IMMUCOTHEL®

for recurrence prevention of superficial urinary bladder carcinomas

Patients appreciate the well-tolerated alternative

- less distressing side effects
- effective alternative to BCG
- established treatment in several countries
- easy, no-cost disposal

we are research

biosyn®

Pre-sensitization with IMMUCOTHEL® 1 mg	
TUR	Therapy can be started before or during TUR [A]
	Apply 1 mg s.c. or i.c. in the forearm (positive skin reaction/DTH desired, but not required)

Instillation therapy with IMMUCOTHEL® 10 mg	
1st – 2nd month	Initial therapy
	20 ml (2 × IMMUCOTHEL® 10 mg) weekly in week 1 – 6
3rd – 12th month	Maintenance therapy
	20 ml (2 × IMMUCOTHEL® 10 mg) monthly

[A] Summary of product characteristics IMMUCOTHEL®, biosyn Arzneimittel GmbH, version May 2017.

Alternative after BCG failure

IMMUCOTHEL® is especially after BCG failure or BCG intolerance advisable. These include severe side effects due to BCG. IMMUCOTHEL® can be an alternative for radical cystectomy in patients, when risks, morbidity, and impaired quality of life outweigh the advantages.[1]

Why pre-sensitization?

Pre-sensitization should be performed at the time of TUR. If no skin reaction occurs, pre-sensitization should be repeated. A recent clinical trial showed that it is advisable to start instillation after four days, even without positive skin reaction.[2] A substantial percentage of patients display no skin reaction. However, the absence of skin reaction does not allow a prognosis regarding treatment response to IMMUCOTHEL®.[2]

Summary of the most important aspects

IMMUCOTHEL® is approved as immunotherapy for the prevention of recurrent superficial bladder carcinoma (Tis, Ta-T1 (G1-G3)) after transurethral resection

IMMUCOTHEL® is approved for high-risk tumors as second-line treatment or in the event of failure or contraindication of BCG

Patients appreciate the advantage of comparable effectiveness with significantly fewer side effects compared to BCG therapy

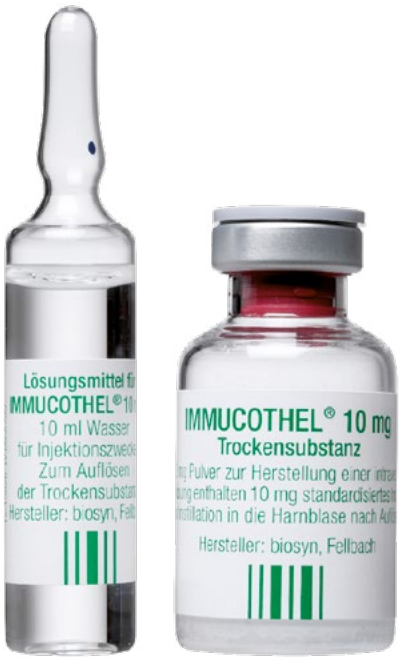
IMMUCOTHEL® can be combined with one immediate instillation of chemotherapy, mostly Mitomycin C, as recommended in the EAU Guidelines

Standard therapy with a cytostatic agent or BCG cannot be used in all patients. Side effects, intolerances, or limited availability (BCG) can present limiting factors

In contrast to cytostatic agents and BCG, IMMUCOTHEL® can be prepared in ready-to-use form without special personal or product protection

The substance can be disposed of along with normal medical practice waste and does not fall under the cytostatic agent/CMR substance ordinance; this is a logistical advantage in daily medical practice routine

Additional information for KLH / IMMUCOTHEL®:
www.biosyncorp.com, www.biosynpharma.com, www.biosyn.de



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Structure of KLH or active component of IMMUCOTHEL®

At a glance
KLH = **K**eyhole **L**impet **H**emocyanin
Isolated from the hemolymph of the sea snail *Megathura crenulata*
Cylindrical, copper-bearing blue protein
One of the largest proteins with 8,000 – 32,000 kDa
Immunocyanin = active component of IMMUCOTHEL®

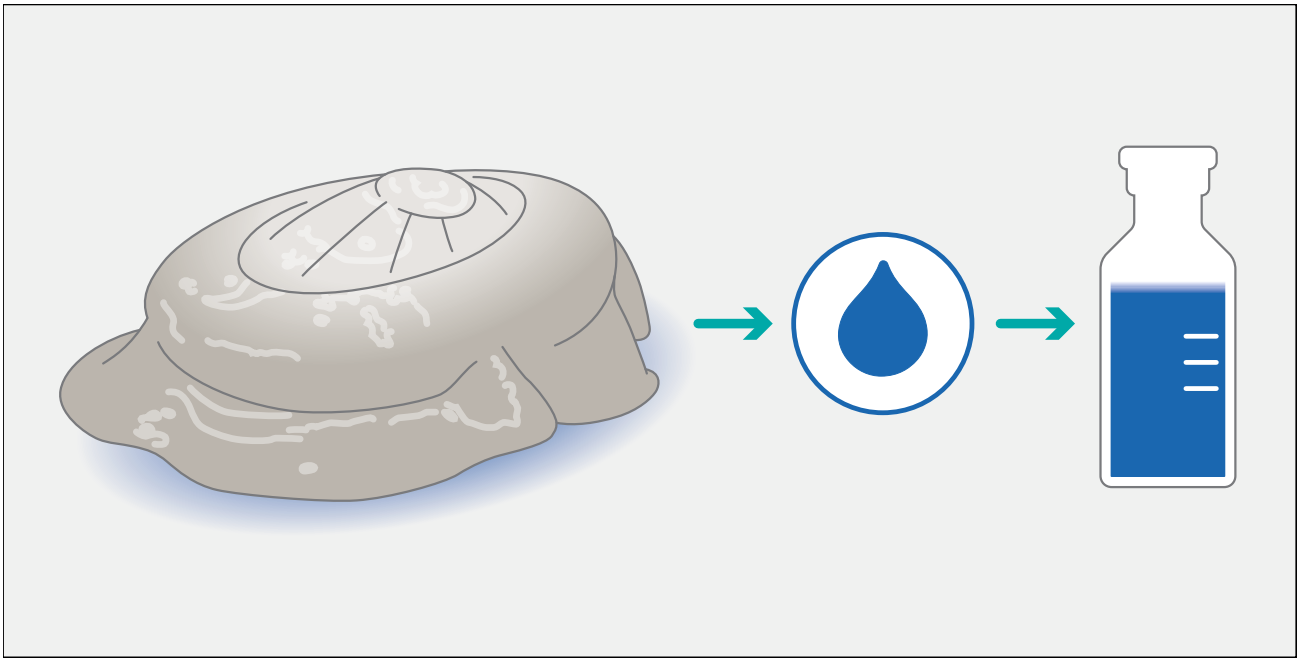
An active ingredient from a sea limpet

Immunocyanin is the active ingredient of IMMUCOTHEL®. It is a stable modification of the hemoglobin hemocyanin (Keyhole Limpet Hemocyanin = KLH), which is isolated from the hemolymph of the sea limpet *Megathura crenulata*. The native KLH is a cylindrical, copper-bearing protein. With a molecular weight of 8,000 – 32,000 kDa, KLH is one of the largest existing proteins.

Why is KLH blue?

Two copper atoms in the active center of KLH cause the blue color of the hemolymph. KLH transports oxygen to the tissues comparable to hemoglobin. As hemoglobin carries iron atoms, it is red.

Giant keyhole limpet, a snail from the family of keyhole snails
(Megathura crenulata)



