BriaCell

*The Future of Cancer Immunotherapy*

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# Mount Sinai's Frontiers in Academic Pathology Symposium
# January 2020

# Cancer Immunotherapy Space

## The Problems

- **Checkpoint Inhibitors:** Keytruda® (anti-PD-1), Yervoy® (anti-CTLA-4) and others reduce the tumor's ability to suppress immune system. They only work in 20%-30% of patients and can cause autoimmune disease.
- **Therapeutic Cancer Vaccines:** Have not been successful in solid tumors or blood cancers as they are not specific enough to the patient.
- **Personalized Immunotherapies:**
  - CAR-T therapies are effective in blood cancers (but not in solid tumors) and must also be individually manufactured in a complex process for each patient.
  - Provenge® is effective for prostate cancer but must be individually manufactured for each patient and as a result of the required manufacturing logistics has not been commercially successful.

## BriaCell's Solution

- **BriaCell's Off-the-Shelf Personalized Immunotherapy:** BriaCell has been developing Bria-IMT™, which is a targeted immunotherapy for breast cancer. Several remarkable responses in patients with late stage cancer have been seen in patients who match Bria-IMT™ at certain HLA alleles. This supports the development of **Bria-OTS™** and **BriaDX™**.

**BriaCell's 15 HLA alleles (8 Class I & 7 Class II) cover/match >99% of the population. This saves time and eliminates the complex manufacturing process associated with other personalized immunotherapies.**

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# *Mechanism of Action*

## *Bria-IMT™ & Bria-OTS™*

# Development of SV-BR-1 and SV-BR-1-GM (Bria-IMT™)

SV-BR-1 was derived from a chest wall metastasis of a patient with grade 2 metastatic breast cancer

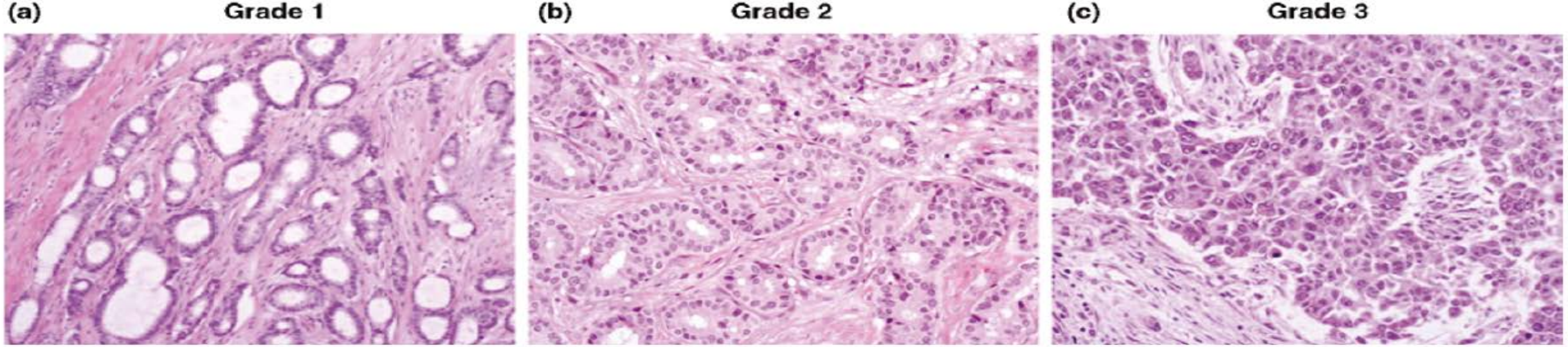



**Figure 1. Histological grade of breast cancer as assessed by the Nottingham Grading System. (a)** A well-differentiated tumor (grade 1) that demonstrates high homology to the normal breast terminal duct lobular unit, tubule formation (>75%), a mild degree of nuclear pleomorphism, and low mitotic count. **(b)** A moderately differentiated tumor (grade 2). **(c)** A poorly differentiated (grade 3) tumor with a marked degree of cellular pleomorphism and frequent mitoses and no tubule formation (<10%).

