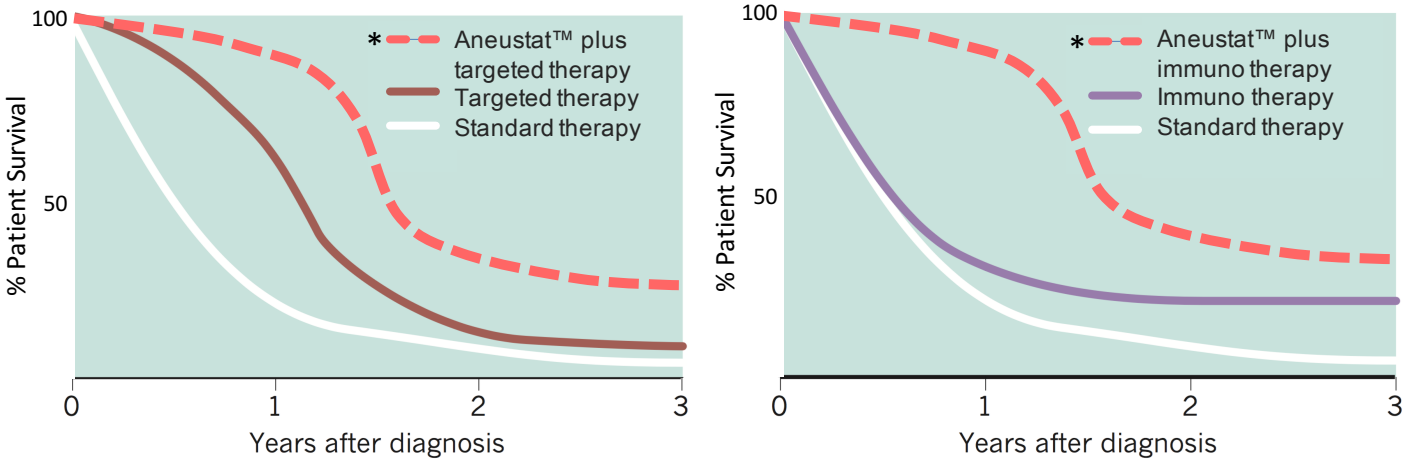
Omnitura Therapeutics

Invitation for R&D Collaboration on a Paradigm Shift to Intercept, Treat and Prevent Recurrence of Cancer and Comorbidities

June 6, 2017

Aneustat™ + Approved Drugs Expected to Improve Survival

Adapted from: Nat vol532; 14Apr2016; 162-164
**Omnitura hypothesis based on pre-clinical and phase I/IIa data.*
Phase II/III clinical trial being planned.



Aneustat™ is an orally delivered, non-toxic multivalent immuno-oncology drug candidate. As the foundational drug for combination therapies, Aneustat™ is expected to improve survival of patients by rebooting the immune system, reversing drug resistance to targeted therapies, improving efficacy through synergy, and disrupting the growth, survival and support systems for cancer.