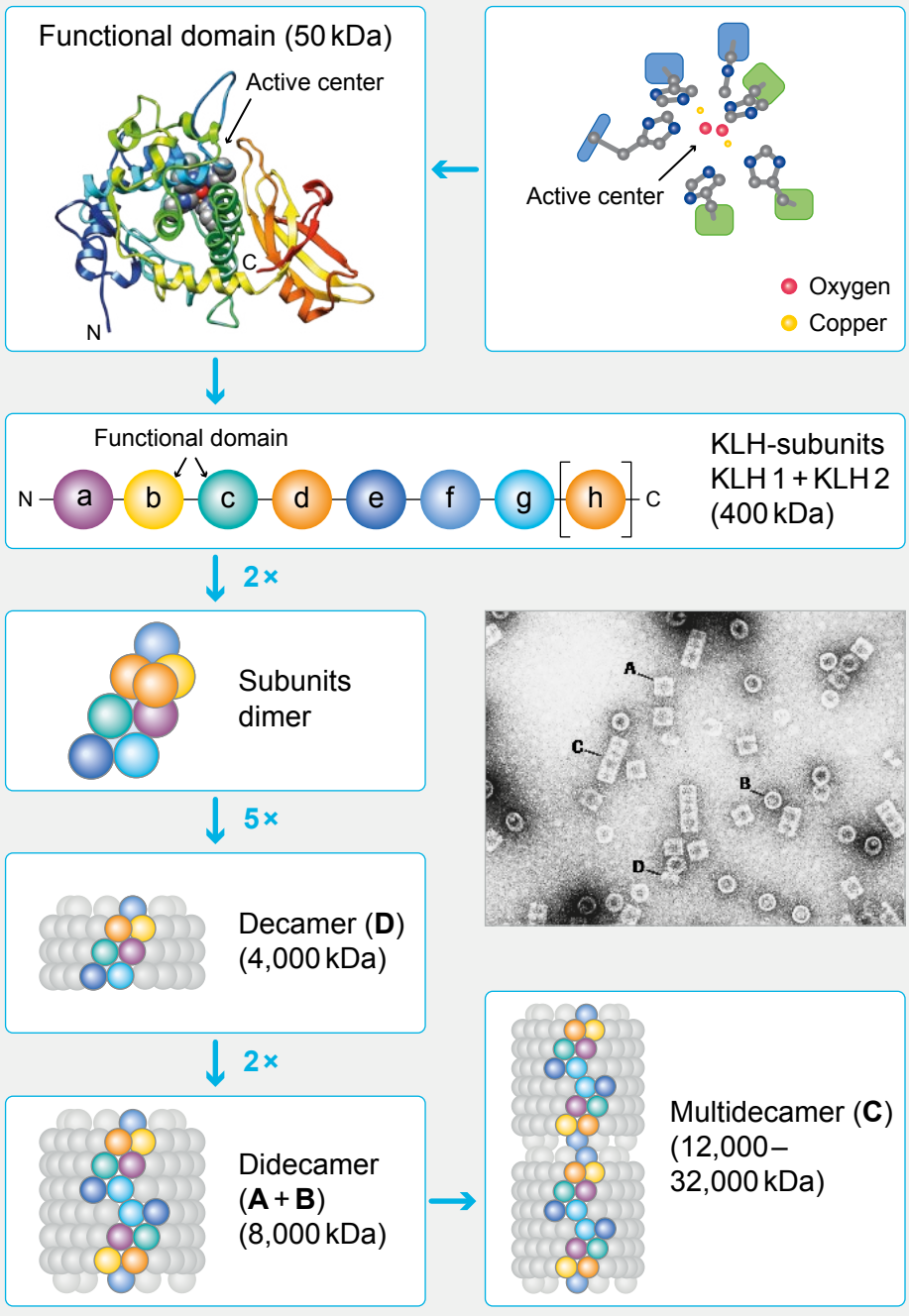
The structure of KLH

KLH is big. It is a multidecamer with a molecular weight of 12,000 – 32,000 kDa. The electronic microscopic image shows that KLH also has a second aggregation type: didecamers with a molecular weight of 8,000 kDa.

Eight functional domains form a KLH subunit (400 kDa), which exists in two different forms: KLH 1 and KLH 2.[3] These two subunits differ both bio-chemically as well as immunologically. Ten KLH subunits form a decamer (4,000 kDa); the basic unit is the dicamer and the multicamer *(Fig. 1)*. The smallest KLH unit is the functional domain (50 kDa) and it contains the active center.[3,4]

KLH is one of the largest known proteins

Structure of KLH



Modified according to:

Markl J. Biochim Biophys Acta. 2013 Sep; 1834(9): 1840-52. Evolution of molluscan hemocyanin structures.

Dissertation “Strukturelle, enzymkinetische und thermodynamische Untersuchungen am KLH, dem Hämocyanin der Schlüssellochschnecke Megathura crenulata” Dr. Kay Büchler (2008).

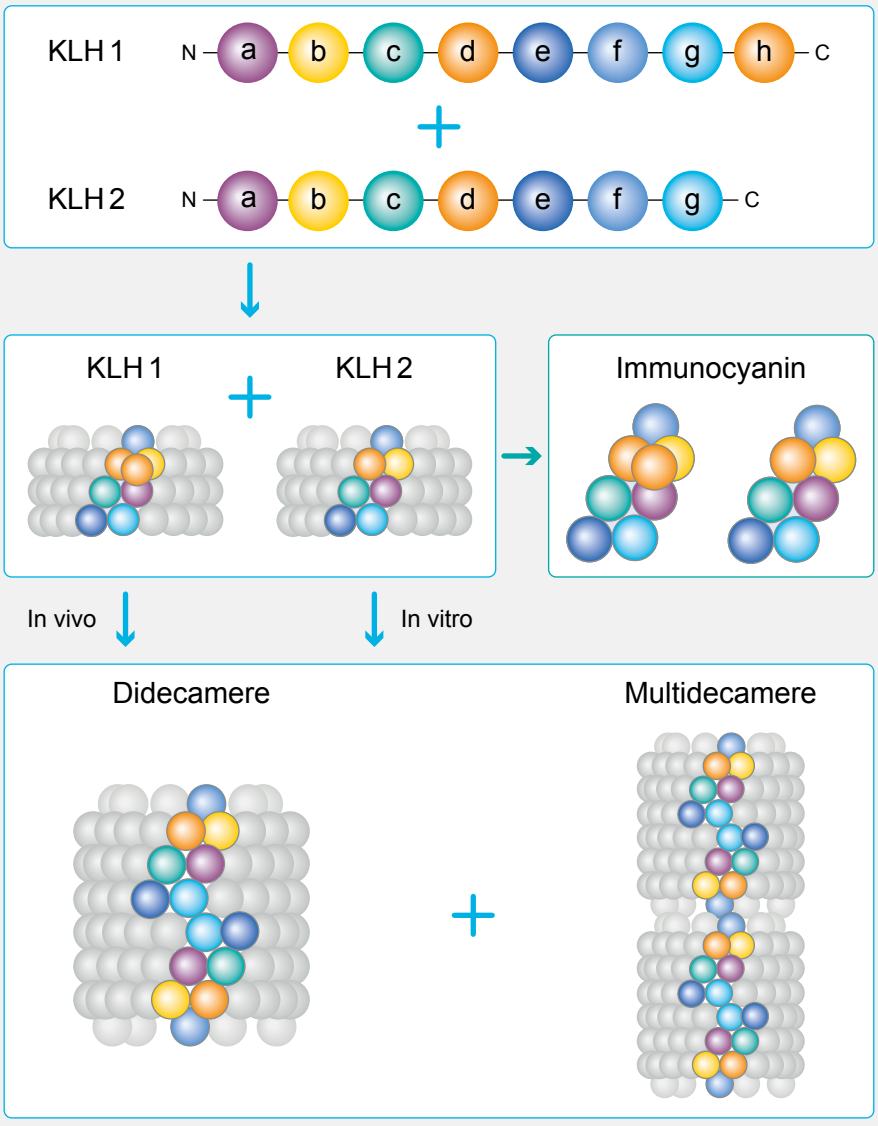
Dissertation “3D-Strukturanalyse von Mollusken-Hämocyaninen aus elektronenmikroskopischen Bildern” Dr. Christos Gatsogiannis (2009).

Fig. 1

What is actually in IMMUCOTHEL®?

As an active ingredient, IMMUCOTHEL® contains immunocyanin, a mixture of the subunits KLH 1 and KLH 2 in a stable modification. Here the native structure of the subunits is completely preserved. Both dicamer and multidecamer KLH forms can be rebuilt again in vitro from IMMUCOTHEL® *(Fig. 2)*.[5]

Composition of IMMUCOTHEL®



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Markl J. Biochim Biophys Acta. 2013 Sep; 1834(9): 1840-52. Evolution of molluscan hemocyanin structures.

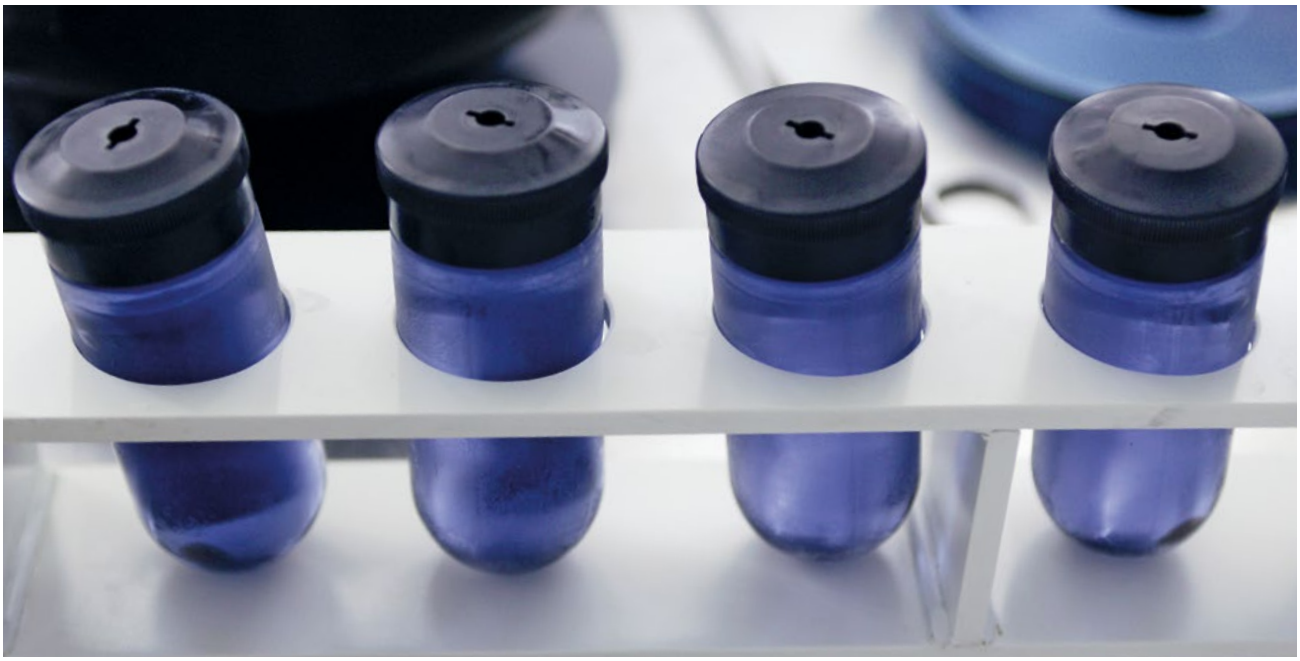
Dissertation “Strukturelle, enzymkinetische und thermodynamische Untersuchungen am KLH, dem Hämocyanin der Schlüssellochschnecke Megathura crenulata” Dr. Kay Büchler (2008).

