %, p=0.022), but not the 5-year survival rate (22 % vs. 8.8 %; p=0.058). Women in the COMB group showed a 91.2 % reduced risk of death: survival rates (COMB vs. control) after 3 years = 66.8 % vs. 26.9 % (p=0.0123), after 5 years = 50.1 % vs. 12 % (p=0.0021).
Benefit of study	• Real World Evidence • The results indicate a potential synergy of Helixor® with ICB therapy, especially in female NSCLC patients, without this combination entailing additional safety risks.

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Patients with Advanced or Metastasised Non-Small-Cell Lung Cancer with *Viscum album* L. Therapy in Addition to PD-1/PD-L1 Blockade: A Real-World Data Study

Schad F, et al. Cancers **2024**, 16, 1609;
https://doi.org/10.3390/cancers16081609

Prüfzentrum, Land	Krankenhaus Havelhöhe, Berlin
Prüfpräparat	Unspecified *Viscum album* (VA) preparations from Helixor®, Abnoba® and/or Iscador®
Begleitende onkologische Behandlung	ICI: PD-1/PD-L1 inhibitors
Studiendesign	controlled, not randomised, RWD-Study COMB group: PD-1/PD-L1 inhibitors + VA Control group: PD-1/PD-L1 inhibitors only
Tumorentitäten	advanced or metastasized (UICC stages III–IV) NSCLC
Anzahl Patienten	415 (Control: n=222, COMB: n=193)
Ergebnis	The COMB group showed a significantly longer median survival time of 13.8 months compared to 6.8 months in the control group (immunotherapy only). The adjusted hazard ratio for the risk of death was reduced by 40 % in the combination group (aHR 0.60; p = 0.004). In a subgroup analysis with PD-L1-positive tumors and first-line therapy, the risk reduction was as high as 56% (aHR 0.44; p = 0.002)
Nutzen/Vorteil der Studie	• Additive VAT (e.g. Helixor®) provides significant survival benefit in NSCLC patients • Clinical benefit is supported by results • Synergistic effects with ICIs create potential for R&D and therapeutic expansion • Real-world data confirm the relevance of Helixor products for evidence-based use in routine clinical practice

Published Helixor studies

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Safety of Combined Targeted and Helixor® Viscum album L. Therapy in Breast and Gynecological Cancer Patients, a Real-World Data Study

Schad F, Thronicke A. Int. J. Environ. Res. Public Health **2023**, 20, 2565;
https://doi.org/10.3390/ijerph20032565

Trial site, country	Network Oncology registry (Hospital Havelhoehe, Berlin, Germany)
Study medication	Helixor® A/M/P (i.v./s.c.)
Concomitant oncological treatment	Targeted Therapies (PARP inhibitors, CDK 4/6 inhibitors, mAB, ICI, TKI)
Study design	controlled, not randomised, RWD-Study COMB group: Targeted Therapy (TT) + Helixor® Control group: Targeted Therapy (TT)
Cancer entities	Breast and gynecological tumors
No. of patients	242 (COMB: n=82; Control: n=160)
Outcome	Included were n = 242 patients (mean age: 54.5 ± 14.2 years): 66.1 % in the control group, 33.9 % in the COMB group. The additional administration of Helixor® did not affect the safety of TT and was not associated with an increased rate of adverse events. On the contrary, no side effects occurred in the combination group and there was a trend towards better treatment adherence. A 56% reduced (not significant) probability of AE/dose reduction/treatment disruption of the targeted therapy when Helixor® therapy was added.
Benefit of study	The present study is the first of its kind to demonstrate the applicability of Helixor® in combination with targeted therapies. The results indicate that the Helixor® add-on does not adversely affect the safety profile of targeted therapies in breast and gynecologic cancer patients and may improve their tolerability.

Published Helixor studies

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Phase I Trial of Intravenous Mistletoe Extract in Advanced Cancer

Paller C et al. Cancer Res Commun **2023**, 3(2)
https://doi.org/10.1158/2767-9764.CRC-23-0002