- Grade is based on the evaluation of three morphological features: (a) degree of tubule or gland formation, (b) nuclear pleomorphism, and (c) mitotic count.
- SV-BR-1 was stably transfected with the *CSF2* gene, encoding GM-CSF to form SV-BR-1-GM = Bria-IMT™

Rakha *et al*. *Breast Cancer Research* 2010, **12**:207 http://breast-cancer-research.com/content/12/4/207

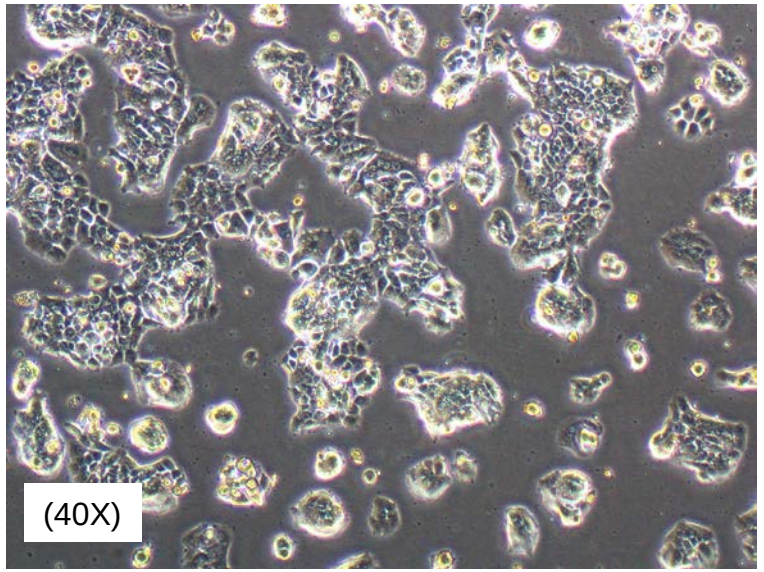
# Characterization of SV-BR-1 Bria-IMT™

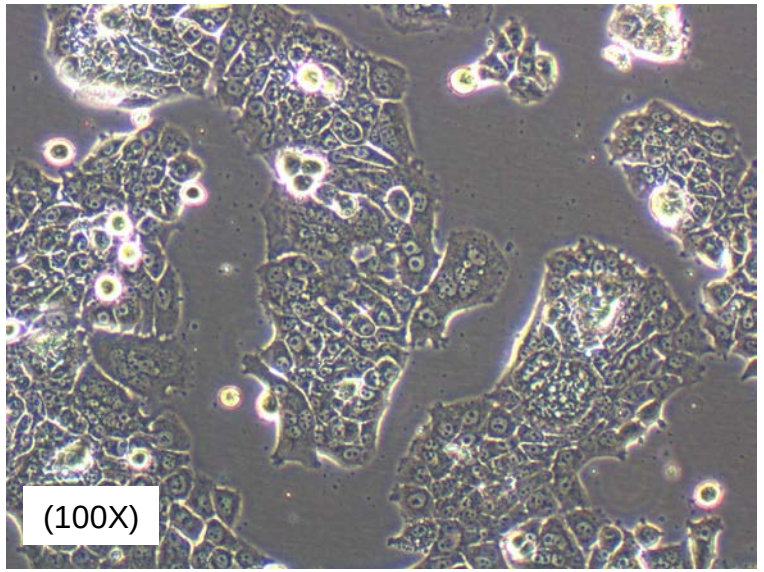
## Bria-IMT™

- Breast cancer cell line derived from a grade 2 tumor
- Whole-cell targeted immunotherapy secreting GM-CSF (“GVAX”).
- Scalable production - grows as cancer cell line in RPMI + 10% FBS.
- Irradiation prior to injection to prevent replication.
- Used in combination with cyclophosphamide, and post-treatment with interferon-α.
- **Expected Result:** Boosting the patient’s overall immune response to the tumor cells.