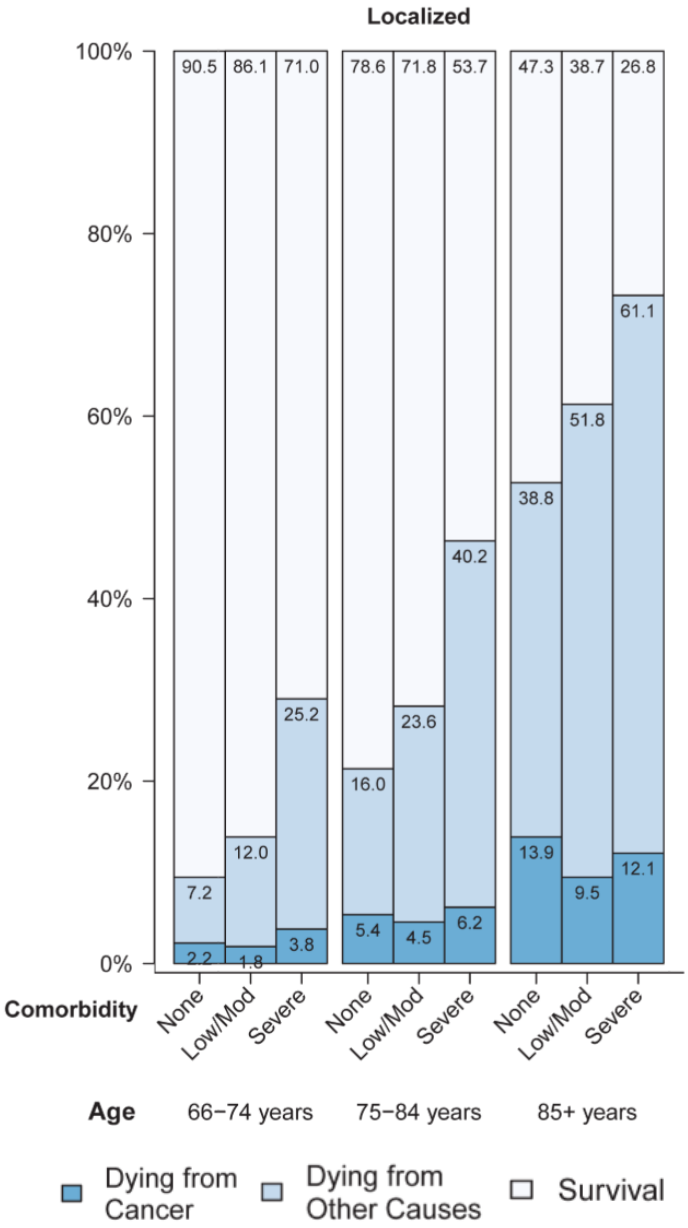
Aneustat™ significantly improves the efficacy and removes drug resistance for standard of care drugs for prostate cancer: bicalutamide, abiraterone, enzalutamide, and docetaxel – see page 8.

Men are at greater risk of dying from comorbidities than they are of dying from prostate cancer if the prostate cancer is localized or regional at time of diagnosis

Prostate cancer is the mostly frequently diagnosed cancer in American men aside from skin cancer. The American Cancer Society estimates there will be 161,360 new cases of prostate cancer diagnosed in the U.S. in 2017, of which 75% is early-stage disease. There will be an estimated 26,730 deaths in 2017 (the third leading cause of cancer death in men). Most prostate cancers are detected at an early stage of development, leading to nearly 3m American men living with prostate cancer.

While mortality due to early-stage prostate cancer is much lower than late-stage prostate cancer, it has been found that men with early-stage (i.e., localized) prostate cancer are much more likely to die of comorbidities than men who do not have comorbidities at time of prostate cancer diagnosis. Furthermore, the risk of dying of comorbidities is much higher than dying of localized prostate cancer, and the risk of dying of comorbidities increases with age.

Figure 1. Probability of Dying from Cancer, Dying from Other Causes and Survival Stratified by Stage and Comorbidity Status in 200,333 Men with Prostate Cancer Diagnosed Between 1999 and 2005*



Comorbidities are co-existing non-cancer medical conditions that are distinct from the principal cancer diagnosis. Between 2% and 14% of men diagnosed with prostate cancer at a localized stage died from their cancer, in all age and comorbidity categories.

These estimates may be useful for cancer treatment planning which often requires balancing treatment toxicity and complications with the expected benefit of potential healthy life years gained.

In addition to providing contemporary cancer rates and trends, this data highlights the considerable prevalence of comorbidities and their impact on overall health and quality of life among cancer patients aged 65 or older in whom 53% of all new cancer cases occur. Analysis of data from 1,056,534 cancer patients showed similar trends in ALL major cancers.