Trial site, country	Johns Hopkins University, Baltimore, USA
Study medication	Helixor® M i.v. (150 – 300 – 600 – 900 mg)
Concomitant oncological treatment	none
Study design	Phase I, dose escalation study, (3+3 dose escalation scheme, monocentric)
Cancer entities	Advanced diseases of solid tumors (colorectal Ca, ovarian Ca, pancreatic Ca, appendix Ca, basal cell Ca, breast Ca, lung Ca, melanoma, neuroendocrine Ca, salivary Ca, synovial and uterine leiomyosarcoma)
No. of patients	21
Outcome	• MTD = 600 mg • (manageable toxicities with disease control and improved QoL in a heavily pretreated solid tumor population) • stable disease and tumor shrinkage were observed in some heavily pretreated patients
Benefit of study	The study is a scientifically sound starting point for establishing and further developing parenteral administration internationally: it showed for the first time that Helixor® M administered intravenously is tolerable and is associated with stable disease and improved quality of life in heavily pretreated patients. The maximum tolerated dose (MTD) was 600 mg three times a week (= basis for further studies). The efficacy as a complementary form of therapy is supported by immunological effects and signs of disease control.

Published Helixor studies

Pharmacokinetics of mistletoe lectin in healthy volunteers after intravenous infusion of Helixor® P

Lederer AK et al. Pharmaceuticals (2024) 17(3):278;
https://doi.org/10.3390/ph17030278

Trial site, country	University Center for Naturopathy, University Hospital Freiburg, Deutschland
Study medication	Helixor® P single infusion of 2000 mg
Concomitant oncological treatment	not applicable, as healthy subjects
Study design	Non-controlled, non-randomized, open-label, monocentric pharmacokinetic phase I study
Cancer entities	not applicable, as healthy subjects
No. of patients	8 (planned: 12)
Outcome	This study demonstrated for the first time that ML from Helixor®, in this case after administration of a single dose of Helixor® P 2.000 mg IV, is detectable in serum. In all 8 subjects, an unexpected increases in the transaminases ASAT and ALAT were observed within a period of 48 - 72 hours after the end of the administration of the investigational product, suggesting a transient acute hepatitis, but without cholestasis and clinical symptoms. Since the dose of 2,000 mg intravenous Helixor® P induced this transient hepatic impairment in healthy volunteers, it should not be used for the initial treatment of patients.
Benefit of study	Important findings on the turnover of mistletoe lectin as a pharmacologically relevant ingredient of mistletoe preparations. For Helixor® preparations in particular, these results may be significant both for regulatory purposes and for the possible further development of intravenous infusion as a supplement to the approved subcutaneous injection.

Published Helixor studies

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Influence of Helixor® P infusion therapy on cancer-related fatigue (CrF) in patients with advanced breast cancer or patients with NSCLC under breast cancer or patients with NSCLC undergoing standard oncologic therapy - pilot study -
(not published)

Trial site, country	• Zentralklinik Bad Berka GmbH • Brustzentrum City Berlin (Sankt Gertrauden-Krankenhaus) • Gemeinschaftskrankenhaus Havelhöhe gGmbH • Interdisziplinäres Tumorzentrum Universitätsmedizin Mannheim • Zentrum für Ganzheitliche Onkologie, Rodgau • Klinikum Chemnitz gGmbH • Krankenhaus für Naturheilweisen, München • Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Universitätsmedizin Greifswald • Städtisches Klinikum Brandenburg GmbH • Klinikum Ludwigsburg GmbH (Mamma-Ca) • Klinikum Ludwigsburg GmbH (NSCLC) • SHG-Kliniken Völklingen
Study medication	Helixor® P i.v. 100 mg (treatment group 1: Helixor® P i.v. 500 mg, treatment group 2: Helixor® P i.v. 1.500 mg, treatment group 3: isotonic NaCl solution = control)
Concomitant oncological treatment	Standard oncological therapy
Study design	prospective, randomized, double-blind, three-arm, multicenter, national phase II pilot study
Cancer entities	advanced breast cancer NSCLC
No. of patients	8 (planned: 144)
Outcome	The primary objective of this prospective randomized, double-blind pilot study was to test the effect of Helixor® P infusion therapy on cancer-related fatigue (CrF) in patients with advanced

	breast cancer or patients with NSCLC undergoing standard oncological therapy. As it was not possible (COVID-19 lockdowns) to recruit a sufficient number of patients in a reasonable time, the study was terminated prematurely; as a result, the primary objective was not achieved.
Benefit of study	• Medical university centers as trial centers • The practical experience gained nevertheless suggests that it is also possible in principle to investigate the effect of infusion therapy with Helixor® in the setting of a double-blind clinical trial. There were no new findings on the safety profile of Helixor®.

