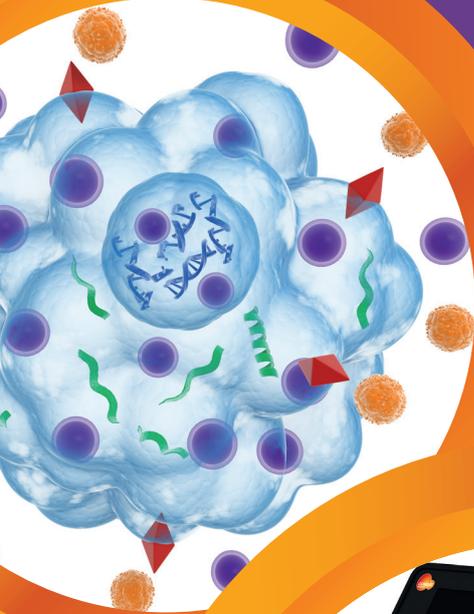


Targeting Bladder Cancer with Hyperthermia



COMBAT BRS

Bladder Recirculation System





The following is a list of **HIVEC™** Trials that are currently running and actively recruiting:

HIVEC-I™

HIVEC-II™

Prospective Randomized International Multicentre Clinical Trials in 494 Intermediate Risk NMIBC Patients.

HIVEC-R™

HIVEC-DUKE™

HIVEC-HR™

Several trials are currently evaluating the efficacy of **HIVEC™** at various stages within the NMIBC treatment pathway.

For more information relating to **HIVEC™** clinical trials please visit us at www.combat-medical.com.



Combat Medical leading the current investigation in thermotherapy device assisted therapies for NMIBC

Combat Medical is committed over the next 5 years to creating its own clinical bibliography of fact based evidence supporting the BRS system in it's fight against bladder cancer. By harnessing the powers of chemo-hyperthermia in an innovative and unique way we hope to prove beyond doubt that the BRS system in combination with Mitomycin C (40mg) can significantly reduce recurrence and progression rates in NMIBC bladder cancer.

Combat Medical is equally committed to improving outcomes without healthcare providers having to significantly alter their treatment model or adding additional resources, in fact we believe over time we will be able to reduce the overall treatment cost due to our streamlined approach and through the reduction in recurrence and progression rates.

We have demonstrated this potential in phase I trials and through its clinical use over the last 3 years. During this time Combat BRS has shown it is easy to use and is well tolerated by the patient with similar side effects to standard MMC instillations, but importantly with little impact in terms of time and effort for the healthcare professional in delivering Combat's new HIVEC™ treatment.

“Our mission is to drive change in order to optimise the efficacy of the conventional chemotherapy instillation, reducing recurrence and progression rates in Non-Muscle Invasive Bladder Cancer in a cost effective way that fits alongside current practices.”

Edward Bruce-White, Combat Medical CEO

Combat Medical helping to combat bladder cancer through thermotherapy

Innovation

The Combat BRS System is an innovative and patented recirculation system for the delivery of Hyperthermic Intra-Vesical Chemotherapy (HIVEC™). Hyperthermia has been shown to significantly increase the effectiveness of Mitomycin-C (MMC) in Non Muscle Invasive Bladder Cancer (NMIBC)^{1,2}. The Combat BRS System has been in clinical use since 2011, it is safe for patients and healthcare professionals, has similar patient tolerability to MMC at room temperature and is easy to use and adopt.³

The Combat BRS System uses an external dry conductive recirculation system. Our innovative and patented aluminium heat exchanger ensures efficient heat transfer and accurate temperature control within $\pm 0.2^{\circ}\text{C}^4$ of the set temperature, whilst providing homogeneous drug and heat distribution throughout the bladder. Patient safety and comfort are paramount and the Combat BRS system has a range of safety features including; over temperature and high pressure audio and visual alarms as well as system auto cut off. At the end of a treatment the Combat BRS system also enables the removal of MMC from the patient for safe disposal.

Combination

The Combat BRS system harnesses accurate and effective heat control in addition to the combined effects of chemo-hyperthermia to target NMIBC. The mutually enhancing effects of chemotherapy drugs and hyperthermia are well documented for their cytotoxic effects and are widely used in treating several types of cancer including bladder cancer⁵. Cancer cells become more permeable and are increasingly affected on many levels because of their inability to dissipate heat, while the heat enhances the body's natural immune response.⁶⁻⁸

Integration

Portable, robust and easy to use, the Combat BRS System is simple to integrate into current treatment practice. The Combat BRS system requires minimal set up, no continuous monitoring and therefore minimal additional resources from a physical, logistical and financial perspective. Both the Combat BRS system and the disposable sets are affordable to use, and through improving patient outcomes, the overall treatment cost can ultimately be reduced.