**The data source for the comorbidity analysis is the linked SEER-Medicare database, the most comprehensive source of population-based information with cancer treatment and outcomes data in the U.S.*

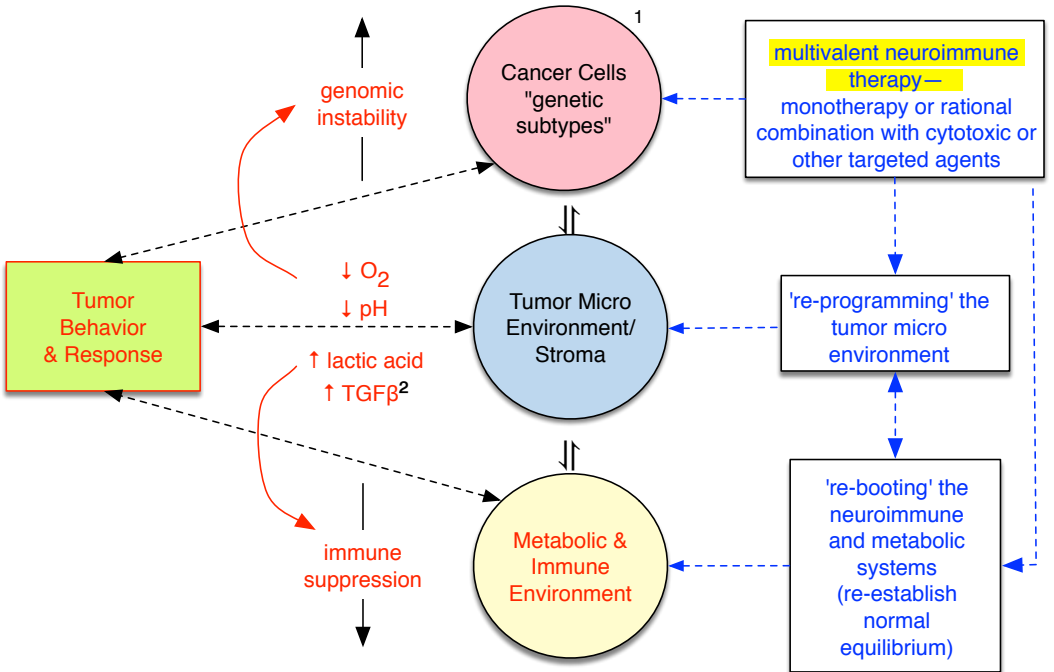
OMNITURA IS READY FOR R&D COLLABORATION WITH PHARMACEUTICAL COMPANIES, ACADEMIC INSTITUTIONS, PROFESSIONAL AND GOVERNMENT RESEARCH CENTERS

- **Aneustat™ monotherapy: proven preclinical efficacy for treatment and prevention of prostate cancers**
  - Improved efficacy at the cellular and genomic levels
  - Modulation of the tumor microenvironment
  - Improvement of body's endogenous response to cancer by boosting the neuroimmune system
  - Synergistic effects of all the above
- **Aneustat™ in combination with standard of care: experimentally verified to improve treatment of late-stage cancers**
  - Synergistic with standard of care: lowers doses/widens the therapeutic window
  - Inhibits/delays development of drug resistance with standard of care therapy
- **Summary: Aneustat™ will reduce disease incidence and healthcare cost:**
  - **Prevent the development of primary prostate cancers from a premalignant state**
  - **Delay or prevent recurrence of primary cancer and the development of secondary cancers**
  - **Reduce effects of comorbid disease** (e.g., diabetes, chronic obstructive pulmonary disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease—see Figure 1)

ANEUSTAT™ FUNCTIONS AS A FOUNDATIONAL DRUG THROUGH THREE KEY SYSTEMS BIOLOGY MECHANISMS OF ACTION:

- **As Master Regulator of the Neuroimmune System (Figures 2-5)**
  - Omnitura, and the parent company Genyous Biomed, have performed extensive research in many academic centers to understand and exploit the key role of systems biology in disease development and human neuroimmune system.
  - Multiple effects have been observed on the neuroimmune system, and extensive biomarker data collected from in vivo and ex vivo experiments.
  - In addition, biomarker studies from a phase I/IIa clinical trial in patients with advanced refractory cancer, and systematic literature reviews/analysis, support the hypothesis that Aneustat™ acts as a multivalent neuroimmune modulator.
- **As Master Controller of the Hallmarks of Cancer (Figure 6)**
  - **Omnitura Therapeutics** conducted extensive pre-clinical in vitro and in vivo testing of cancer cells and tumors, which have demonstrated that our lead oncology drug candidate, Aneustat™ directly inhibits multiple "druggable" targets in key pathways of **all** the "Hallmarks of Cancer", which is the term for the biological systems responsible for survival, support and proliferation of cancer.
  - This occurs at potencies comparable to those of FDA approved therapies. Aneustat™ was tested, using prostate cancer as a model, in combination with current standards of care (bicalutamide, enzalutamide, abiraterone and docetaxel).
  - The combinations showed significant synergy in efficacy at ***all*** biological levels: proteins, genes, cell and tumor growth. In the same studies, Aneustat™ also overcame drug resistance to these standard of care therapies.
- **As Master Regulator of Glucose Metabolism and Anti-Tumor Immune Responses**
  - Treatment of a near patient xenograft model of human prostate cancer with Aneustat™ resulted in a switch from the anaerobic to aerobic mechanism of glucose. Multiple enzymes in the anaerobic signaling pathway, favored by tumor cells (the Warburg Effect), were inhibited.
  - The primary result was a decrease in the secretion of lactic acid, which acts to block the body's immune response to tumor cells. The restoration of normal metabolism and an increase in effector immune cells was seen in sections of the tumor tissues.
  - This provides experimental evidence that Aneustat treatment in combination with the current immunotherapy protocols will boost control of tumor cell growth.

Figure 2. Cancer Biology: Impacts at Cellular, Microenvironment, and Neuroimmune System



1. tumor microenvironment (stroma) influences tumor biology, treatment, and prognosis. Intra-tumor and inter-tumor microenvironment heterogenous and dynamic
2. Calon, A. et al. Stromal gene expression defines poor-prognosis subtypes in colorectal cancer; Nat Gen, 47(4) ; Apr 2015

Figure 3. Aneustat™ Biological Mechanisms of Action on Neuroimmune System and Hallmarks of Cancer

ANEUSTAT™ BIOLOGICAL MECHANISMS OF ACTION ON THE NEUROIMMUNE SYSTEM AND THE HALLMARKS OF CANCER

Suppresses the Chronic Disease Engine (the interplay of Microbial Infection, Oxidative Stress, & Inflammation) to Intercept Chronic Diseases including Cancer
Positively Affects Cell Growth, Immune System, and Tumor Microenvironment
Modulates Signaling Proteins for all Pathways to Non-Disease, Homeostatic Levels
Does NOT Block Signaling Proteins to Cause Immune Dysfunction
Preclinical data suggests Synergism with many Other Disease Treatments

CANCER CELLS			TUMOR MICROENVIRONMENT & STROMA	NEUROIMMUNE & METABOLIC SYSTEMS		
Tumorigenesis Metastasis	Mitosis	Angiogenesis	Infection Oxidative Stress Inflammation	Innate Immunity	Adaptive Immunity	Metabolism
IMPROVED FUNCTIONALITY						
Modulates Multiple Hallmarks of Cancer	Regulates Cell Cycle	Normalizes Angiogenesis	Reduces Infection Oxidative Stress Inflammation	Modulates the Immune Effector Cells (Hallmarks of Cancer)		Normalizes Metabolic Activity
•Increased Apoptosis •Reduced Cell Migration •Normalize Tumor pH to Support Immune Effector Cell Infiltration	•Promotes Cell Cycle Control - G1/S Regulation	•Reduced Tumor Angiogenesis	•Decreased Viral Replication •Decreased Bacterial Replication •Increased Oxygenation •Decreased Lactic Acid	•Restores Immune Equilibrium and Apoptosis •Reboots function of NK Cells, Dendritic Cells, Neutrophils, and Macrophages	•Restores Immune Equilibrium and Apoptosis •Reboots function of NK Cells Cytotoxic T cells T Reg Cells T Helper Cell B Cells and Macrophages	•Promotes Aerobic Glycolysis and Improved Cellular Energetics •Reduces Lactic Acid Production, Resulting in Normal Intracellular pH
•Overcomes Drug Resistance to AR Blockers & Docetaxel						
MODULATES SIGNAL PROTEIN AND RECEPTOR ACTIONS						
Reduces TGF-β, EGF & Akt, P-stat, C-Myc, RANTES, VEGF, FGFβ, Androgen Receptor, NFkB, STAT-3, FN-1, IL-6, KLK3, ABCB1 & BCL2 Increases p53 & BAX	Reduces Polo-like Kinase, CHK Proteins, TGF-β, Akt, EGF, FGFβ, Myc , Her2/Neu, ERα, AR, KLK3, Stat3, FOS, Cyclin-B, Increases p53 & BAX	Reduces TGF-β, VEGF	Reduces TGF-β,TNF-α, IL-8, NFκB, IL-6, Cox-2, Stat3, IL-1β, GM-CSF, IFNγ, Cyclin B	Reduces IL-1B, IL-6, TNF-α, IL-10	Reduces IL-12, IFNγ, GM-CSF, IL-17, IL-6, TGF-β, IL2ra, CD70, CD74, CFP, IFIT2, OASL, OPRK1, CD24	Reduces HIF1a, GPCR, cAMP synthesis Increases p53, GADD45