Helixor® Infusion Study: a prospective dose finding study

Huber R et al. BMC Complementary and Alternative Medicine (**2017**) 17:465;
DOI 10.1186/s12906-017-1971-1

Trial site, country	Center for Complementary Medicine, University Medical Center Freiburg, Germany
Study medication	Helixor® P IV 100 mg – 2000 mg (dose groups 200 – 400 – 700 – 1200 – 2000 mg)
Concomitant oncological treatment	None
Study design	Phase I, dose escalation study (3+3 dose escalation); monocenter
Cancer entities	Different types of advanced cancer: prostate cancer, colorectal cancer, renal cell carcinoma, hepatocellular cancer, sarcoma, glioblastoma, lung cancer, stomach cancer, pancreatic cancer, gall bladder cancer, tonsil cancer, thyroid (C-cell) cancer, thrombocythemia
No. of patients	21
Outcome	Weekly infusions of 2000 mg Helixor® P were well tolerated but had a certain risk for allergic reactions and fever
Benefit of study	• Medical center of university as trial site • Determination of maximum tolerated dose (MTD) of Helixor® P: 2000 mg as dose frame for further eligible studies

NCCAM/NCI Phase 1 Study of Mistletoe Extract and Gemcitabine in Patients with Advanced Solid Tumors

Mansky P.J et al. Hindawi Publishing Corporation. Evidence-Based Complementary and Alternative Medicine Volume **2013**, Article ID 964592, 11 pages; http://dx.doi.org/10.1155/2013/964592

Trial site, country	National Naval Medical Center, Bethesda, Maryland, United States
Study medication	Helixor® A s.c. 1 mg – 250 mg
Concomitant oncological treatment	Gemcitabine
Study design	Phase I, dose escalation study with 2 stages; monocenter; Investigator initiated trial (IIT)
Cancer entities	Far advanced solid tumors (stage IV): pancreatic, colorectal and breast cancer, NSCLC
No. of patients	44
Outcome	• Helixor® A enables better tolerance of chemotherapy, allowing a 30 % higher dose of gemcitabine as compared to monotherapy. In this way, a higher efficiency of chemotherapy might be expected • indications for stabilization of immune system (e.g. increase instead of expected decrease of neutrophils in stage 1) • metabolism of gemcitabine is not affected.
Benefit of study	• USA • outcome shows efficacy • higher chemo dose or less side effects at same chemo dose possible • proof of lack of interaction with chemotherapy.

Published Helixor studies

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Impact of Complementary Mistletoe Extract Treatment on Quality of Life in Breast, Ovarian and Non-small Cell Lung Cancer Patients. A Prospective Randomized Controlled Clinical Trial

Piao B.K et al. Anticancer Research 24: 303-310 **(2004**)

Trial site, country	Oncological centers in Beijing, Shenyang and Tianjin, China
Study medication	Helixor® A s.c. 1 mg – 200 mg vs. Lentinan
Concomitant oncological treatment	Breast cancer: CAP, CAF Ovarian cancer: CP, IcP NSCLC: VP, MVIP
Study design	Phase III, prospective, randomized, open; multicenter (3)
Cancer entities	Breast cancer, ovarian cancer, NSCLC
No. of patients	233 (analyzed: verum: n=115, control=109)
Outcome	• significant superiority of Helixor® A compared to Lentinan in all three test systems used for assessment of Quality of life • KPI increase 50.4 % (verum) as compared for 32.5 % (control) • FLIC-score improve by 6 points (verum) as compared to 3 points (control) • TCM-score improved by 1 point (verum) as compared to no change (control) • the following QoL parameters were significantly improved with mistletoe therapy: fatigue, insomnia, anorexia, nausea, pain, physical activity • significantly less side effects of chemotherapy (i.a. nausea, vomiting, bone marrow depression, infections) in the verum group • good tolerance and low rate of side effects of Helixor® A
Benefit of study	• statistical analysis conducted by the Institute for Biometrics and Informatics of the Heidelberg University

	• amount of patients • superiority of Helixor® even compared to an active comparator with similar indication

Published Helixor studies

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Additional Therapy with a Mistletoe Product during Adjuvant Chemotherapy of Breast Cancer Patients Improves Quality of Life: An Open Randomized Clinical Pilot Trial

Tröger W et al. Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume **2014**, Article ID 430518, 9 pages;
http://dx.doi.org/10.1155/2014/430518