### Target Population

- Late stage **breast cancer** initial indication.
- Potential use for early stage breast cancer (adjuvant and neo-adjuvant approaches).
- Maintenance therapy for duration of disease



# Immune Signature of Bria-IMT™

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| Gene symbol | Official full name/description | Aliases |
|---|---|---|
| ADA | Adenosine deaminase | |
| ADGRE5 | Adhesion G protein-coupled receptor E5 | CD97, TM7LN1 |
| B2M | Beta-2-microglobulin | IMD43 |
| CAV1 | Caveolin 1 | BSCL3, CGL3, LCCNS, MSTP085, PPH3, VIP21 |
| CD58 | CD58 molecule | LFA-3, LFA3, ag3 |
| CD74 | CD74 molecule; invariant chain and CLIP | DHLAG, HLADG, II, Ia-GAMMA |
| CD83 | CD83 molecule | BL11, HB15 |
| CSF2 | Colony-stimulating factor 2 | GMCSF |
| CXCL8 | C-X-C motif chemokine ligand 8 | GCP-1, GCP1, IL8, LECT, LUCT, LYNAP, MDNCF, MONAP, NAF, NAP-1, NAP1 |
| CXCL16 | C-X-C motif chemokine ligand 16 | CXCLG16, SR-PSOX, SRPSOX |
| HLA-A | Major histocompatibility complex, class I, A | HLAA |
| HLA-B | Major histocompatibility complex, class I, B | AS, B-4901, HLAB |
| HLA-DMA | Major histocompatibility complex, class II, DM alpha | D6S222E, DMA, HLADM, RING6 |
| HLA-DMB | Major histocompatibility complex, class II, DM beta | D6S221E, RING7 |
| HLA-DRA | Major histocompatibility complex, class II, DR alpha | HLA-DRA1, MLRW |
| HLA-DRB3 | Major histocompatibility complex, class II, DR beta 3 | HLA-DR1B, HLA-DR3B |
| HLA-F | Major histocompatibility complex, class I, F | CDA12, HLA-5.4, HLA-CDA12, HLAF |
| ICAM3 | Intercellular adhesion molecule 3 | CD50, CDW50, ICAM-R |
| IL6 | Interleukin 6 | BSF-2, BSF2, CDF, HGF, HSF, IFN-beta-2, IFNB2, IL-6 |
| IL15 | Interleukin 15 | IL-15 |
| IL18 | Interleukin 18 | IGIF, IL-18, IL-1g, IL1F4 |
| KITLG | KIT ligand | DCUA, DFNA69, FPH2, FPHH, KL-1, Kitl, MGF, SCF, SF, SHEP7 |

*Genes with immunostimulatory roles expressed in SV-BR-1-GM cells. Gene symbols refer to the NCBI designations and HUGO Gene Nomenclature Committee (HGNC) recommendations. Gene symbols, official full names/descriptions, and aliases are indicated as shown on the respective NCBI gene sites with or without additional information.*

