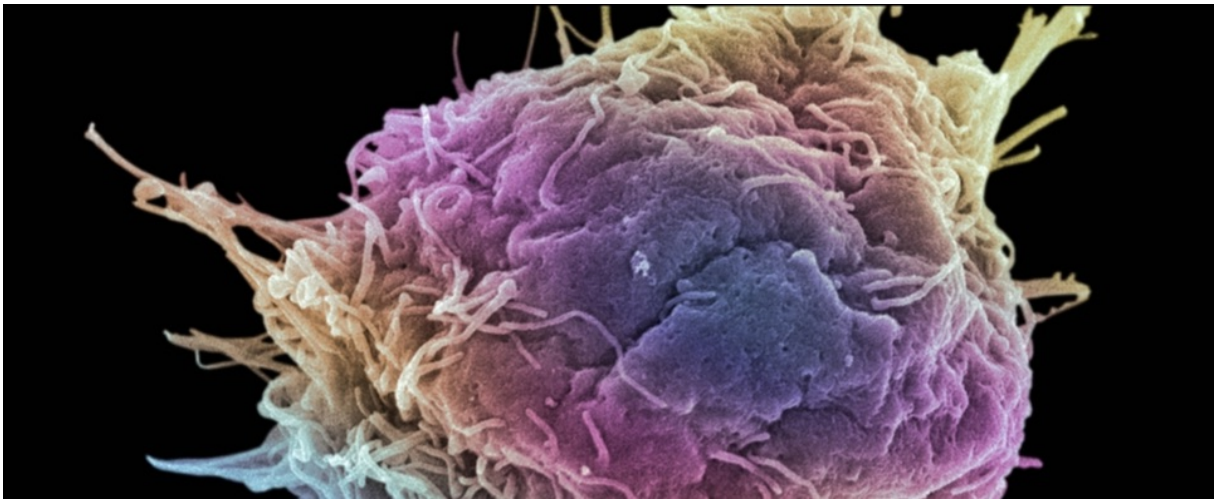
Hamlet Biopharma

An innovative pharmaceutical company with a wide and robust portfolio of projects for the treatment of cancer and infections.



Cancer

A central goal of cancer therapy is to selectively target the tumor and minimize toxicity for healthy tissue. Hamlet Biopharma is developing new therapeutic solutions for targeting and killing tumor cells with greater precision. Alpha1H is one of Hamlet Biopharma's main drug candidates. Alpha1H is a synthetically manufactured peptide in complex with oleic acid and an efficient anti-tumor drug candidate for the treatment of bladder cancer and brain tumors.

Bladder cancer
(Non-Muscle Invasive Bladder Cancer)

Problem: lack of effective bladder cancer therapeutics, in particular for early-stage bladder cancer

Bladder cancer is the fifth most common cancer in the European Union (EU) and has the highest recurrence rate of all cancer indications. Each year, around 500,000 patients worldwide are diagnosed with bladder cancer, and this number is rising. Worldwide, bladder cancer results in around 165,000 deaths each year. The high mortality of bladder cancer is mainly caused by the lack of effective therapies and the high recurrence rate (~70%). Moreover, bladder cancer places a significant burden on the health care system with high healthcare expenses. In fact, it accounts for the highest treatment cost per patient in the cancer area. The total costs associated with bladder cancer treatment in the EU amount to €4.9 billion (2012), of which €2.9 billion are direct treatment costs. These data clearly demonstrate the significance of bladder cancer as a health care problem.