Markl J. Chemie in unserer Zeit 1996, 30: 6-18. Blaues Blut – Struktur, Funktion und Evolution der Hämocyanine.

Fig. 2

Preparation of the chromatographic cleaning
of keyhole limpet hemocyanin

The blue color comes from copper atoms that bind to the active
center of the glycoprotein hemocyanin of the oxygen



Mechanism of action

At a glance
IMMUCOTHEL® induces a systemic immune response
Strong IMMUCOTHEL® immunogenicity is based on the attached oligosaccharides
Specific antibody reaction against bladder carcinoma cells

IMMUCOTHEL® triggers a strong immune reaction

IMMUCOTHEL® induces a systemic immune response. When the immune system encounters IMMUCOTHEL® for the first time, macrophages are activated. They can immediately act directly against tumor cells. Secondly, macrophages increase the activity of natural killer cells and granulocytes by means of cytokines. Thirdly, macrophages present the antigen with T- and B-lymphocytes for information transfer and at the same time stimulate them by means of cytokines *(Fig. 3)*.

Macrophages can act against tumor cells

Simplified representation of the immune response using IMMUCOTHEL® therapy

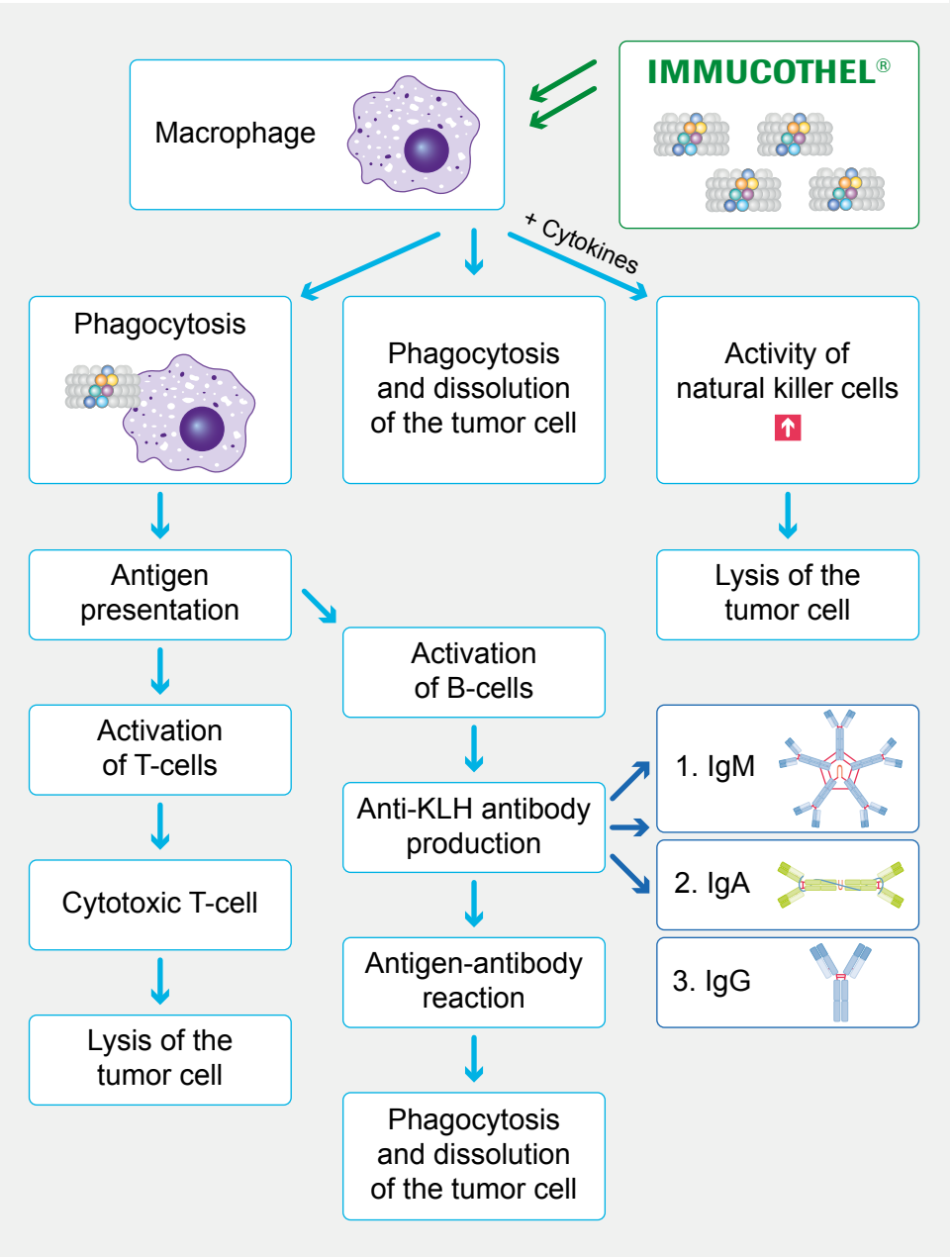


Fig. 3

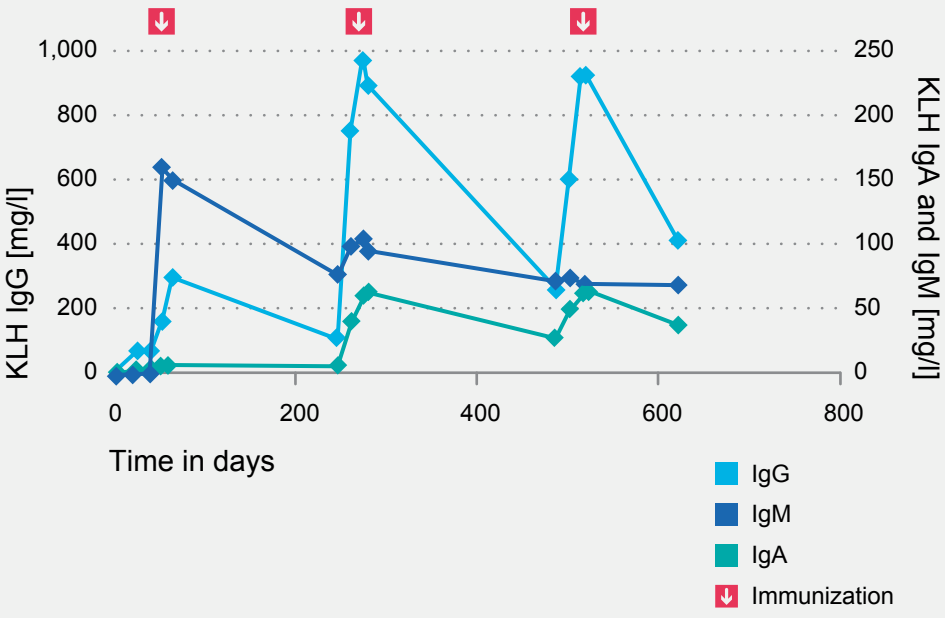
Why subsequent treatment over a long period?

Using quantitative human anti-KLH ELISA assays, a study in 2012 showed that KLH increased the concentration of several immunoglobulins after an immunization.[6] Older studies demonstrated that the IgM-concentration increased with initial immunization, and then subsequently KLH-specific IgGs increased.

In the treatment-free interval, the IgG titer significantly declined. However, the decrease in IgG- and IgA-concentration reduced after every immunization and resulted in a sustained anti-KLH titer *(Fig. 4)*.[6]

Furthermore, the study was able to show that KLH was not detectable in any of the 35 investigated patients before treatment.[6]

Evolution of anti-KLH antibody concentration after multiple immunization with KLH



Modified according to: Aarntzen EH et al. Cancer Immunol Immunother. 2012 Nov; 61(11): 2003-11. Humoral anti-KLH responses in cancer patients treated with dendritic cell-based immunotherapy are dictated by different vaccination parameters.