Figure 4. Aneustat™ is a Master Regulator of the Neuroimmune System

What is the neuroimmune system?

- **The neuroimmune system is the combined systemic interactions between neural and immune systems which regulate innate and adaptive responses against disease.**
- **It involves the immune system (APC, T, NK cells, etc.) and related components such as cytokines, neural-endocrine interactions (HPA), endorphins[1], and hormonal signaling proteins (steroids); the lymphatic system connects these potent control processes[2].**
- **These natural responses can be augmented or modified by exogenous agents (therapy).**

Aneustat™ is a master regulator of the neuroimmune system

1. Genetics and the placebo effect: the placebome. Hall, K et al. Trends in Molecular Medicine, 21:4, Apr 2015
2. Structural and functional features of central nervous system lymphatic vessels. Louveau, A et al. Nature.14432

Figure 5. Aneustat™, An Orally Delivered Non-toxic Drug, Is the Master Regulator of Neuroimmune Signaling—Cytokines, Chemokines and Growth Factors—To Maintain Equilibrium in and Reboot the Human Immune System to Fight Cancer

- Under non-disease conditions, Aneustat™ neither blocks nor inhibits signaling protein expression, which avoids an adverse impact on the normal operation of the immune system—demonstrated pre-clinically and in human studies
- Aneustat™ prevents mitogen stimulated overexpression of signaling proteins involved in the inflammatory response
- In disease states characterized by signaling protein overexpression, Aneustat™ modulates them to within normal ranges, thereby restoring homeostasis and counteracting immune suppression—data from human phase I/IIa clinical trial
- **Aneustat™ does not block, but restores signaling pathway activity to normal levels, thus avoiding immune dysfunction, drug resistance, toxicity, and other side effects.**
- **Aneustat™ reboots immune related genes and immune effector cells**

Figure 6. Aneustat™ is a Master Controller of the Hallmarks of Cancer (Initiation, Survival and Support Pathways) in Cancer Cells and the Tumor Microenvironment