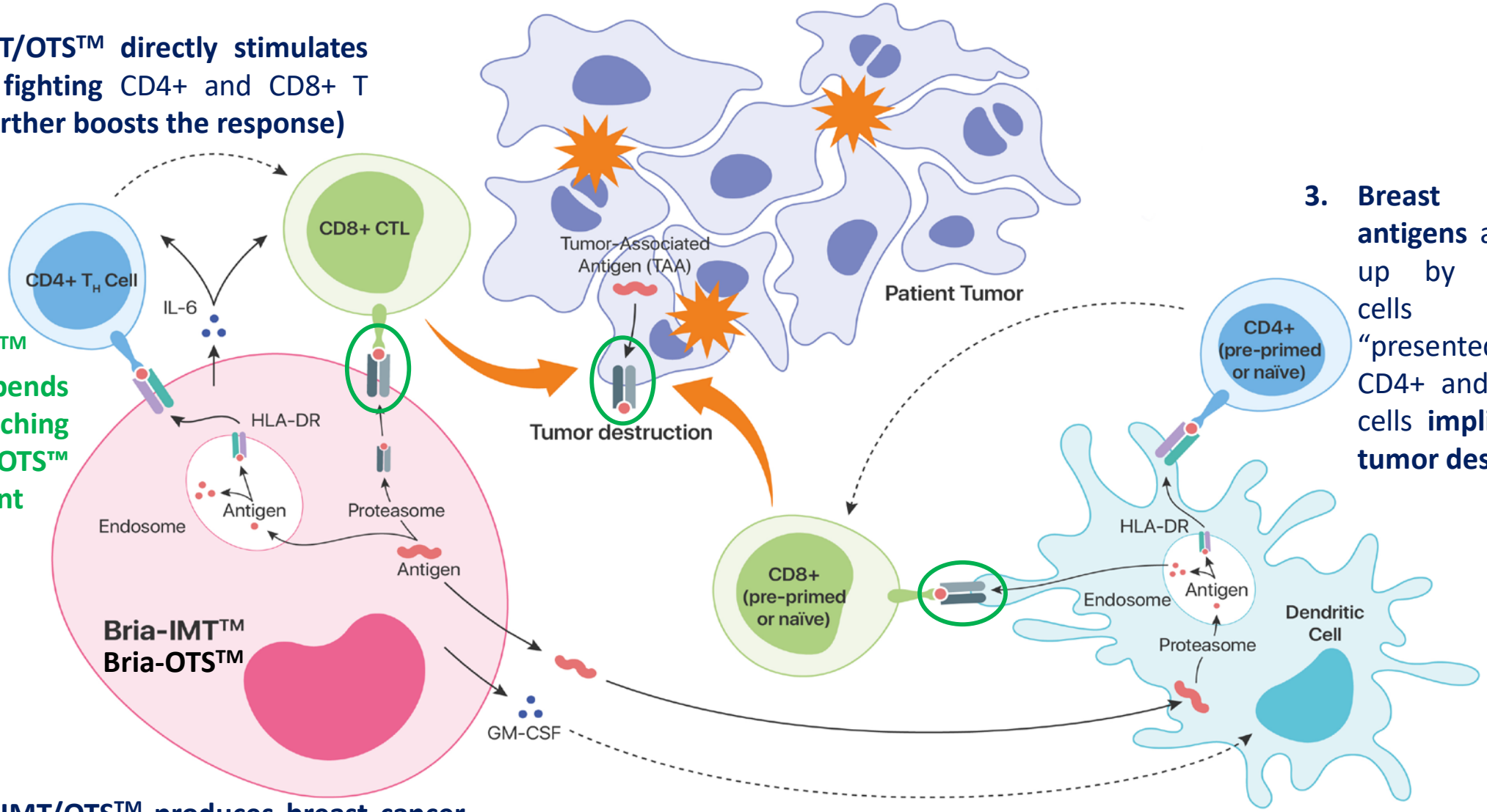
- **Bria-IMT™ expresses multiple immunostimulatory genes**

# Bria-IMT™ & Bria-OTS™

## *Potential Mechanisms of Specific Immune Activation in Advanced Breast Cancer*

4. **Bria-IMT/OTS™ directly stimulates cancer fighting** CD4+ and CD8+ T cells **(further boosts the response)**

5. **Bria-IMT/OTS™ efficacy depends on HLA matching of Bria-IMT/OTS™ and the patient**




3. **Breast cancer antigens** are taken up by dendritic cells and "presented" to CD4+ and CD8+ T cells **implicated in tumor destruction**.