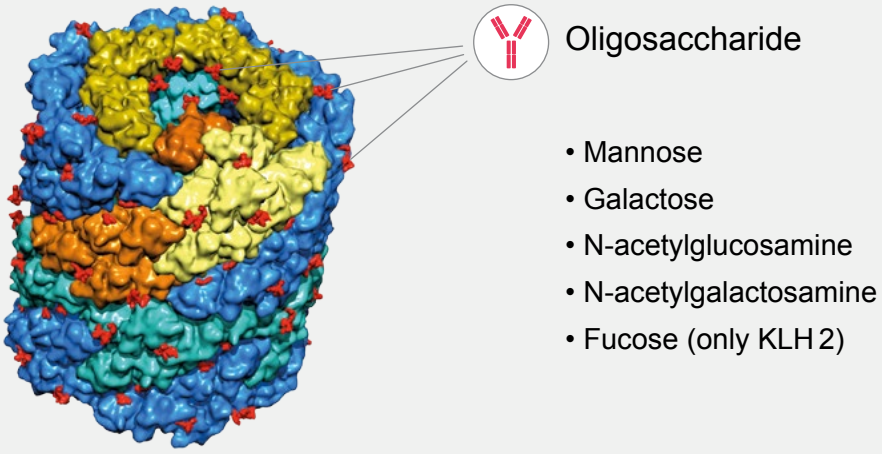
Fig. 4

Strong immunogenicity due to oligosaccharides

What a difference oligosaccharides can make

The strong immunogenicity of KLH is probably based on the numerous attached oligosaccharides that account for about 4 % of the molecular mass of KLH *(Fig. 5)*.[7] Different mechanisms of action play a role here: on the one hand a non-specific stimulation of the immune system, and on the other hand the stimulation of cytotoxic T-cells.[8] The third mechanism of action is the induction of anti-tumoral antibodies. After an immunization with KLH, mice produced antibodies that bind tumor-associated oligosaccharide antigens.[9] In addition, studies with bladder carcinoma patients showed an increase of anti-KLH antibodies in patients, who responded to KLH treatment.[10]

Strong immunogenicity of KLH due to several oligosaccharides



Modified according to: Gatsogiannis C, Markl J. J Mol Biol. 2009 Jan 23; 385(3): 963-83. Keyhole limpet hemocyanin: 9-A CryoEM structure and molecular model of the KLH1 didecamer reveal the interfaces and intricate topology of the 160 functional units.

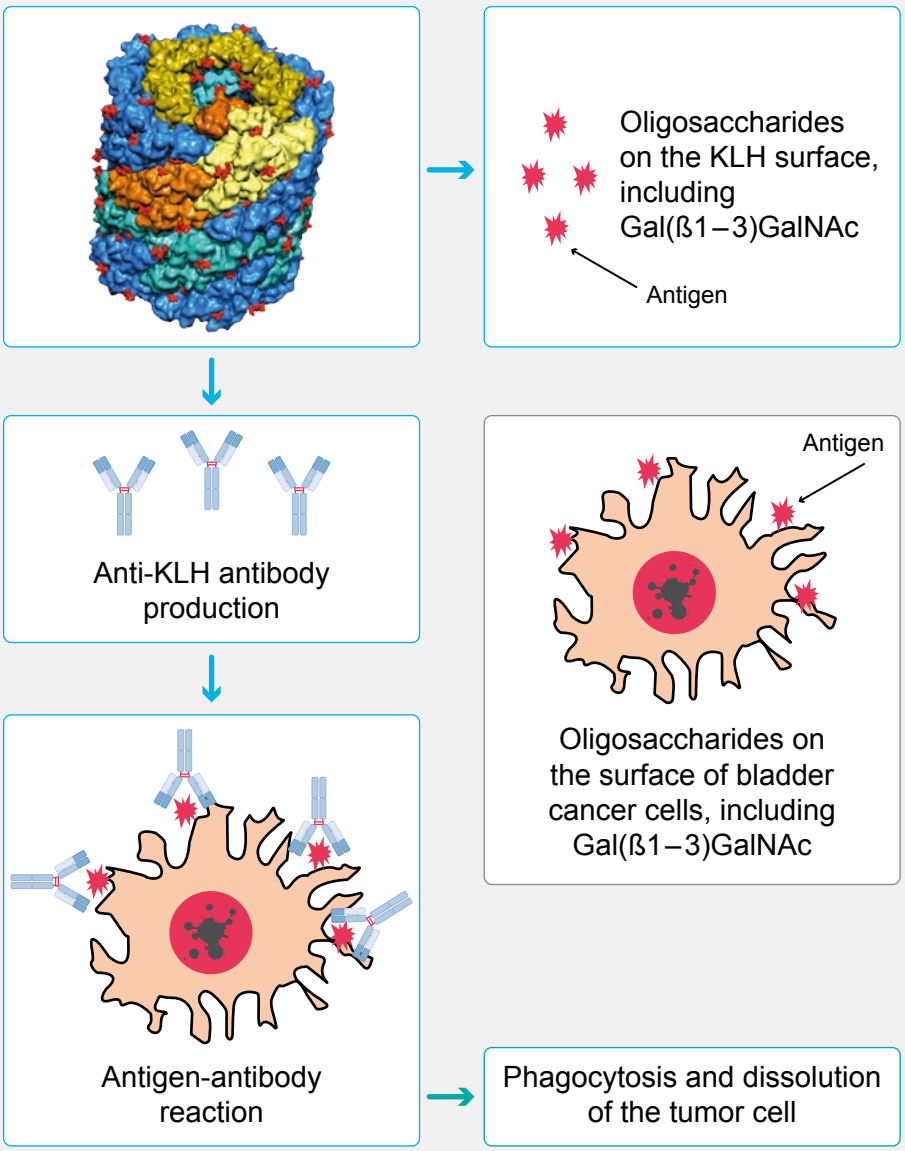
Fig. 5

Specific antibody reaction against bladder carcinoma cells

KLH expresses Gal(beta 1-3)GalNAc-bearing oligosaccharides.[11] The immunization of rats with KLH induced the production of anti-Gal(beta 1-3)GalNAc antibodies. Bladder carcinomas express cross-reactive Gal(beta 1-3)GalNAc epitopes (called Thomsen-Friedenreich antigens).[12] Also, Thomsen-Friedenreich antigens are associated with cancer progression and metastasis.[13] Anti-KLH antibodies can bind to the Thomsen-Friedenreich antigens on the bladder carcinoma cell and destroy them *(Fig. 6)*. The effectiveness of immunotherapy with IMMUCOTHEL® for superficial bladder carcinoma is most likely based on this fact.[11]

IMMUCOTHEL® – systemic and specific immune response

KLH antibodies can recognize and destroy bladder carcinoma cells



Modified according to:

Wirguin I et al. Cancer Immunol Immunother. 1995 May; 40(5): 307-10. Keyhole limpet hemocyanin contains Gal(beta 1-3)-GalNAc determinants that are cross-reactive with the T antigen.

Yokoyama M et al. Hinyokika Kiyo. 1988 Feb; 34(2): 255-8. Thomsen-Friedenreich antigen in bladder cancer tissues detected by monoclonal antibody.

Fig. 6

IMMUCOTHEL® for recurrence prevention

At a glance
Reduced recurrence risk from 70 % (TUR) to 30 %
Progression risk of only 15 %
Tumor downgrading probability 26 %

Discovery in the 1970s – KLH reduces recurrence of bladder carcinoma

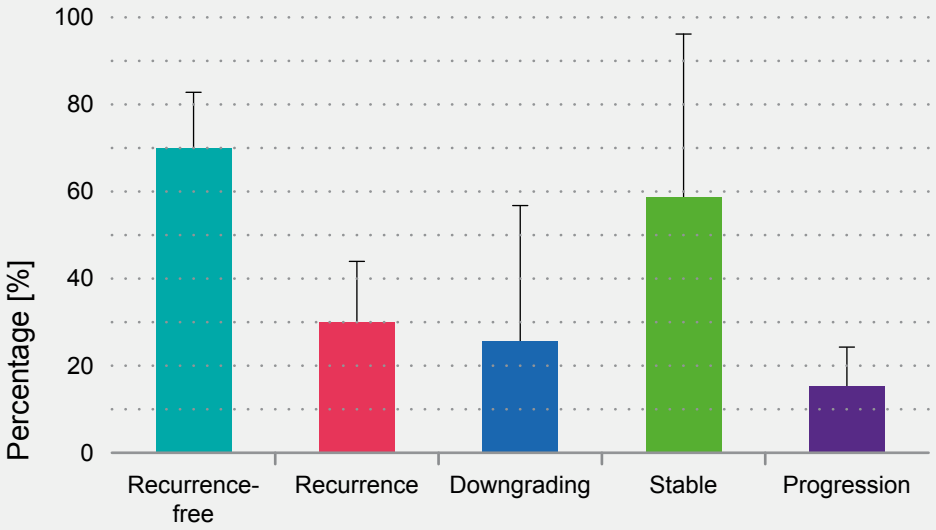
Already in 1974 Olsson et al. reported that for patients with a recurrent urinary bladder carcinoma, the recurrence frequency after a KLH treatment declined from 70 % to 30 %.[14] Numerous studies followed, both controlled as well as uncontrolled, which confirmed the recurrence prevention effect of KLH.[15–20]

By chance – KLH for bladder cancer therapy

IMMUCOTHEL® – only 30 % recurrence rate

In an analysis of six trials (mainly Ta- and T1 bladder carcinomas) with comparable appraisal criteria, the probability of recurrence was 30 %.[15–20] Only a small proportion of the recurrences (15 %) indicated progression, while downgrading was determined for 26 % of the tumors *(Fig. 7)*.[15–20] In many trials, no distinction was made between primary and recurrent tumors for the effectiveness assessment of IMMUCOTHEL®.[15–20] The probability of recurrence of 30 % is therefore independent of the risk assessment of the Ta- and T1 bladder carcinomas.

Reduced recurrence risk with IMMUCOTHEL®



Summary of 6 studies, n = 346

Modified according to:

Jurincic CD et al. J Urol. 1988 Apr; 139(4): 723-6. Immunotherapy in bladder cancer with keyhole-limpet hemocyanin: a randomized study.

Weymann H. Ergebnisse einer Phase-II-Studie beim Harnblasenkarzinom mit IMMUCOTHEL® (KLH). IN: Kurth KH (Hrsg): IMMUCOTHEL®-Workshop III. Istanbul, 1. – 3. Dezember 1989; Schönaich, Papierhaus Mach (1992), pp. 101-107.