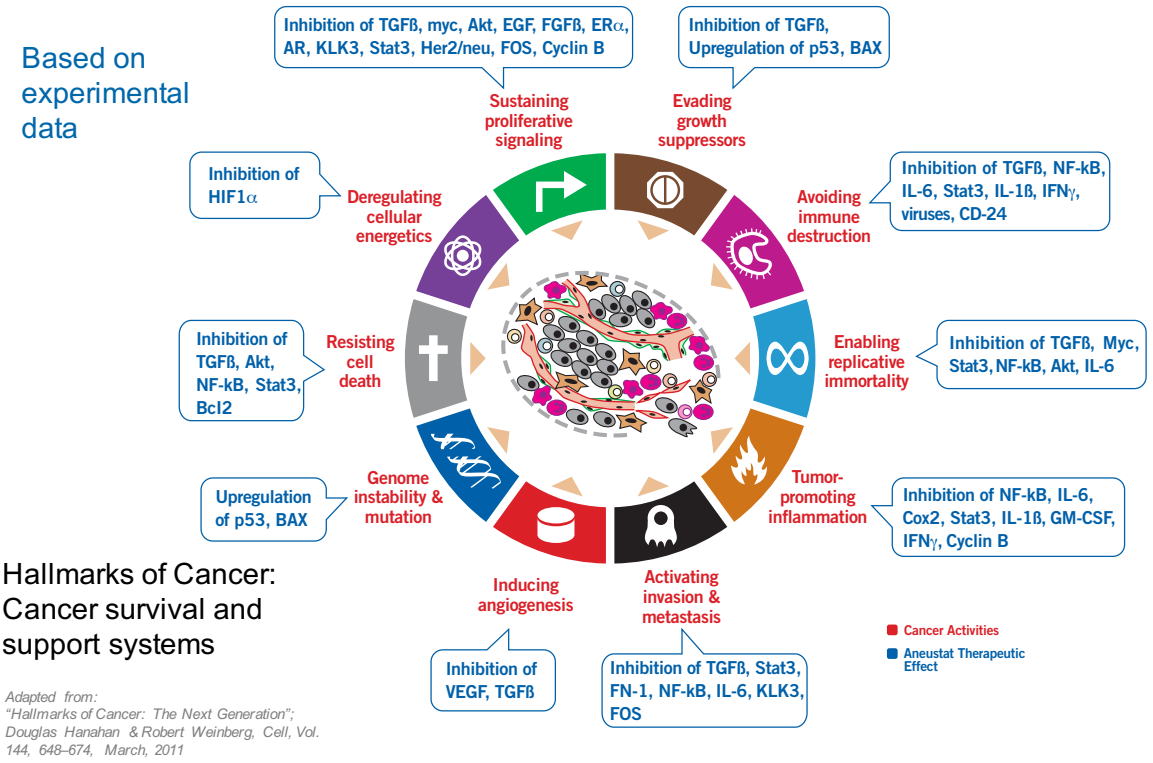


Figure 7. Aneustat™ Potential Ubiquitous Application to Intercept, Treat, and Prevent Cancer and Co-Existing Diseases to Reduce Disease Incidence and Healthcare Cost

Clinical Strategy	**Cancer Interception**		**Treat/Prevent Metastasis Prevent Recurrence**			
Target Organ	Chronic Benign Diseases ⇉	Pre-Cancerous Condition ⇉	Early Stage Cancer **X**	Late Stage Cancer **X** in combination with other standard of care		
Prostate	**X** BPH Prostatitis	**X** PIN/PIA	○ Active Surveillance	**X** Standard of care for Chemo-Naïve mCRPC/adjuvant	○ Standard of Care for Chemo or AR refractory mCRPC	**X** Treatment for triple-refractory mCRPC
Breast	**X** Chronic Inflammation (dense breasts)	**X** Atypical DH BRCA1&2 Family History	△ Post initial curative surgery DCIS	**X** Standard of care for Chemo-Naïve/adjuvant	△ Standard of care for previously treated	**X** Standard of care for refractory
Pancreas	**X** Diabetes And Pancreatitis	**X** Family history and predictive genetics IPMN	△ progression after initial radical surgery	**X** Standard of care for Chemo-Naïve/adjuvant	**X** Standard of care for previously treated	**X** Standard of care for refractory
Lung	**X** COPD	High risk population	**X** Post radical surgery progression	**X** Standard of care for Chemo-Naïve/adjuvant	**X** Standard of care for previously treated	**X** Standard of care for refractory
Colon	**X** IBD	**X** FAP HNPCC	△ progression after curative surgery for localized disease	**X** Standard of care for Chemo-Naïve/adjuvant	△ Standard of care for previously treated	**X** Standard of care for refractory
Liver	**X** Cirrhosis	**X** HBV HCV	△ progression after initial surgical resection	**X** Standard of care for Chemo-Naïve/adjuvant	**X** Standard of care for previously treated	**X** Standard of care for refractory

○ *Initial company clinical development (2017)*

△ *R&D partnership projects with cancer foundations (in discussions)*

Figure 8. Aneustat™—The Foundational Drug to Create Rational Combination Immuno-Oncology For Precision Personalized Cancer Medicine to Improve Efficacy and Safety and Delay Therapy Resistance