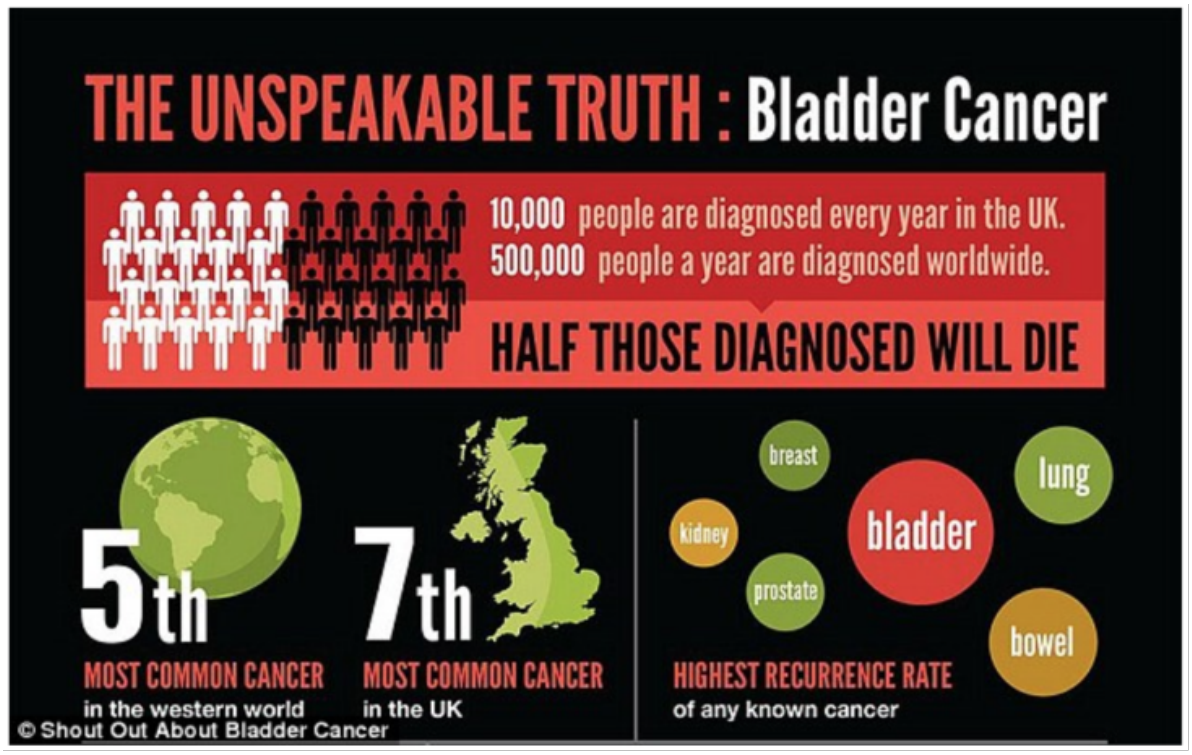


Figure: Illustration of the societal impact of bladder cancer. Source: bladdercancer.org.au

Bladder cancer is classified into three different clinical stages:

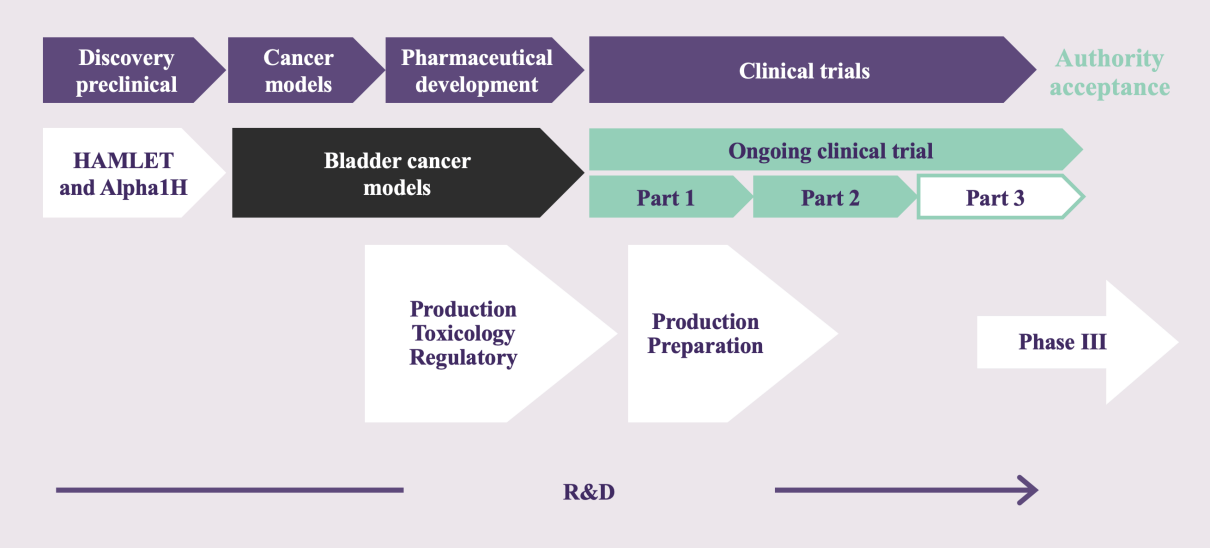
- Non-muscle invasive bladder cancer (NMIBC): Stages Ta, T1 and Tis
- Locally invasive bladder cancer: Stages T2 and T3
- Metastatic bladder cancer (spreading to other parts of the body): Stage T4

At diagnosis, around 70% of the diagnosed bladder cancers are classified as NMIBC, corresponding to 1.6 million patients currently suffering from NMIBC in the EU. The main challenge in NMIBC management is to prevent progression towards metastatic bladder cancer. At present, however, all available treatment options for NMIBC are suboptimal due to a lack of efficiency and significant side-effects. To prevent progression towards muscle invasion, and thus metastatic bladder cancer, radical removal of the bladder ('cystectomy') is often the only treatment option, which is a drastic surgical procedure, significantly impairing the patient's quality of life. In view of the high risk of tumor recurrence and the limited treatment options, there is an urgent need for novel NMIBC treatments that combine efficacy and selectivity for the targeted tumor, without causing side-effects.