1. **Bria-IMT/OTS™ produces breast cancer antigens** (proteins made by breast cancer cells)

2. **Bria-IMT/OTS™ secretes GM-CSF** which further promotes dendritic cell-based antigen presentation (**boosts the response**)

# Bria-IMT™ and Bria-OTS™ Mechanism of Action

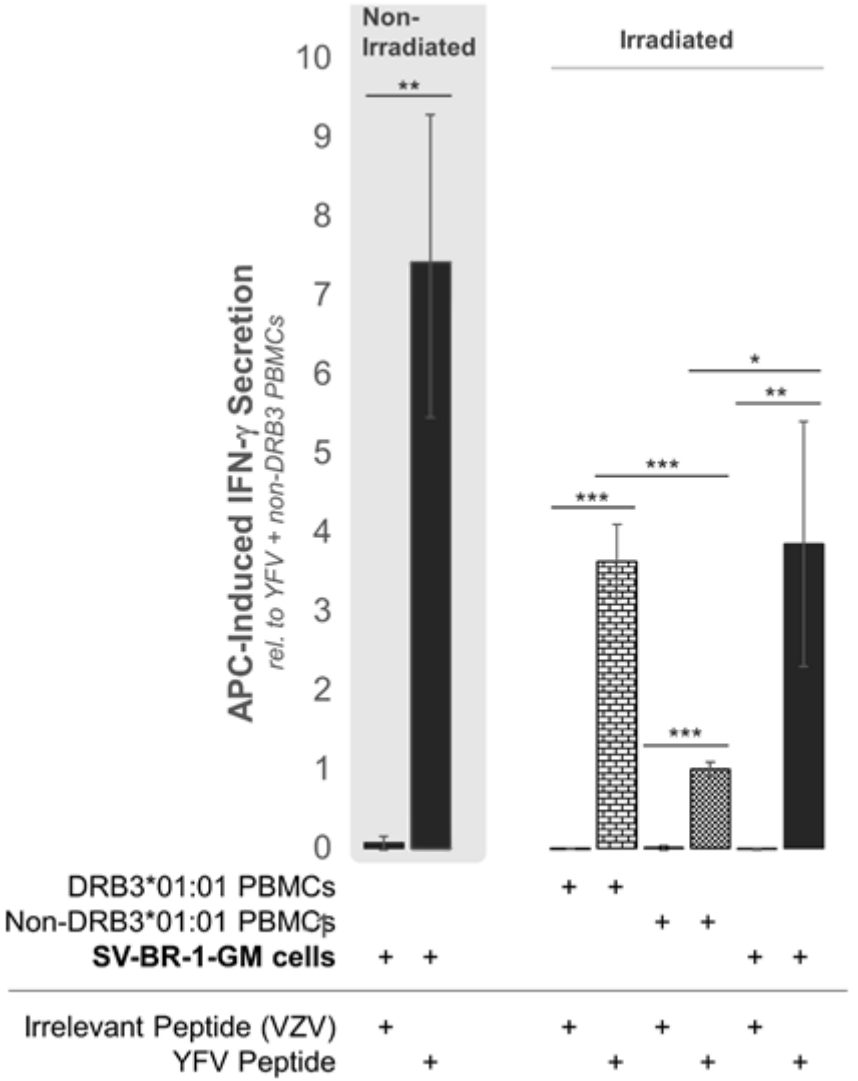
## The Problems

- **Therapeutic Cancer Vaccines:** Have not been successful in solid tumors or blood cancers with the exception of personalized approaches.

- **Personalized Immunotherapies:**
  - Provenge® is effective for prostate cancer and uses a prostate-specific antigen coupled to GM-CSF to pulse dendritic cells.
  - This indicates that immune responses to a tissue-specific antigen can be an effective immunotherapy.
  - This further suggests that a Class II HLA restricted CD4+ Helper T cell response may be key in effectiveness of the immunotherapy.