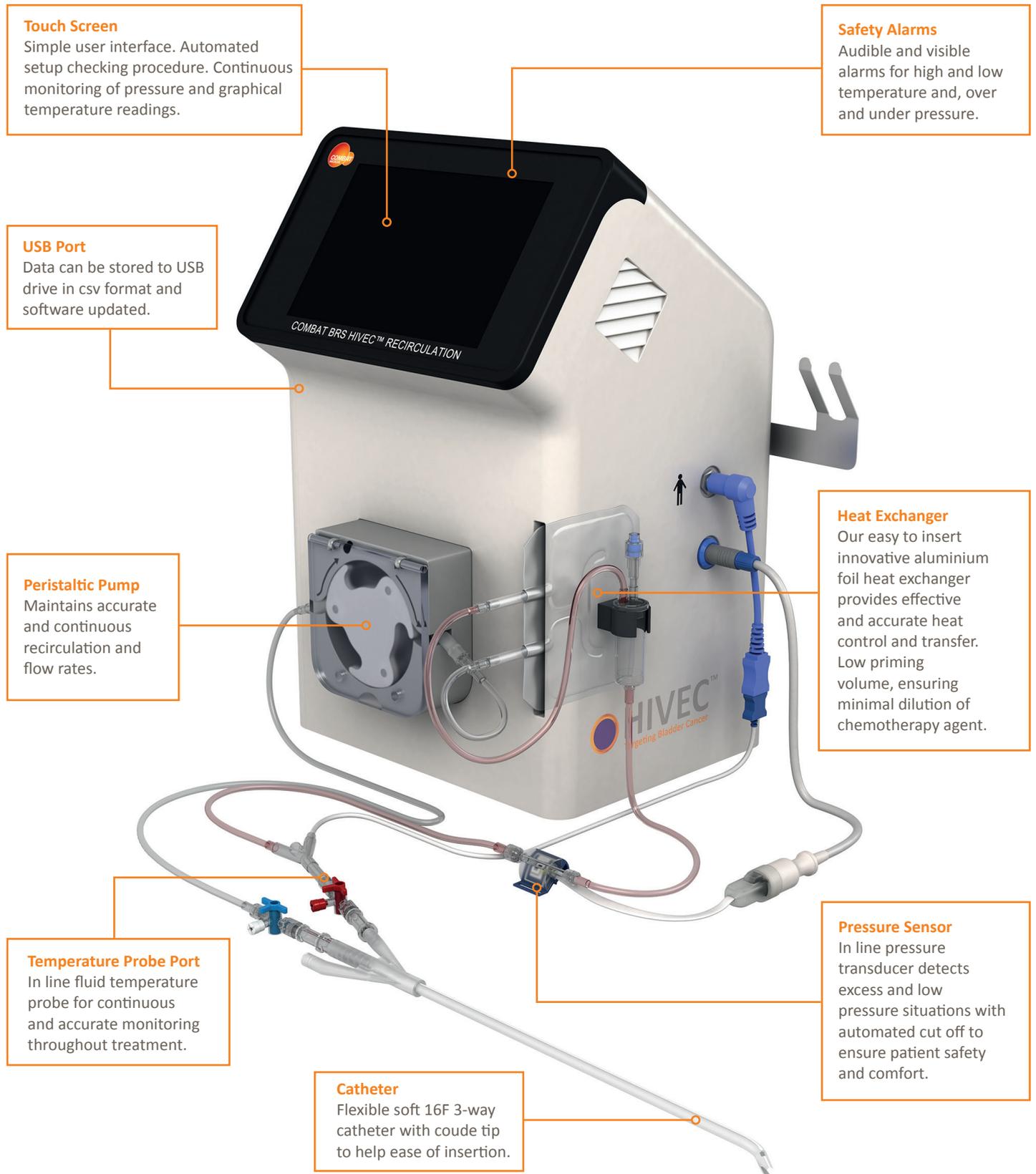
“I now have over 400 uses of the Combat BRS system and in my experience the system only takes 5 minutes more to set up compared to normal installations of MMC or BCG. During the 60 minute treatment I am able to continue my normal clinical routine because the system doesn't require continuous monitoring. I also particularly like that you are able to safely remove and dispose of the drug after the treatment.”

Alfonso Piñeiro, Urology Nurse, Hospital Comarcal de Monforte, Galicia (Spain)



COMBined Antineoplastic Thermotherapy Bladder Recirculation System

COMBAT BRS System V5



Combined effects of hyperthermia

Clinical hyperthermia is defined as the therapeutic use of temperature between 41°C to 44°C⁶. 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 cells⁷. **Mitomycin C (MMC)** an alkylating chemotherapy agent is stable at temperatures up to 50°C, but importantly it has shown to be **1.4 times more active at 43°C**⁹. Hyperthermia inhibits the formation of new blood vessels (angiogenesis) by the tumour mass¹⁰. At 43°C the **cytotoxicity increases by 10 times**, importantly without any increase in the toxicity to the patient⁹. At elevated temperatures the lipid-protein cellular membrane bilayer 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 division⁶. Thermo-therapy 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