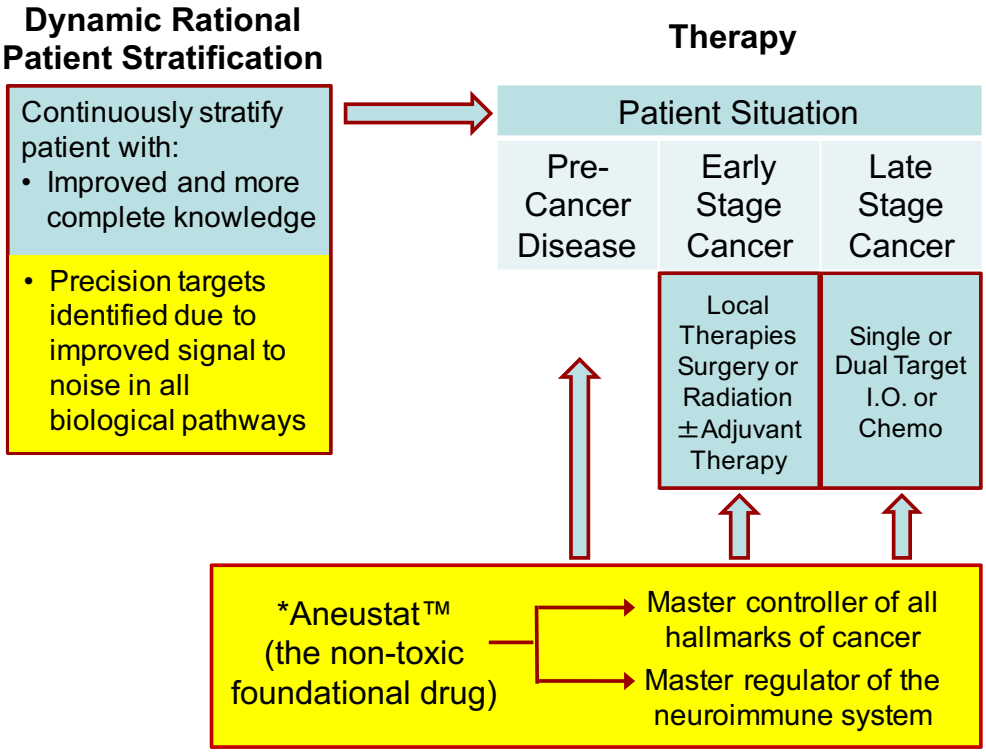


Figure 9. Rationale for Combination of Checkpoint Inhibitors (i.e. Opdivo®, Keytruda®) and Other Immunotherapies With Aneustat™

1. **Responses to checkpoint inhibitors (CPI) are currently variable both within and between tumor types.**

2. **It is well known that CPI work more effectively if undesirable inflammation, unchecked cellular growth, angiogenesis and suppression of growth regulating factors are kept under control during the treatment process.**

3. **Aneustat™ has been shown in pre-clinical and clinical testing to be non-toxic, and to create immune equilibrium by rebooting the innate and adaptive immune system in patients.**

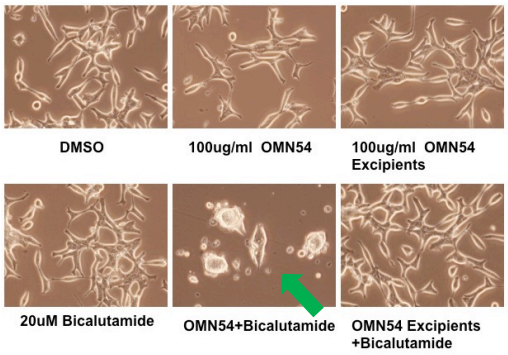
4. **Omnitura invites partners for R&D collaboration to improve safety and long-term efficacy while minimizing side effects and drug resistance for patients, thus reducing clinical trial risk for CPI and other targeted immunotherapies.**

Appendix:

Selected Pre-Clinical Data For Aneustat™ Activity From Prostate Cancer

Aneustat™(OMN54) significantly improves the efficacy and removes drug resistance for standard of care drugs for prostate cancer.