Jurincic-Winkler C et al. Zentralbl Bakteriol. 1995 Oct; 282(4): 409-15. Efficacy of local Bacillus Calmette-Guérin treatment in superficial bladder cancer relapsing under Keyhole-Limpet Hemocyanin immunotherapy.

Flamm J et al. J Urol. 1990 Aug; 144 (2 Pt 1): 260-3. Recurrent superficial transitional cell carcinoma of the bladder: adjuvant topical chemotherapy versus immunotherapy. A prospective randomized trial.

Flamm J, Bucher A. Br J Urol. 1991 Jan; 67(1): 70-3. Adjuvant topical chemotherapy versus immunotherapy in primary superficial transitional cell carcinoma of the bladder.

Kälble T et al. Urologe A. 1991 Mar; 30(2): 118-21. [Intravesical prevention of recurrence of superficial urinary bladder cancer with BCG and KLH. A prospective randomized study].

Fig. 7

IMMUCOTHEL® for recurrence prevention of carcinoma in situ

At a glance
49 % “long-term disease-free rate” with IMMUCOTHEL®
Progression risk of only 13 %

Carcinoma in situ – a special case

A special case of the superficial bladder carcinoma is the carcinoma in situ (CIS). After a TUR, progression to a muscle-invasive bladder tumor with CIS without further treatment is 54 %.

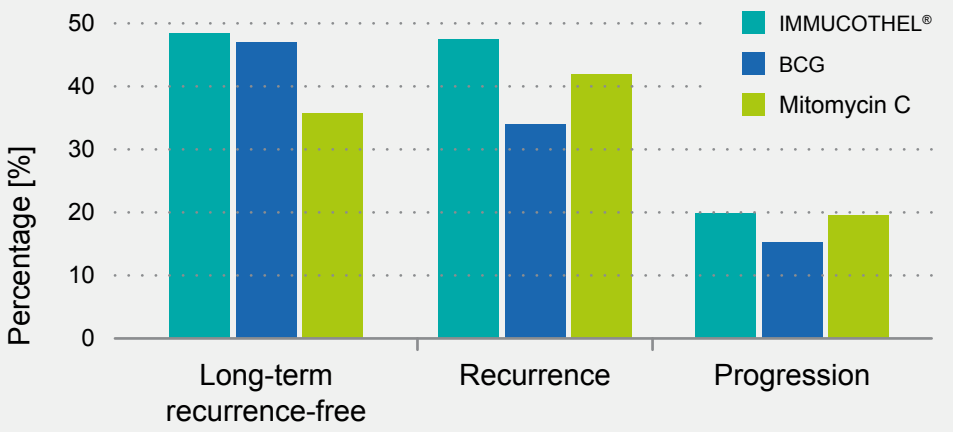
In comparison, only 2 % of the patients with a Ta grade one tumor progress to a muscle-invasive bladder carcinoma. Also after treatment with BCG or chemotherapy, the recurrence rate was 34 % or 50 %, whereby Mitomycin C was more effective in the treatment of CIS than other chemotherapeutics. The “long-term disease-free rate” with a Mitomycin C treatment was 36 %, for BCG it is 46 %.[21]

An option for carcinoma in situ

IMMUCOTHEL® effectively reduced recurrence of CIS

Several small trials (n = 86) have specifically investigated the efficacy of IMMUCOTHEL® for carcinoma in situ (CIS).[22–25] The recurrence rate with an IMMUCOTHEL® treatment was 48 %. Progression also declined to 20 % *(Fig. 8)*. Especially relevant was the “long-term disease-free rate” of 49 %.[22–25]

Comparison of BCG- and Mitomycin C-therapy with IMMUCOTHEL® treatment in CIS



Modified according to:

Sylvester RJ et al. J Urol. 2005 Jul; 174(1): 86-91; discussion 91-92. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials.

Jurincic-Winkler C et al. Anticancer Res. 1995 Nov-Dec; 15(6B): 2771-6. Effect of keyhole limpet hemocyanin (KLH) and bacillus Calmette-Guérin (BCG) instillation on carcinoma in situ of the urinary bladder.

Bassi P et al. European Urology. 2000; 37 Suppl 2: 113. KLH immunotherapy of BCG resistant carcinoma in situ of the bladder. A phase II trial.

Lamm DL et al. J Urol. 1996; 155: A1405. Keyhole limpet hemocyanin (KLH) immunotherapy of papillary and in situ transitional cell carcinoma of the bladder: A multicenter phase I-II clinical trial.

Lamm DL, Dehaven JI, Riggs DR. Eur Urol. 2000; 37 Suppl 3: 41-4. Keyhole limpet hemocyanin immunotherapy of bladder cancer: laboratory and clinical studies.

Fig. 8

IMMUCOTHEL® vs. BCG – immunotherapies in comparison

At a glance
Frequent side effects result in a discontinuation of therapy with BCG treatment in up to 20 % of the patients
IMMUCOTHEL® recurrence risk is comparable with BCG treatment
Minor side effect spectrum for IMMUCOTHEL® vs. severe side effects for BCG
BCG-non-responsive tumors respond well to IMMUCOTHEL®

Severe side effects with BCG treatment

A treatment with BCG is frequently accompanied by severe side effects. The most frequent local side effects are cystitis, disorders in voiding from the urinary bladder and hematuria, which occur in approx. 75 % of the patients.

Systemic side effects such as flu-like symptoms, general malaise and fever occur with approx. 40 % of the patients. It is recommended to discontinue subsequent instillations in the event of side effects.

Therefore, sometimes only 16 % of the patients receive all planned instillations.[26] Local and systemic side effects result in the discontinuation of the BCG therapy in approx. 20 % of the cases.[27]

Contraindications for a BCG therapy

To reduce the occurrence of side effects, the following contraindications were compiled for a BCG therapy:[28]

- TUR within the last 2 weeks;
- traumatic catheter examination;
- macroscopic hematuria;
- urethral stenosis;
- active tuberculosis;
- prior BCG sepsis;
- immunosuppression;
- urinary tract infection.

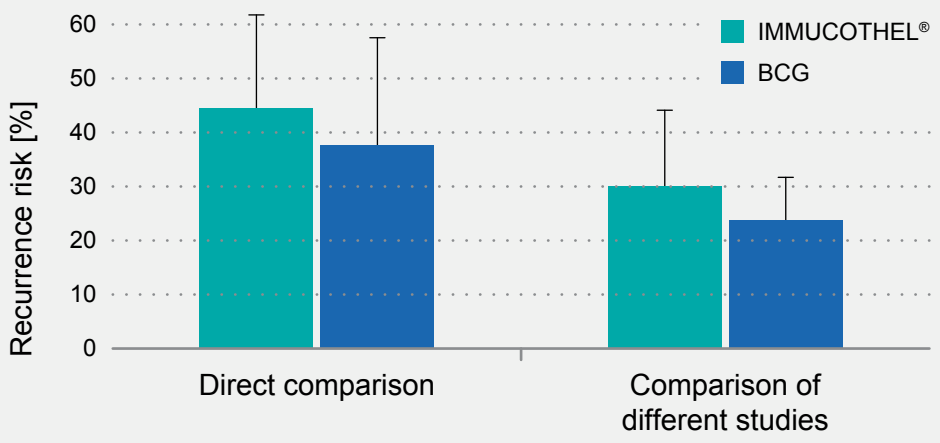
A BCG treatment is considered to have failed if one or more of the following occurs:[27]

1) occurrence of a muscle-invasive bladder carcinoma;
2) occurrence of severe papillary tumors and/or CIS after 3 and 6 months;
3) progression during the BCG treatment;
4) BCG-intolerance;
5) severe side effects due to the BCG therapy.

IMMUCOTHEL® vs. BCG – comparable recurrence rate with significantly lower side effects

Only in two studies (n = 212) the recurrence rate for IMMUCOTHEL® and BCG was compared directly.[17,20] These trials showed a slightly increased recurrence rate with an IMMUCOTHEL® treatment, but without statistical significance (44 % vs. 38 %; p = 0.4988).[17,20] A comparison with other studies in which either IMMUCOTHEL® or BCG was investigated also reveals a slightly increased, non-significant probability of recurrence.[17,20] The greater number of total patients increases the significance of these values, which is also reflected in the lower standard deviation *(Fig. 9)*.

IMMUCOTHEL® vs. BCG – comparable recurrence risk



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Kälble T et al. Urologe A. 1991 Mar; 30(2): 118-21. [Intravesical prevention of recurrence of superficial urinary bladder cancer with BCG and KLH. A prospective randomized study].