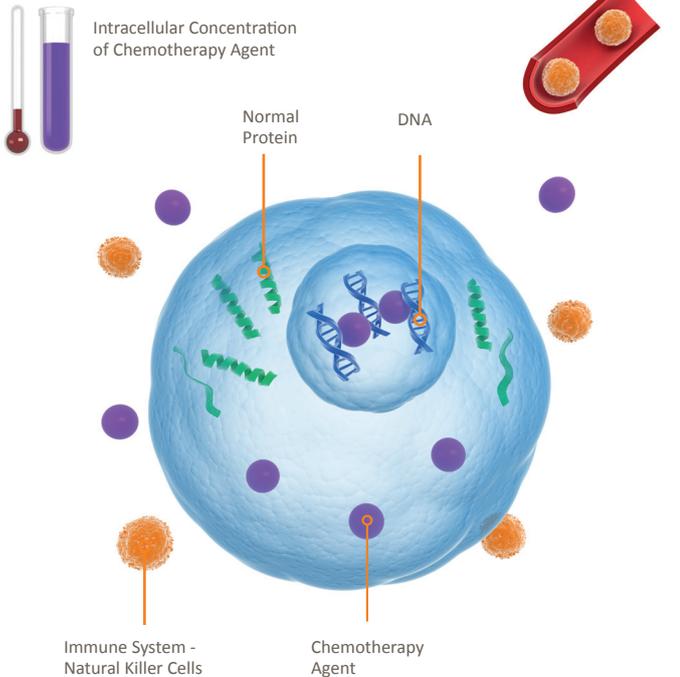
signal heat shock proteins on the cancer cell surface⁸. The consequence of all these actions on the cancer cells is that they actively participate in their own demise through the natural process of **apoptosis**.

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 thermo-therapy within the tight parameters necessary to optimise the delivery of chemo-hyperthermia without compromising patient safety or increasing resources required.

Based on the strong body of evidence cited above to achieve the best results with the Combat BRS system in adjuvant treatment it should be used at a temperature setting of 43°C for 1 hour using a 40 mg dose of Mitomycin C.

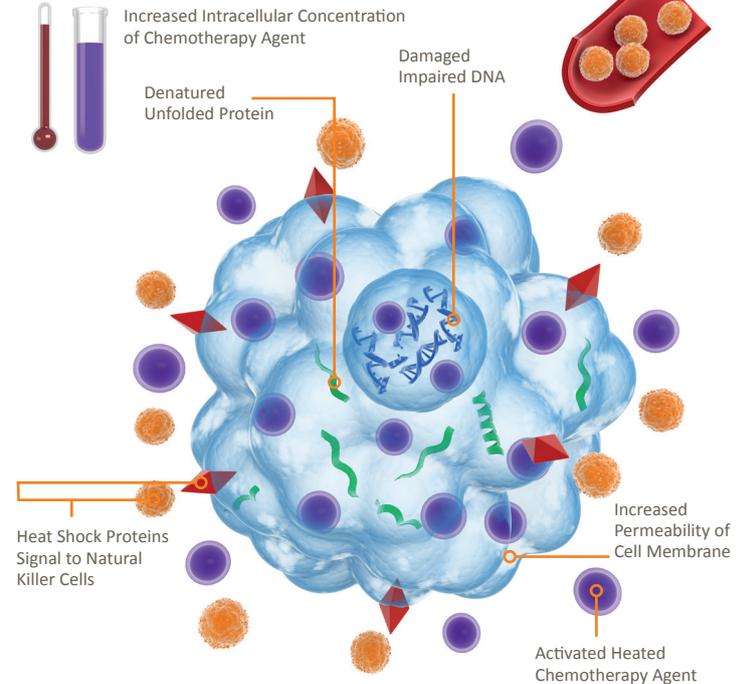
Cancer cell with Mitomycin C delivered at room temperature

Normothermia



Cancer cell with Mitomycin C delivered at 43°C

Hyperthermia



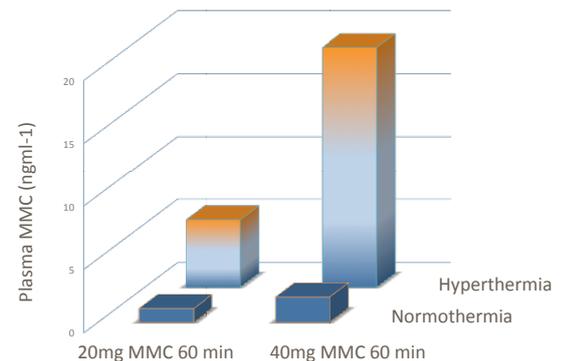
Effect of hyperthermia on alkylating agents

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.⁹

Mitomycin C (MMC) plus hyperthermia achieves greater plasma concentration than MMC alone¹², but is well below 400 ng/ml associated with systemic side effects like myelosuppression.¹³

Mitomycin C remains stable at higher temperatures 1 ^o						
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.



Technical Specifications:

Physical characteristics COMBAT BRS V5 System

Equipment external dimensions:

Height 400 mm Width 250 mm Depth 255 mm

Equipment weight:

BRS system 8 Kg plus optional portable stand

Safety alarms:

High & Low temperature alarms
High & Low pressure alarms
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 ± 0.2°C

Certification:

IEC/UL 60601 - 1; IEC 60601 - 1 - 2; EN 55011; CAN/
CSA - C22.2; CE 0086

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Visit: www.combat-medical.com



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