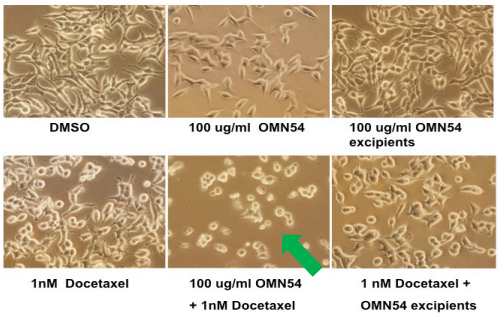
Synergy of Combination of Aneustat™(OMN54) and Bicalutamide on LNCaP Androgen Sensitive Prostate Cancer Cell Proliferation



LNCaP androgen sensitive prostate cancer cells were treated with OMN54 and bicalutamide either alone or combination for 48 hr. These pictures show that the combination of OMN54 and bicalutamide induces apoptosis, while OMN54 alone mostly inhibits cell proliferation, while bicalutamide has no effect on LNCaP androgen sensitive prostate cancer cells.

OMN54 Excipients: inert substances used in Aneustat (OMN54) formulation

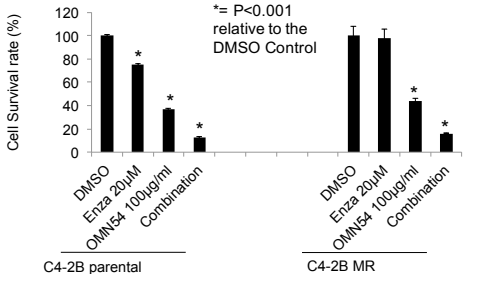
Synergistic Effect of Combination of Aneustat™(OMN54) and Docetaxel on C4-2B Castration Resistant Prostate Cancer Cell Proliferation



C4-2B cells were treated with OMN54 and docetaxel either alone or in combination for 48 hr. These pictures show that the combination of OMN54 and docetaxel (1nM) synergistically kills C4-2B cells. Expect to minimize toxicity and side effects.

OMN54 Excipients: inert substances used in Aneustat (OMN54) formulation

Combination Treatment of Aneustat™(OMN54) with Enzalutamide Demonstrates Synergistic Inhibition of Proliferation of Prostate Cancer Cells



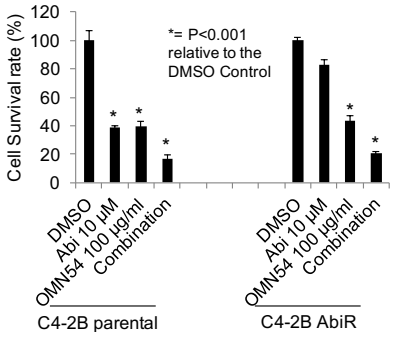
C4-2B cells and C4-2BMR (enzalutamide-resistant C4-2B cells) were treated *in vitro* for 48 hours with either enzalutamide (Enza) alone, OMN54 alone, or in combination, and then cells were counted.

Combination:
20 µM Enzalutamide + 100 µg/ml OMN54

C4-2B: castration resistant prostate cancer cells
C4-2BMR: enzalutamide-resistant castration resistant prostate cancer cells

Conclusions: The results show that OMN54 inhibits the proliferation of castration-resistant prostate cancer cells (C4-2B) as well as enzalutamide-resistant castration resistant prostate cancer cells (C4-2BMR). The combination of OMN54 with enzalutamide demonstrates synergistic anti-cancer effect.

Combination Treatment of Aneustat™(OMN54) with Abiraterone Demonstrates Synergistic Inhibition of Proliferation of Prostate Cancer Cells



C4-2B cells and C4-2B AbiR (abiraterone resistant C4-2B cells) were treated *in vitro* for 48 hours with either abiraterone (Abi) alone, OMN54 alone, or in combination, and then cells were counted.

Combination:
10 µM abiraterone + 100 µg/ml OMN54

C4-2B parental: castration resistant prostate cancer cells
C4-2BAbiR: abiraterone-resistant castration resistant prostate cancer cells

Conclusion: The results show that OMN54 inhibits the proliferation of castration resistant prostate cancer cells (C4-2b) and abiraterone-resistant castration resistant prostate cancer cells (C4-2BAbiR). The combination of OMN54 with abiraterone demonstrates synergistic anti-cancer effect.

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