## Bria-IMT™ can Directly Activate Helper T cells

- **Our data indicates that Bria-IMT™ expresses Class II HLA molecules and can directly activate helper T cells in an HLA-Restricted Fashion.**
- **Published in Frontiers in Immunology**



# Bria-IMT™ Expresses Multiple Breast/Cancer related Antigens

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ABCA12 | C5orf46 | EIF3H | IRX3 | **MIEN1** | PIGK | SLC35A2 | UBR5 |
| AKR1B15 | CABYR | **ERBB2** | KIF2C | MTHFD2 | PLAC1 | SPAG1 | VTCN1 |
| AKR1C2 | CBX2 | FOXI1 | KRT15 | MYEOV | **PRAME** | STAC2 | XDH |
| ALDH3B2 | CCL28 | HIST1H2AE | KRT17 | NQO1 | PTHLH | **STARD3** | XPOT |
| ALG8 | CENPN | HIST1H2BG | KRT19 | OIP5 | RFC5 | STC2 | |
| ARHGEF38 | COL8A1 | HIST1H4H | KRT81 | PAK1 | RSF1 | SYCP2 | |
| ARPC5L | DCAF10 | IGFBP5 | LMX1B | PBK | SCGB1D2 | SYNE4 | |
| ATP6V1B1 | DHRS2 | IL22RA2 | MGAT4A | PDCD6 | SCGB2A2 | TFAP2A | |
| AWAT2 | DUSP4 | INTS7 | MGP | PDRG1 | SFRP1 | TNPO1 | |
| AZIN1 | EFHD1 | IRX2 | MIA | **PGAP3** | SHB | TRPS1 | |

**ERBB2, MIEN1, PGAP3, STARD3: on "HER2 amplicon. Green shading indicates cell surface or extracellular expression. PRAME is a cancer testis antigen.**

- SV-BR-1-GM expresses dozens of breast tissue and cancer-related antigens (by RNA-seq).
- This enhances the chance for a broad immune response against multiple breast tissue and breast cancer-related antigens.
- There is evidence for immune responses against some of these antigens in patients treated with the Bria-IMT™ regimen.

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# *Bria-IMT™ Clinical Studies*

# Origin of the Technology: Bria-IMT™

## *Positive Human Proof-of-Concept Trials in Advanced Breast Cancer*

**First Proof-of-Concept Phase I used SV-BR-1 *(1999-2003)*:**

- Used unmodified irradiated cell line +
  - Pre-Rx low dose cyclophosphamide (reduces immune suppression) +
  - Post-Rx local GM-CSF
- N = 14 late stage, treatment-refractory breast cancer patients
- Well tolerated, no severe drug related AEs
- Median Overall Survival = **12.1 months**