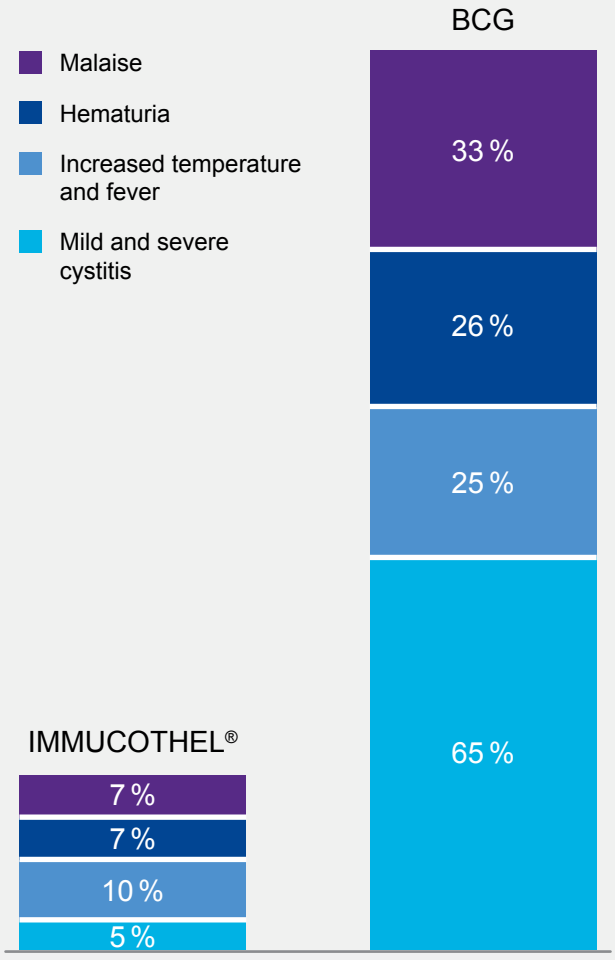
Jurincic-Winkler C et al. Anticancer Res. 1995 Nov-Dec; 15(6B): 2771-6. Effect of keyhole limpet hemocyanin (KLH) and bacillus Calmette-Guérin (BCG) instillation on carcinoma in situ of the urinary bladder.

Fig. 9

Minor side effect spectrum for IMMUCOTHEL®

Three trials compared the side effects of IMMUCOTHEL® and BCG for superficial bladder carcinoma.[17,20,29] Side effects associated with an IMMUCOTHEL® treatment were overall significantly less frequent ($p < 0.0001$) *(Fig. 10)*. In addition, the severity of the side effects induced by a BCG therapy was significantly higher.[17,20,29] Whereas no serious side effects have developed with IMMUCOTHEL® until now, in the case of BCG therapy < 5 % of the patients developed serious side effects.[27] Ten patients have since died after an intravesical BCG therapy.[30]

Minor side effect spectrum for IMMUCOTHEL® compared to BCG



Modified according to:

Kälble T et al. Urologe A. 1991 Mar; 30(2): 118-21. [Intravesical prevention of recurrence of superficial urinary bladder cancer with BCG and KLH. A prospective randomized study].

Jurincic-Winkler C et al. Anticancer Res. 1995 Nov-Dec; 15(6B): 2771-6. Effect of keyhole limpet hemocyanin (KLH) and bacillus Calmette-Guérin (BCG) instillation on carcinoma in situ of the urinary bladder.

Lamm DL. J Urol. Urogynäkol 2003; 10(2): 18-21. Laboratory and clinical experience with keyhole limpet hemocyanin (Immucothel) in superficial bladder cancer.

Fig. 10

Problem – BCG-non-responsive tumors

If a CIS does not respond to a BCG therapy or if there is progression of other superficial urinary bladder carcinomas, usually a radical cystectomy is recommended, since there is little likelihood that patients will react positively to a further BCG treatment.[1] Furthermore, several studies with conservative therapies such as chemotherapeutics have only delivered disappointing results.

BCG-non-responsive tumors respond well to IMMUCOTHEL®

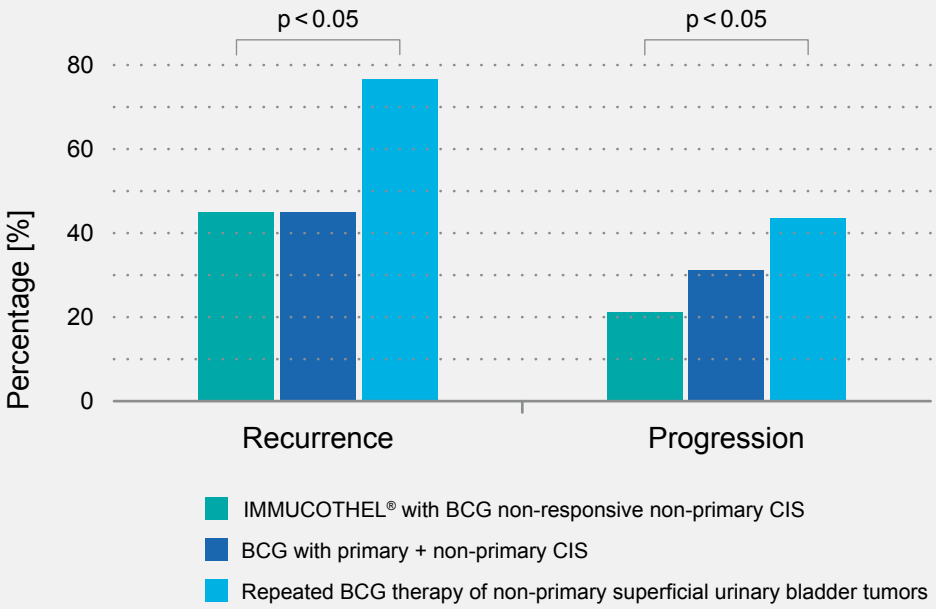
An option for BCG-non-responsive tumors

Two studies have investigated the effect of IMMUCOTHEL® on superficial urinary bladder carcinomas that did not respond to a BCG therapy.[23,31] 97 % of the tumors were carcinoma in situ (CIS). The trials showed that that IMMUCOTHEL® was positive for these patients in two respects. Firstly, only 45 % of the patients had a recurrence with IMMUCOTHEL®.[23,31] Secondly, in the case of these recurrences, only 21 % of the tumors showed progression.[23,31]

IMMUCOTHEL® – promising alternative for BCG-non-responsive tumors

Mitrakas et al. investigated the recurrence rate of non-primary bladder carcinomas with a BCG therapy, of which about one third were CIS.[32] The recurrence rate of a further BCG therapy after a failed BCG treatment was 71 %. This indicates a significant advantage of IMMUCOTHEL® therapy after a failed BCG therapy compared to a further BCG therapy (45 % vs. 71 %; p = 0.0074).[23,31,32] A comparison of probability of progression for non-primary urinary bladder carcinomas, that were further treated with BCG, to non-primary BCG non-responsive CIS, that were treated with IMMUCOTHEL®, also showed a clear advantage for IMMUCOTHEL® vs. BCG (21 % vs. 43 %; p = 0.0174) *(Fig. 11)*.[23,31,32]

Significant advantage in risk of recurrence or progression with IMMUCOTHEL® in BCG non-responsive non-primary CIS compared to further BCG therapy



Modified according to:

Mitrakas LP et al. Cancer Res Treat. 2015 Jul; 47(3): 495-500. Previous Bladder Cancer History in Patients with High-Risk, Non-muscle-invasive Bladder Cancer Correlates with Recurrence and Progression: Implications of Natural History.

Bassi P et al. European Urology. 2000; 37 Suppl 2: 113. KLH immunotherapy of BCG resistant carcinoma in situ of the bladder. A phase II trial.

Echarti C, Jurincic-Winkler CD, Klippel KF. Eur Urol. 2000; 37 Suppl 3: 50-3. Efficacy of prophylactic Immucothel in patients pretreated with conventional drugs to prevent recurrence of superficial bladder carcinoma.

Fig. 11

A look at other application areas

At a glance

KLH as additive of immunotherapeutic agents in treating cancer

KLH as carrier protein for tumor vaccines

KLH increases the effect of standard immunotherapeutic treatment of melanomas

McFadden et al. were able to demonstrate in an in vitro study, that KLH had an anti-proliferative effect on melanomas or an additive effect in combination with alpha-interferon and interleukin-2.[33] Alpha-interferon and interleukin-2 are both standard immunotherapeutic treatments for melanomas.

Studies conducted on mice have substantiated these results *in vivo*.[34] A combination of KLH and interleukin-2 reduced the tumor volume by 30 % ($p = 0.014$). With KLH and alpha-interferon, the tumor volume was reduced by 28 % ($p = 0.031$).

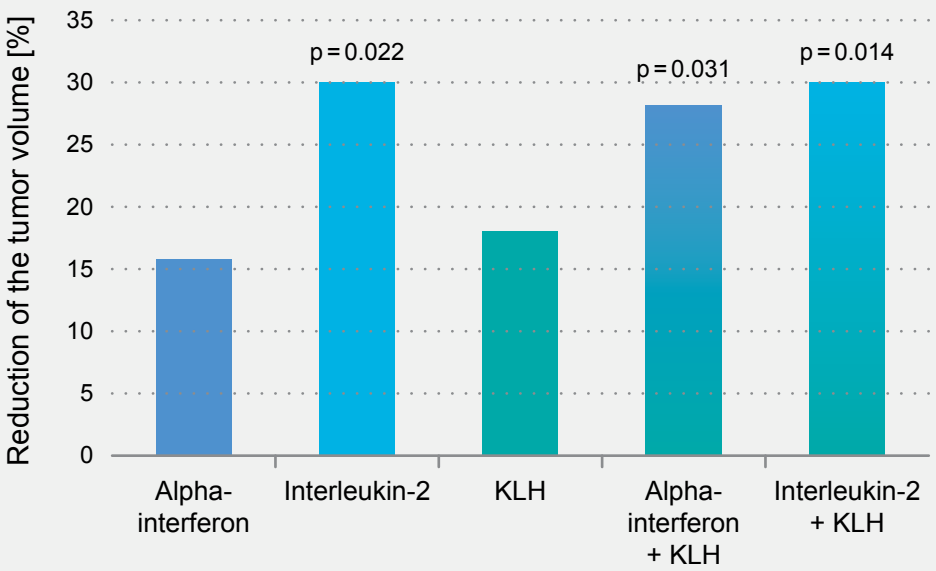
KLH – boosting immune therapy

In contrast, an individual treatment only showed a significant reduction (30 %; $p = 0.022$) with interleukin-2, whereas KLH and alpha-interferon reduced the tumor insignificantly by 18 % and 16 % respectively *(Fig. 12)*.[34]

Immunostimulating properties of KLH as the basis for tumor vaccines

In the rapidly growing area of tumor vaccines, KLH has special significance. A large number of important tumor associated antigens show poor immunogenicity when injected into humans.