Our solution: Alpha1H, a novel biological anti-cancer drug that acts with great selectivity

Hamlet BioPharma chose bladder cancer (NMIBC) as the first indication because previous studies with HAMLET had shown clear effects on this particular form of cancer. As the entire HAMLET molecule is difficult to manufacture, the synthetic peptide drug Alpha1H was developed for clinical trials. Alpha1H has powerful positive effects in animal cancer models and the clinical study program has been able to be designed with high precision thanks to the extensive research. In preparation for the clinical studies, Alpha1H has been analyzed for toxicity by an external CRO and toxicity has not been detected.

Clinical studies with Alpha1H in bladder cancer patients



Successful placebo-controlled Phase I/II trial published in Nature Communications

A randomized, placebo-controlled study of Alpha1H was carried out by a medical team at the University Hospital in Prague in collaboration with Hamlet Pharma with good results. Patients did not experience more side effects caused by Alpha1H than those treated with placebo. The treatment had clear effects on the tumors, which decreased significantly in size. Cells and pieces of the tumors were detached from the tumor and released into the urine, where large amounts of cells that had taken up the drug were seen by microscopy. The tumors also showed signs of apoptosis, which is a form of cell death with low toxicity. Advanced molecular analyzes also showed interesting and specific responses in tumors treated with Alpha1H, inhibiting the expression of a large number of different cancer genes. Reaching these clinical and molecular effects is an important milestone.

Read the paper published in Nature Communications.

The clinical study was extended with a dose-escalation part.

The effects of Alpha1H increased with the higher dose, reducing the tumor size, increasing tumor cell shedding and tumor cell death by apoptosis.

Strong anti-tumor effects detected in Alpha1H-treated patients, for a combination of clinical and molecular endpoints

The combined data analysis from the two clinical study parts has now been completed, including extensive laboratory analyses of patient samples. The results, which have been submitted for publication, are summarized below.

1. Reduction in tumor size

Treatment resulted in a complete or partial response in 82% of the tumors treated with 8.5 mM and in 45% treated with 1.7 mM of Alpha1H.

2. Changes in the tumor

- Treatment resulted in tumor fragmentation and release of fragments and cells into the urine. This effect increased markedly with the higher dose of Alpha1H.
- The tumor cells died by apoptosis, after taking up Alpha1H.
- Tissues left in the patient after treatment had lost their tumor characteristics and become more “healthy-like”, as shown by gene expression analysis.

Extended treatment with Alpha1H – *ongoing study*

The positive effects on the tumor and the absence of significant side effects compared to placebo, now make it possible to add a second round of treatment after the patients have undergone the first treatment according to the original protocol in the current study.
The goal of prolonging the treatment is to optimize the effect on the tumor by introducing repeated treatment, which better corresponds to the future clinical reality. The treatment will be tested in a small number of patients and will not delay the regulatory process.

The FDA has approved Hamlet BioPharma's application for an IND

Hamlet BioPharma has recently announced that the U.S. Food and Drug Administration (FDA) has cleared the Investigational New Drug (IND) application for Alpha1H, a highly selective synthetic peptide for treatment of non-muscle invasive bladder (NMIBC). Hamlet BioPharma is proceeding with the clinical trial to optimize the design of further clinical trials in dialogue with the FDA.

Clinical use of Alpha1H

Overall, an effective neoadjuvant therapy could significantly enhance treatment approaches, improving outcomes and quality of life for patients with this condition. A novel neoadjuvant therapy holds the promise of improving the standard of care for multiple reasons.

- First, it could lead to an enhanced tumor response to subsequent treatment, facilitating more effective surgical removal.
- Second, this approach might reduce the recurrence rate by targeting residual cancer cells that could otherwise lead to tumor regrowth post-surgery.
- Third, by down-staging tumors, the therapy could limit the extent of cancer spread into deeper layers of the bladder wall, potentially enabling less invasive surgical interventions.