**SV-BR-1 was genetically engineered to produce GM-CSF creating Bria-IMT™**

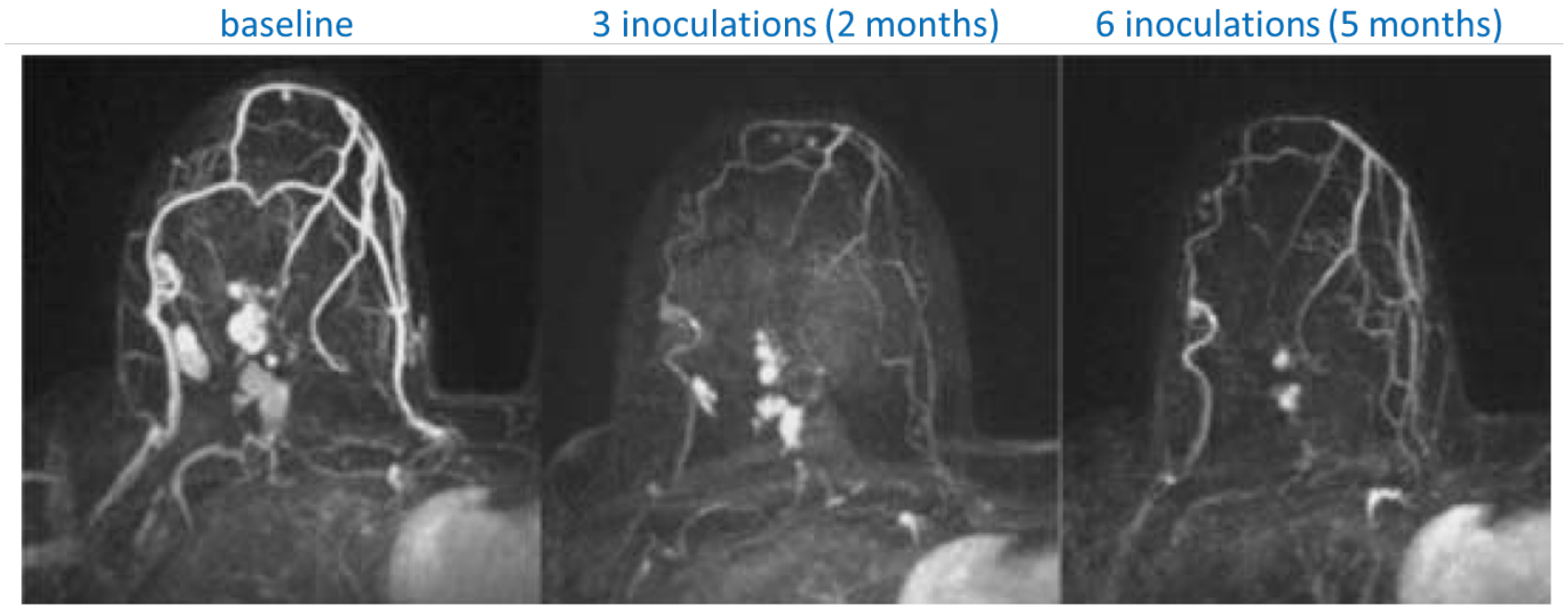
**Second Proof-of-Concept Phase I *(2004-2006)*:**

- Used Bria-IMT™+
  - Pre-Rx low dose cyclophosphamide +
  - Post-Rx local interferon-α (**the Bria-IMT™ regimen**)
- N = 4 late stage, treatment-refractory (3 breast cancer, and 1 ovarian cancer) patients
- Well tolerated, no life-threatening drug related adverse events
- One patient with transient urticaria reported as grade 3, responded to antihistamines
- Median Overall Survival = **35 months**
- One robust responder with **>90% regression during treatment**, subsequent relapse (upon halting treatment) **responded to re-treatment**

# Bria-IMT™
## *Human Proof-of-Concept Trials in Breast Cancer (Patient A002)*

**Bria-IMT™ Second Proof-of-Concept Phase I (*2004-2006*):**

- Patient A002 had breast cancer that had spread to the lungs, soft tissues and bone
- She initially responded to chemotherapy, but then relapsed with tumor spread to the breast, lungs, soft tissues and bone
- She was treated with the Bria-IMT™ regimen and had a robust response with substantial tumor regression in the breast and bone, and complete clearance in the lungs and soft tissues
- **Patient A002 matched Bria-IMT™ at HLA-DRB3 and HLA-DRB1**



# Bria-IMT™

## *Human Proof-of-Concept Trials in Breast Cancer (Patient A002)*

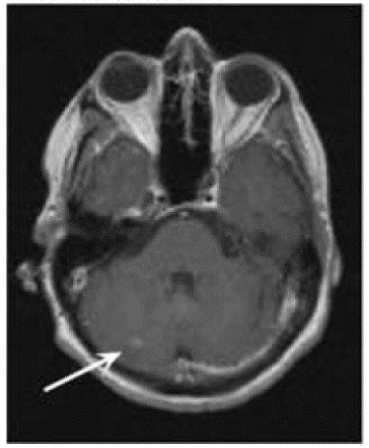
- Treatment stopped as per FDA requirements, and approximately 3 months (106 days) after the last inoculation, Patient A002's breast cancer returned and spread to brain, lung and other sites