KLH increases the effect of alpha-interferon, a standard immunotherapeutic treatment against melanoma, in vivo



Modified according to: Rizvi I et al. Am J Surg. 2007 Nov; 194(5): 628-32.
Keyhole limpet hemocyanin: an effective adjunct against melanoma in vivo.

Fig. 12

Increased immunogenicity due to carrier proteins

KLH – size matters

Immunogenicity of antigens can be increased significantly, when they are conjugated on highly immunogenic protein carriers such as KLH. A large number of cancer antigens have meanwhile been coupled to KLH, creating very promising tumor vaccine candidates, among others against follicular or non-Hodgkin lymphomas, glioblastomas, melanomas, breast and ovarian carcinomas.[35]

KLH-coupled tumor vaccines for glioblastoma therapy

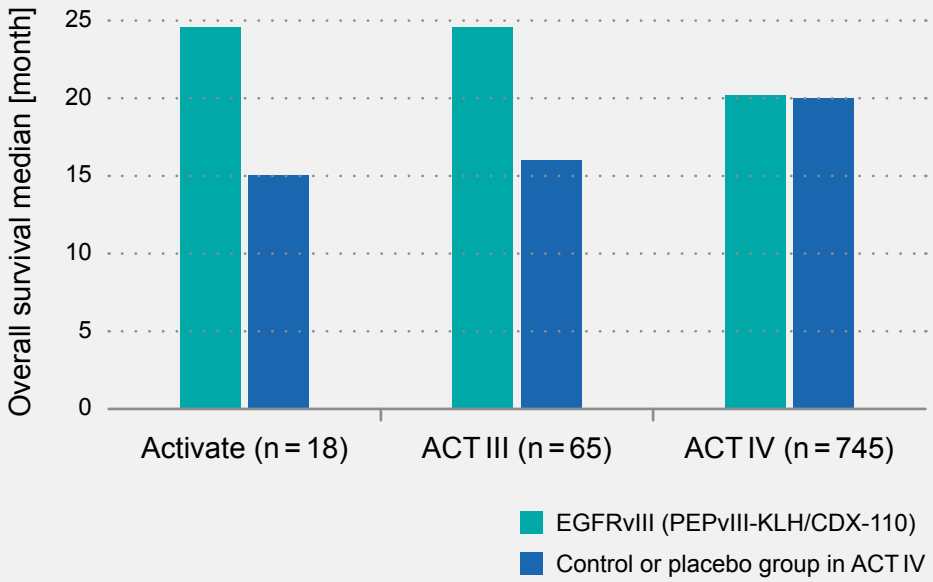
Phase I and II studies are meanwhile available for several cancer types.[36–38] A phase II study with glioblastoma patients is of particular interest here. Glioblastomas are highly aggressive brain tumors that until now have always ended fatally and non-responsive to available conventional therapies. One of the most frequent genetic changes in glioblastomas is the amplification of the EGFR gene, whereby most changes concern the mutant EGFR gene EGFRvIII. EGFRvIII is expressed in approx. 30 % of newly diagnosed glioblastoma patients and is a negative prognostic factor for long-term survival. Eighteen patients were treated with a vaccine against EGFRvIII (PEPvIII-KLH/CDX-110).[37] In contrast to the routinely applied chemotherapeutics, the vaccine showed only a minimum toxicity. The duration until progression was significantly prolonged from 6.3 to 14.2 months among the vaccinated patients ($p = 0.0102$).[37]

No prolonged survival with KLH-coupled tumor vaccines in phase III trial

Glioblastoma – therapy combinations as an option?

The survival time was likewise prolonged from 15 to 26 months ($p < 0.0001$) *(Fig. 13)*.[37] In addition, the effect of the vaccination on the standard chemotherapy with temozolomide was investigated. The time period until progression increased from 6.4 to 15.2 months ($p = 0.0004$) or for survival from 15.2 to 23.2 months.[37] In the phase III trial EGFRvIII (PEPvIII-KLH/CDX-110) was not associated with a prolonged survival.[39] Now therapy combinations are considered to show efficacy of immune therapy in glioblastoma.

No prolonged overall survival with KLH-coupled tumor vaccine in glioblastoma patients in phase III trial



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Heimberger AB, Sampson JH. Expert Opin Biol Ther. 2009 Aug; 9(8): 1087-98. The PEPvIII-KLH (CDX-110) vaccine in glioblastoma multiforme patients.

Schuster J et al. Neuro Oncol. 2015 Jun; 17(6): 854-61. A phase II, multicenter trial of rindopepimut (CDX-110) in newly diagnosed glioblastoma: the ACT III study.

Weller M et al. Lancet Oncol. 2017 Oct; 18(10): 1373-85. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial.

Fig. 13

KLH-coupled tumor vaccines for breast cancer therapy

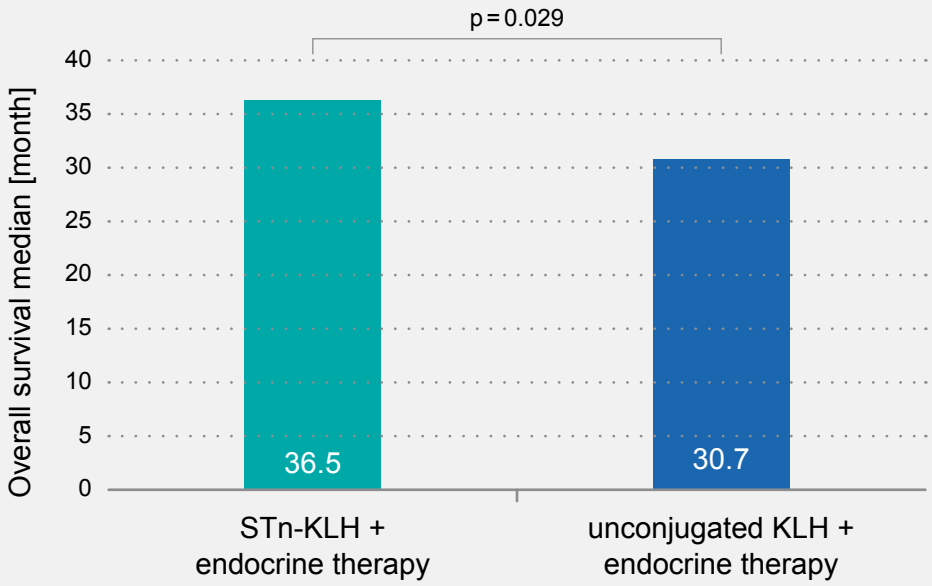
Phase III studies for breast cancer patients with metastases are already available in which the tumor-associated antigen Sialyl-Tn, whose expression is also associated with a poor prognosis among other things for breast cancer, is coupled to KLH.[40] The study comprised 1,028 women and compared Sialyl-Tn-KLH with KLH alone. Although the Sialyl-Tn-KLH vaccine was well tolerated, there was no significant advantage in the time until progression (3.4 vs. 3.0 months) or survival (23.1 vs. 22.3 months).[40] However, the authors posed the question whether the clinical advantage had been distorted by using a KLH control group instead of a placebo control group, due to a non-tumor-specific immune response to KLH.[40] Significantly higher anti-KLH antibody titers in the KLH control group supported this statement.

Prolonged survival in combination with endocrine therapy

A retrospective blinded review of the data from this study also showed that women, who had additionally received a concomitant endocrine therapy, had longer time until progression or survival in the Sialyl-Tn-KLH group (36.5 vs. 30.7 months) *(Fig. 14)*.[41]

Better outcome for a specific subgroup of breast cancer patients

Prolonged overall survival with KLH-coupled tumor vaccine in metastatic breast cancer patients



