# COMBAT Bladder Cancer with Hyperthermia



# **COMBAT BRS** Bladder Recirculation System





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Results from the recently presented HIVEC<sup>®</sup> HR trial reports that HIVEC<sup>®</sup> is non inferior to BCG with a similar tolerability and safety profile.

**50,000**+

(JUNE 2020)

ROUTINELY USED IN

250 CENTRES ACROSS 35+ COUNTRIES

PATIENTS IN RANDOMISED CONTROLLED HIVEC® TRIALS

Data presented at the AUA concluded that HIVEC<sup>®</sup> represents an attractive alternative to BCG therapy<sup>5</sup>.

> HIVEC<sup>®</sup> represents a safe and well tolerated intravesical treatment for NMIBC<sup>12</sup>.



## **Combat Medical** transforming cancer treatments through world leading hypertherthermic technology.

Combat has significantly invested in clinical trials to prove the effectiveness of the technology in certain NMIBC patients. HIVEC<sup>®</sup> has been used as a treatment option in the following patient groups.

### **High Risk Patients:**

According to preliminary trial results presented in 2020, "CHT in high risk NMIBC patients seems at least not to be inferior to BCG in terms of efficacy". Conclusions from the data also stated that "patients under CHT have milder side effects than those under BCG treatment" <sup>4-7</sup>.

### Intermediate to High Risk Patients:

In an adjuvant and neo-adjuvant setting<sup>8</sup>.

### Neo-Adjuvant:

Clinical data presented in 2019 for 43 patients showed a 51 month median follow up with DFS of  $81\%^9$ . Trial data including 68 patients, presented in 2020 showed a 60% complete response rate at 38 months mean follow up<sup>14</sup>.

### Peri-Operative:

Trial data shows  $\mathsf{HIVEC}^{\circledast}$  is a safe and well tolerated alternative to immediate post-operative  $\mathsf{MMC}^{10}.$ 

**Sequential Therapy Regime with BCG for High Risk Patients:** 2-year results showed a DFS of 76%, low progression rates, PFS 94% and good tolerability<sup>11</sup>.

The Combat BRS device increases MMC penetration into the bladder wall but does not result in an increase of MMC levels in the liver, heart, kidney, spleen, lung, lymph node tissue and plasma<sup>13</sup>.

For copies of all published and presented clinical data please contact Combat Medical.

"HIVEC<sup>®</sup> offers a new treatment option for patients with high and intermediate risk bladder cancer. For patients where BCG is not tolerated, not available, or has failed, HIVEC<sup>®</sup> offers a promising well tolerated alternative bladder preserving treatment in selected patients."

Mr D Wilby | Consultant Urologist Portsmouth Hospitals NHS Trust



"In light of the BCG crisis, HIVEC<sup>®</sup> was the treatment of choice by our trust in Leicestershire in continuing to manage the fight against High Risk Non Muscle Invasive Bladder Cancer for our patients. The Combat BRS is efficient, user friendly and has proven to be a pioneering treatment delivery system that's well tolerated by patients." Michelle Brewster | Urology Clinical Nurse Specialist,

# **COMBAT** Bladder Cancer with Hyperthermia

The COMBAT BRS delivers heated chemotherapy, HIVEC<sup>®</sup>, to optimise the chemotherapy treatment for NMIBC patients. The COMBAT BRS is a closed, conductive, recirculation system with accurate temperature control that ensures homogenous heated drug distribution.

**HIVEC®** real world data shows promising results for reducing recurrence and progression rates in certain patient groups. 867 patients are currently in randomised controlled **HIVEC®** trials. Results from these trials are expected to be consistent with the evidence being seen in the real world data published to date.

### Innovation

The COMBAT BRS delivers homogenous drug and heat distribution to maximise chemotherapeutic and hyperthermic benefit and treatment outcomes. Utilising an external, dry, conductive recirculation method, the innovative and patented aluminum heat exchanger ensures efficient heat transfer and accurate temperature control within  $\pm$  0.2 of set temperature.

### Combination

Hyperthermia has been shown to significantly increase the effectiveness of Mitomycin C (MMC) in NMIBC<sup>1,2</sup>.

The **mutually enhancing** effects of **chemotherapy** in combination **with hyperthermia** have been **well documented for their cytotoxic effects.** Chemo-Hyperthermia (CHT) is widely used in the treatment of several types of cancer including bladder cancer<sup>3</sup>.