Trial site, country	Institute of Oncology and Radiology, National Cancer Research Center of Serbia, Belgrade
Study medication	Helixor® A s.c. 1 mg – 200 mg
Concomitant oncological treatment	CAF
Study design	Phase II, prospective randomized open label pilot study
Cancer entities	Breast cancer patients, stage I-III
No. of patients	95 (Helixor® A: n=34; control: n=31, other mistletoe product: n=30)
Outcome	• Helixor® A group superior to control group with respect to almost all EORTC-QLQ-C30 scores • 10 out of 15 scores significantly different ($p < 0.05$) • 8 of these 10 differences were of clinical relevance
Benefit of study	• improved quality of life during chemotherapy • better tolerance of chemotherapy • fewer delayed CAF cycles • beneficial application of Helixor® A in adjuvant therapy situation

Fünf-Jahres-Nachbeobachtung von Patientinnen mit Brustkrebs nach einer randomisierten Studie mit Viscum album (L.) Extrakt

Tröger W et al. Deutsche Zeitschrift für Onkologie 48: 105-110 (**2016**)

Follow up after 5 years
as add on-analysis to main study

Trial site, country	Institute of Oncology and Radiology, National Cancer Research Center of Serbia, Belgrade
Study medication	Helixor® A s.c. 1 mg – 200 mg
Concomitant oncological treatment	CAF
Study design	5-year follow up observation as follow up to main study
Cancer entities	Breast cancer patients, stage I-III
No. of patients	• Main study: 95 (Helixor® A: n=34; control: n=31, other mistletoe product: n=30) • 5-year follow up: analyzed: Helixor® A: n=28, control: n=29
Outcome	• no negative effects on the effectiveness of chemotherapy of breast cancer patients with regard to relapse and metastasis within 5 years
Benefit of study	• proof that better tolerance of chemotherapy is not the result of reduced effectiveness

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Impact of Complementary Treatment of Breast Cancer Patients with Standardized Mistletoe Extract during Aftercare: A Controlled Multicenter Comparative Epidemiological Cohort Study

Beuth J et al. Anticancer Research 28: 523-528 (2008)

Trial site, country	53 representative trial centers Germany
Study medication	Helixor® A/M/P s.c.
Concomitant oncological treatment	None
Study design	Epidemiologic cohort study, randomized, retrospective, multicenter
Cancer entities	Breast cancer stage I-III
No. of patients	741 (Helixor® A/M/P: n=167; control: n=514; therapy changed: n=60)
Outcome	• complementary treatment with Helixor® A/M/P during aftercare proved to be beneficial for breast cancer patients • significantly improved quality of life • significantly fewer complaints of patients • reduced number of disease / therapy-related symptoms
Benefit of study	• 5 year time window of Helixor® monotherapy • Helixor® treatment in the tumor after-care • pharmaeconomic aspects were included • best benefit achieved in the 5th year justifying long-term treatment

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Signifikant höherer Anteil aktivierter NK-Zellen durch additive Misteltherapie bei chemotherapierten Mamma-Ca-Patientinnen in einer prospektiv-randomisierten doppelblinden Studie

Auerbach L et al. Fortschritte in der Misteltherapie. Aktueller Stand der Forschung und klinische Anwendung. 543 – 554 (**2005**)

Trial site, country	Department of Special Gynecology, University Hospital Vienna, Austria
Study medication	Helixor® A s.c. 1 mg – 100 mg
Concomitant oncological treatment	CMF or radio-chemotherapy (CMF – radiotherapy – CMF)
Study design	Phase IV, randomized, double blinded clinical pilot study, monocenter
Cancer entities	Breast cancer
No. of patients	23 (analyzed: verum: n=9, control: n=11)
Outcome	• no impact on general QoL (EORTC QLQ-30) found • significant stabilization of 'activated natural killer cell count' during chemotherapy / radio-chemotherapy • patients from the verum group showed no leucopenia and used less supportive treatment during the period of chemotherapy • feasibility: early unblinding of all patients and physicians
Benefit of study	• double-blinded randomized controlled trial (for Helixor® A therapy s.c.) demonstrating non-feasibility of double-blinding of mistletoe therapy • demonstration of immunoprotection under clinical conditions

Published Helixor studies

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Comparison of survival time of patients with different tumor entities - results of retrospective investigations for efficacy of mistletoe therapy vs. data from a tumor registry

Stumpf C et al. Phytomedicine 14 (Suppl VII): 42 (**2007**)

Vergleich der Überlebenszeit bei Patienten mit verschiedenen Tumorentitäten – Retrospektive Untersuchung zur Wirksamkeit von Misteltherapie vs. Daten eines Tumorregisters