Trial (NCT00003638), n = 265

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Fig. 14

Literature

1. Babjuk M et al. Eur Urol. 2017 Mar; 71(3): 447-61. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016.
2. Lammers RJ et al. J Clin Oncol. 2012 Jun 20; 30(18): 2273-9. Intracutaneous and intravesical immunotherapy with keyhole limpet hemocyanin compared with intravesical mitomycin in patients with non-muscle-invasive bladder cancer: results from a prospective randomized phase III trial.
3. Gebauer W et al. Zoology 98, 51-68 (1994). Quaternary structure, subunits and domain patterns of two discrete forms of keyhole limpet hemocyanin: KLH1 and KLH2.
4. Söhngen SM et al. Eur J Biochem. 1997 Sep 1; 248(2): 602-14. Mass determination, subunit organization and control of oligomerization states of keyhole limpet hemocyanin (KLH).
5. Harris JR et al. Micron. 1997 Feb; 28(1): 43-56. Keyhole limpet hemocyanin (KLH), II: Characteristic reassociation properties of purified KLH1 and KLH2.
6. Aarntzen EH et al. Cancer Immunol Immunother. 2012 Nov; 61(11): 2003-11. Humoral anti-KLH responses in cancer patients treated with dendritic cell-based immunotherapy are dictated by different vaccination parameters.
7. Kurokawa T et al. Eur J Biochem. 2002 Nov; 269(22): 5459-73. Hemocyanin from the keyhole limpet Megathura crenulata (KLH) carries a novel type of N-glycans with Gal(beta1-6)Man-motifs.
8. Tzianabos AO. Clin Microbiol Rev. 2000 Oct; 13(4): 523-33. Polysaccharide immunomodulators as therapeutic agents: structural aspects and biologic function.
9. May RJ, Beenhouwer DO, Scharff MD. J Immunol. 2003 Nov 1; 171(9): 4905-12. Antibodies to keyhole limpet hemocyanin cross-react with an epitope on the polysaccharide capsule of Cryptococcus neoformans and other carbohydrates: implications for vaccine development.
10. Jurincic-Winkler CD et al. Anticancer Res. 1996 Jul-Aug; 16(4A): 2105-10. Antibody response to keyhole limpet hemocyanin (KLH) treatment in patients with superficial bladder carcinoma.
11. Wirguin I et al. Cancer Immunol Immunother. 1995 May; 40(5): 307-10. Keyhole limpet hemocyanin contains Gal(beta 1-3)-GalNAc determinants that are cross-reactive with the T antigen.
12. Yokoyama M et al. Hinyokika Kiyo. 1988 Feb; 34(2): 255-8. Thomsen-Friedenreich antigen in bladder cancer tissues detected by monoclonal antibody.
13. Yu LG. Glycoconj J. 2007 Nov; 24(8): 411-20. The oncofetal Thomsen-Friedenreich carbohydrate antigen in cancer progression.
14. Olsson CA, Chute R, Rao CN. J Urol. 1974 Feb; 111(2): 173-6. Immunologic reduction of bladder cancer recurrence rate.
15. Weymann H. Ergebnisse einer Phase-II-Studie beim Harnblasenkarzinom mit IMMUCOTHEL® (KLH). IN: Kurth KH (Hrsg): IMMUCOTHEL®-Workshop III. Istanbul, 1. – 3. Dezember 1989; Schönaich, Papierhaus Mach (1992), pp. 101-107.
16. Jurincic CD et al. J Urol. 1988 Apr; 139(4): 723-6. Immunotherapy in bladder cancer with keyhole-limpet hemocyanin: a randomized study.
17. Jurincic-Winkler C et al. Zentralbl Bakteriol. 1995 Oct; 282(4): 409-15. Efficacy of local Bacillus Calmette-Guérin treatment in superficial bladder cancer relapsing under Keyhole-Limpet Hemocyanin immunotherapy.
18. Flamm J et al. J Urol. 1990 Aug; 144 (2 Pt 1): 260-3. Recurrent superficial transitional cell carcinoma of the bladder: adjuvant topical chemotherapy versus immunotherapy. A prospective randomized trial.
19. Flamm J, Bucher A. Br J Urol. 1991 Jan; 67(1): 70-3. Adjuvant topical chemotherapy versus immunotherapy in primary superficial transitional cell carcinoma of the bladder.
20. Kälble T et al. Urologe A. 1991 Mar; 30(2): 118-21. [Intravesical prevention of recurrence of superficial urinary bladder cancer with BCG and KLH. A prospective randomized study].
21. Sylvester RJ et al. J Urol. 2005 Jul; 174(1): 86-91; discussion 91-92. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials.

22. Jurincic-Winkler C et al. Anticancer Res. 1995 Nov-Dec; 15(6B): 2771-6. Effect of keyhole limpet hemocyanin (KLH) and bacillus Calmette-Guérin (BCG) instillation on carcinoma in situ of the urinary bladder.

23. Bassi P et al. European Urology. 2000; 37 Suppl 2: 113. KLH immunotherapy of BCG resistant carcinoma in situ of the bladder. A phase II trial.

24. Lamm DL et al. J Urol. 1996; 155: A1405. Keyhole limpet hemocyanin (KLH) immunotherapy of papillary and in situ transitional cell carcinoma of the bladder: A multicenter phase I-II clinical trial.

25. Lamm DL, Dehaven JI, Riggs DR. Eur Urol. 2000; 37 Suppl 3: 41-4. Keyhole limpet hemocyanin immunotherapy of bladder cancer: laboratory and clinical studies.

26. Lamm DL et al. J Urol. 2000 Apr; 163(4): 1124-9. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study.

27. Babjuk M et al. Eur Urol. 2013 Oct; 64(4): 639-53. EAU Guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013.

28. Sylvester RJ. Int J Urol. 2011 Feb; 18(2): 113-20. Bacillus Calmette-Guérin treatment of non-muscle invasive bladder cancer.

29. Lamm DL. J Urol. Urogynäkol 2003; 10(2): 18-21. Laboratory and clinical experience with keyhole limpet hemocyanin (Immucothel) in superficial bladder cancer.

30. Lamm DL. Urol Clin North Am. 1992 Aug; 19(3): 565-72. Complications of bacillus Calmette-Guérin immunotherapy.

31. Echarti C, Jurincic-Winkler CD, Klippel KF. Eur Urol. 2000; 37 Suppl 3: 50-3. Efficacy of prophylactic Immucothel in patients pretreated with conventional drugs to prevent recurrence of superficial bladder carcinoma.

32. Mitrakas LP et al. Cancer Res Treat. 2015 Jul; 47(3): 495-500. Previous Bladder Cancer History in Patients with High-Risk, Non-muscle-invasive Bladder Cancer Correlates with Recurrence and Progression: Implications of Natural History.

33. McFadden DW et al. Am J Surg. 2007 Feb; 193(2): 284-7. Keyhole limpet hemocyanin potentiates standard immunotherapy for melanoma.

34. Rizvi I et al. Am J Surg. 2007 Nov; 194(5): 628-32. Keyhole limpet hemocyanin: an effective adjunct against melanoma in vivo.

35. Kantele A et al. Clin Dev Immunol. 2011; 2011: 614383. Humoral immune response to keyhole limpet haemocyanin, the protein carrier in cancer vaccines.

36. Curti A et al. Br J Haematol. 2007 Nov; 139(3): 415-24. Phase I/II clinical trial of sequential subcutaneous and intravenous delivery of dendritic cell vaccination for refractory multiple myeloma using patient-specific tumour idiotype protein or idiotype (VDJ)-derived class I-restricted peptides.

37. Heimberger AB, Sampson JH. Expert Opin Biol Ther. 2009 Aug; 9(8): 1087-98. The PEPvIII-KLH (CDX-110) vaccine in glioblastoma multiforme patients.

38. Baek S et al. Cell Mol Immunol. 2015 Jan; 12(1): 87-95. Therapeutic DC vaccination with IL-2 as a consolidation therapy for ovarian cancer patients: a phase I/II trial.

39. Weller M et al. Lancet Oncol. 2017 Oct; 18(10): 1373-85. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial.

40. Miles D et al. Oncologist. 2011;16(8):1092-100. Phase III multicenter clinical trial of the sialyl-TN (STn)-keyhole limpet hemocyanin (KLH) vaccine for metastatic breast cancer.

41. Ibrahim NK et al. J Cancer. 2013 Aug 22; 4(7): 577-84. Survival Advantage in Patients with Metastatic Breast Cancer Receiving Endocrine Therapy plus Sialyl Tn-KLH Vaccine: Post Hoc Analysis of a Large Randomized Trial.

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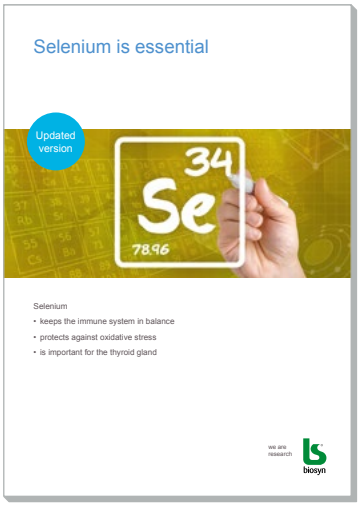

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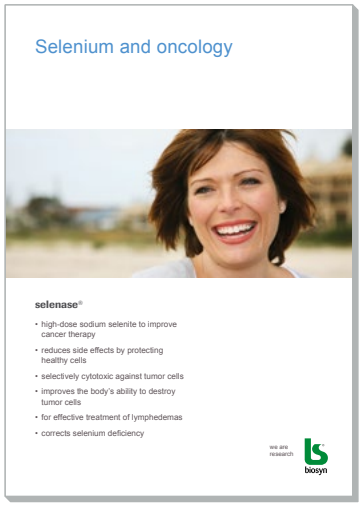

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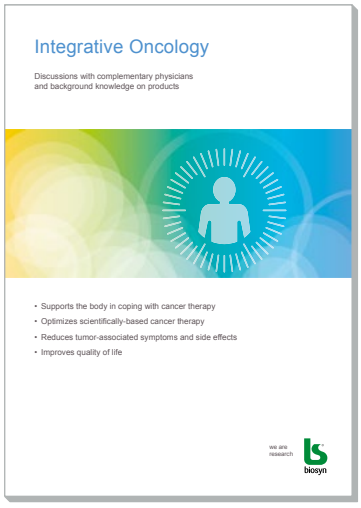

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