The investigational drug, Alpha1H, has the potential to be an effective neoadjuvant therapy for several key reasons

- There is limited or even no toxicity associated with the administration of Alpha1H; nonclinical studies of Alpha1H all found no evidence of symptoms or signs or effects on body weight or organ weights, gross pathology or histopathology.
- An ongoing clinical trial evaluating the safety and efficacy of Alpha1H in Adult Patients with Non-Muscle Invasive Bladder Cancer Awaiting Transurethral Surgery (Study HP002-001), has found that Alpha1H is safe and well tolerated in this patient population

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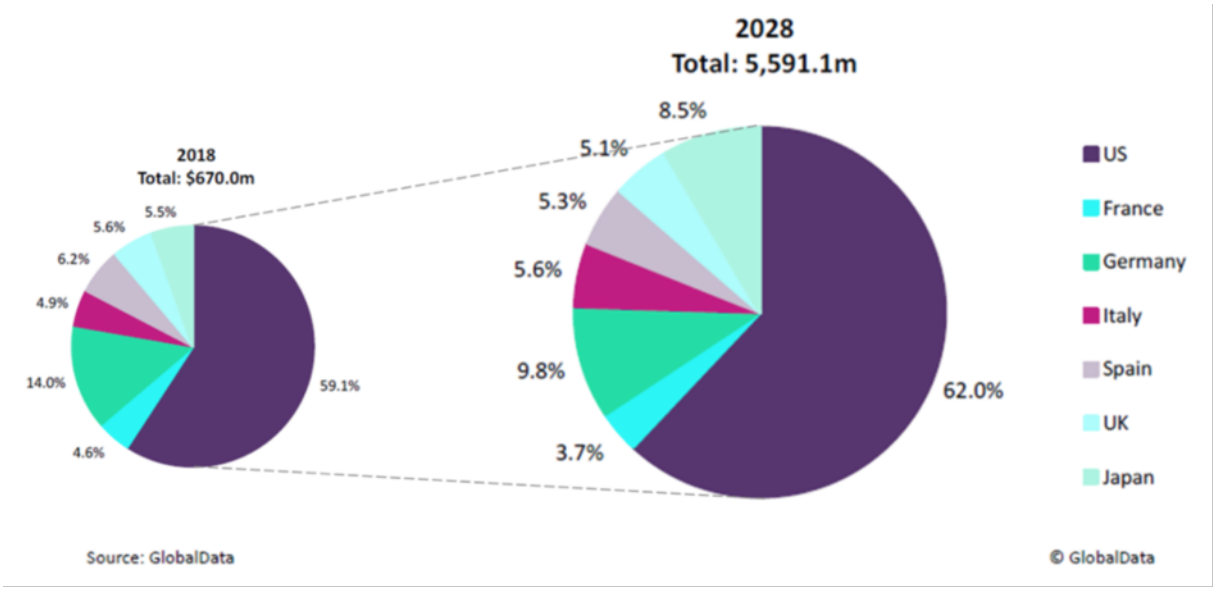
Bladder cancer market trends

Bladder cancer is the fourth most common malignancy in the United States and the fifth in Europe, with a prevalence of approximately 1/4000 (Antoni, S et al, 2016). Each year, approximately 500,000 patients worldwide are diagnosed with bladder cancer, and this number is increasing (Globocan WHO, 2012). Worldwide, bladder cancer results in approximately 165,000 deaths each year. In addition, bladder cancer has the highest recurrence rate of all cancer indications (EUCAN, Bladder cancer statistics, 2012; NIH Cancer Stat Facts: Bladder cancer 2015) as more than 80% recur after complete surgical removal of the first tumor and 15% progress to muscle invasive disease (Van Rhijn, B.W, et al., 2009).



Commercialization of Alpha1H will initially focus on the bladder cancer market, which is estimated by GlobalData to be worth **SEK 6.8 billion in 2018 in the 7 largest markets (USA, France, Germany, Italy Spain, UK and Japan**).

In 2018, the US accounted for approximately 60% of bladder cancer drug sales in these 7 countries, while the 5 largest markets of the EU and Japan contributed 35% and 6% respectively. It is expected that the bladder cancer market will grow with an annual growth rate (CAGR) of 24% and thus reach a market equivalent to **SEK 57 billion in 2028**. In 2028, the USA is expected to account for 62% of the market, while the 5 largest countries within the EU and Japan will account for 30% and approximately 9% respectively.
For Non–Muscle Invasive Bladder Cancer (NMIBC), where Alpha1H currently has its focus, the market is expected to increase significantly. About 70% of diagnosed bladder cancer cases are NMIBC, which corresponds to about 1.6

million patients annually in the EU. **Bladder cancer is also the most expensive form of cancer in the United States** (NIH Cancer Stat Facts: Bladder cancer 2015).

Summary

Hamlet BioPharma's investigational new drug Alpha1H has a huge potential as a general cancer therapeutic, with future impact on the treatment of cancer. Alpha1H directly taps into the growing bladder cancer therapeutics market (estimated value in 2025: €1B) characterized by high need for new more effective and safe treatment options.

Hamlet BioPharma AB (publ) is listed on the Spotlight Stock Market and publishes all regulatory information through press releases available on the website.