Stumpf C et al. Die Mistel in der Tumortherapie 2: 427 – 440 (**2009**)

<table>
<tr><td>Trial site, country</td><td>Gemeinschaftskrankenhaus Herdecke (GHK) Germany</td></tr>
<tr><td>Study medication</td><td>Helixor® A/M/P vs. comparative collectives (Epidemiologic tumor register of Saarland (EKRS))</td></tr>
<tr><td>Concomitant oncological treatment</td><td>Oncological standard therapies (resp. unknown therapies) according to tumor entity</td></tr>
<tr><td>Study design</td><td>Retrospective, epidemiologic cohort study, monocenter</td></tr>
<tr><td>Cancer entities</td><td>Breast cancer, colorectal cancer, pancreatic cancer, malignant melanoma, lymphoma</td></tr>
<tr><td>No. of patients</td><td>41.757 Patients (analyzed: verum (V): n=1475, control (C): n=12214)</td></tr>
<tr><td>Outcome</td><td>• Significantly longer survival (both 5- / 10-year-survival) as compared to patients of GHK for all tumor entities:
<table>
<tr><td colspan="3">Lymphoma (V: n=221, C: n=5209)</td></tr>
<tr><td>V: 86.4% / 81.4%</td><td>p < 0.001 / < 0.001</td><td>C: 38.7% / 29.3%</td></tr>
<tr><td colspan="3">Colon cancer (V: n=323, C: n=8121)</td></tr>
<tr><td>V: 55.1% / 50.8%</td><td>p = 0.009 / = 0.002</td><td>C: 47.7% / 41.9%</td></tr>
<tr><td colspan="3">Breast cancer (V: n=857, C: n=6808)</td></tr>
<tr><td>V: 90.3% / 86.1%</td><td>p < 0.001 / < 0.001</td><td>C: 70.8% / 61.2%</td></tr>
</table></td></tr>
</table>

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	Malignant melanoma (V: n=52, C: n=515) V: 88.5% / 88.5% | p = 0.001 / < 0.001 | C: 63.7% / 57.3% **Pancreatic cancer** (V: n=22, C: n=438) V: 13.6% / 13.6% | p = 0.022 / = 0,003 | C: 3.6% / 2.5 %
Benefit of study	Percentage of patients with one of 5 tumor entities receiving mistletoe therapy surviving 5 and 10 years higher than in control group.

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Immunologic response to mistletoe extract (Viscum album L.) after conventional treatment in patients with operable breast cancer

Son G.S et al. Journal of Breast Cancer 13(1): 14-18 (**2010**)

Trial site, country	Korea University College of Medicine Seoul Korea
Study medication	Helixor® A 1mg – 100 mg after conclusion of chemotherapy
Concomitant oncological treatment	none
Study design	Phase IV prospective randomized, Investigator initiated trial (IIT), monocenter
Cancer entities	Breast cancer stage I-II (invasive ductal)
No. of patients	20 (verum: n=10, control: n=10)
Outcome	• significant higher IFN-γ levels after Helixor® A treatment as compared to controls • slightly increased serum levels of IL-2, IL-4, IL-6, IL-10*, but difference to control group not significant *only in verum group
Benefit of study	• Proof of immunomodulatory effect of Helixor® A under therapy conditions • IFN-γ of special interest (as stimulator of NK cell activity)

Published final report in the study portal "EudraCT"

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Changes of circulating tumour cells in female patients with breast cancer – comparison of a complementary mistletoe therapy with no complementary mistletoe therapy

Klinischer Studienabschlussbericht 26.11.2015

Principal investigator	OA Dr. med. Lars-Olof Mügge
Trial site, country	Fachambulanz für Naturheilkunde in der Onkologie, Klinik für Innere Medizin II der FSU Jena, Germany
Study medication	Helixor® M s.c. 0.1 mg – 200 mg
Concomitant oncological treatment	Hormonal therapy, Herceptin allowed
Study design	Prospective, randomized, phase IV, open, pilot study, monocenter
Cancer entities	Breast cancer stage I-III
No. of patients	52 (27 verum group, 25 control group)
Outcome	• increase of circulating tumor cells no significant difference between verum and control • QoL: a) FACT-G: significant increase of 3 dimensions of exclusively in verum group b) MFI: no effects c) KPI: significant increase in verum group
Benefit of study	• Medical center of university as trial site • medically and scientifically interesting topic: circulating tumor cells but unsatisfying results • supporting QoL-improvement during mistletoe therapy