### Integration

Simple to integrate into current clinical practice, the COMBAT BRS is portable, robust and easy to use. It requires minimal set-up without continuous monitoring, allowing for multiple simultaneous treatments by a single clinician. System and kit are affordable and reimbursed in an expanding number of countries. As clinical evidence grows we continue to show cost savings for the healthcare provider through improved patient outcomes.

Our clinical and product teams are supporting the integration of COMBAT BRS in hospitals in a growing number of countries.



The **COMBAT BRS** and its unique patented features for enhanced usability and patient comfort in the delivery of HIVEC<sup>®</sup> for NMIBC treatment.

### **COMBAT BRS** System V4



# Why use Hyperthermia to Treat NMIBC

Clinical hyperthermia is defined as the therapeutic use of temperature between 41°C to 44°C<sup>a</sup>. The introduction of thermal energy at these temperatures into cancer tumours affects the cancer cells more because of their inability to manage the heat as well as good cells<sup>b</sup>. Mitomycin C (MMC) an alkylating chemotherapy agent is stable at temperatures up to 50°C<sup>f</sup>, but importantly it has shown to be 1.4 times more active at 43°C°. Hyperthermia inhibits the formation of new blood vessels (angiogenesis) by the tumour mass<sup>d</sup>. At 43°C the cytotoxicity increases by 10 times, importantly without any increase in the toxicity to the patient<sup>c</sup>. At elevated temperatures the lipid-protein cellular membrane bilaver will become more permeable, due to the unfolding (denaturing) of the cellular membrane and cytosolic proteins. resulting in higher intracellular concentration of the chemotherapy agent. Direct effects on the DNA include; strand breaking, impaired transcription (production of messenger RNA for protein synthesis), reducing replication and cell division<sup>a</sup>. Thermotherapy has profound effects on the immune system resulting in increased activation of more natural killer cells (NKC) that target heat stressed cancer cells as they

signal heat shock proteins on the cancer cell surface. The consequence of all these actions on the cancer cells is that they actively participate in their own demise through the natural process of apoptosis.

Chemo-hyperthermia multifactorial modes of action create a strong combination effect, ensuring cancer tumours and cells are specifically targeted. Therefore hyperthermia substantially increases the effectiveness of chemotherapy compared to instillation at room temperature. The Combat BRS has the potential to be the first system to allow the delivery of thermotherapy within the tight parameters necessary to optimise the delivery of chemo-hyperthermia without compromising patient safety or increasing resources required.

Based on the available body of evidence including real world experience data, the recommended protocol for Intermediate Risk patients receiving HIVEC<sup>®</sup> is 6 weekly induction treatments plus an additional 1 year maintenance schedule for High Risk patients.



Effect of hyperthermia on alkylating agents Teicher et al (1981) demonstrated activation rates 1.3 – 1.4 times higher at 41°C, 42°C, and 43°C compared to 37°C<sup>c</sup>.

Mitomycin C remains stable at higher temperatures 1 <sup>of</sup>						
Temp.	Solvent	Parameter	Storage Period			
			0 hr*	1 hr	3 hr	6 hr
37°C	5 ml water	Content %	100.0	94.9	92.8	91.6
	5 ml of saline	Content %	100.0	94.2	90.6	90.4
50°C	5 ml water	Content %	100.0	91.0	88.0	87.3
	5 ml of saline	Content %	100.0	91.3	90.2	89.7
*0 hr : immediately after reconstitution.						

Mitomycin C (MMC) plus hyperthermia achieves greater plasma concentration than MMC alone<sup>g</sup>, but is well below 400 ng/ml associated with systemic side effects like myelosuppression<sup>h.</sup>



# **Technical Specifications:**

### **Physical characteristics COMBAT BRS V4**

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#### Equipment external dimensions:

Height 400 mm | Width 250 mm | Depth 255 mm

Equipment weight: BRS system 9.6kg plus optional portable stand

#### Safety alarms:

High & Low temperature alarms High pressure alarm Auto safety cut off End of treatment alarm & auto stop

### Electrical risk classification:

Class I, Type B

Fluid ingress protection: IPX2

### Function mode:

Continuous delivery at set temperature between 41 - 44 °C  $\pm 0.5$  °C

### **Certification:**

UL 60601-1; IEC 60601-1; IEC 60601-1-2; EN 55011; CAN/CSA-C22.2; CE 2797

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