- Patient A002 was then re-treated with 10 inoculations of Bria-IMT™ over 4 months

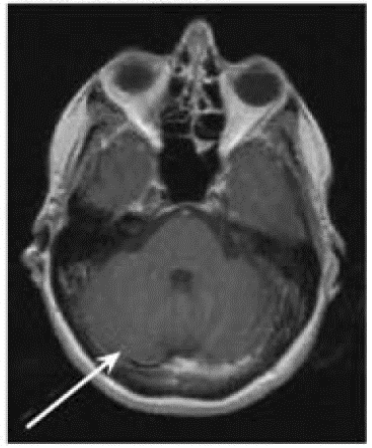
- Repeat imaging studies showed a **complete remission of the previous multiple central nervous system metastases** as shown in the brain scans below:

Lesion 1

baseline

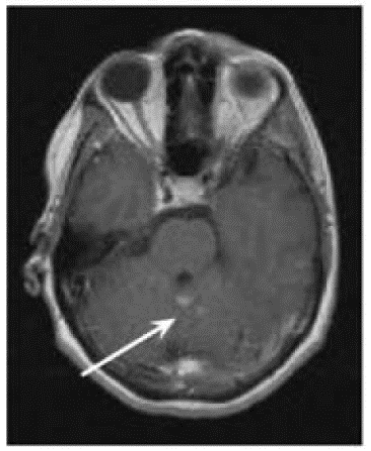


3 re-inoculations

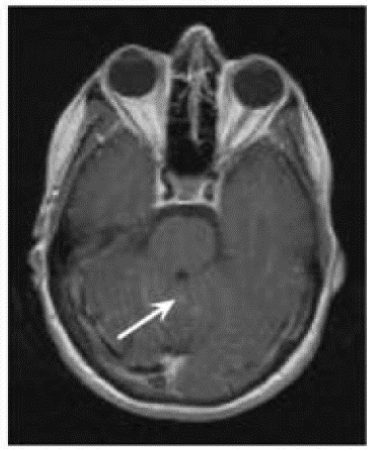


Lesion 2

baseline



3 re-inoculations



# Bria-IMT™

## *Human Proof-of-Concept Trials in Breast Cancer (Patient A002)*

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**Bria-IMT™ Non-Personalized Immunotherapy – Given as "Monotherapy"**

**Second Proof-of-Concept Phase I:**

- **Patient A002 matched Bria-IMT™ at HLA-DRβ3 and HLA-DRβ1 and experienced tumor regression with complete remission at some metastatic sites**

| | Tumor Type | Survival (months) | Tumor regression | HLA-A Alleles | | HLA-B Alleles | | HLA-C Alleles | | HLA-DRB3 Alleles | | HLA-DRB1 Alleles | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bria-IMT™ | Breast | | | - | 24:02 | 35:08 | 55:01 | 01:02 | 04:01 | 01:01 | 02:02 | 11:04 | 13:03 |
| **Patient A001** | Breast | 40.7 | No | 02:01 | 24:02 | 13:02 | 41:01 | 06:02 | 17:01 | 03:01 | - | 07:01 | 13:02 |
| **Patient A002** | Breast | 33.7 | YES | 02:01 | 11:01 | 18:03 | 44:02 | 05:01 | 07:01 | 02:02 | - | 11:04 | 13:01 |
| **Patient A003** | Ovarian | 35.6 | No | 02:01 | 03:01 | 07:02 | 13:02 | 06:02 | 07:02 | Negative | - | 07:01 | 07:01 |
| **Patient B001** | Breast | 7.0 | No | 11:01 | - | 35:01 | 40:01 | 03:04 | 04:01 | Negative | - | 07:01 | 15:01 |

# Bria-IMT™ Phase IIa Monotherapy Trial Design

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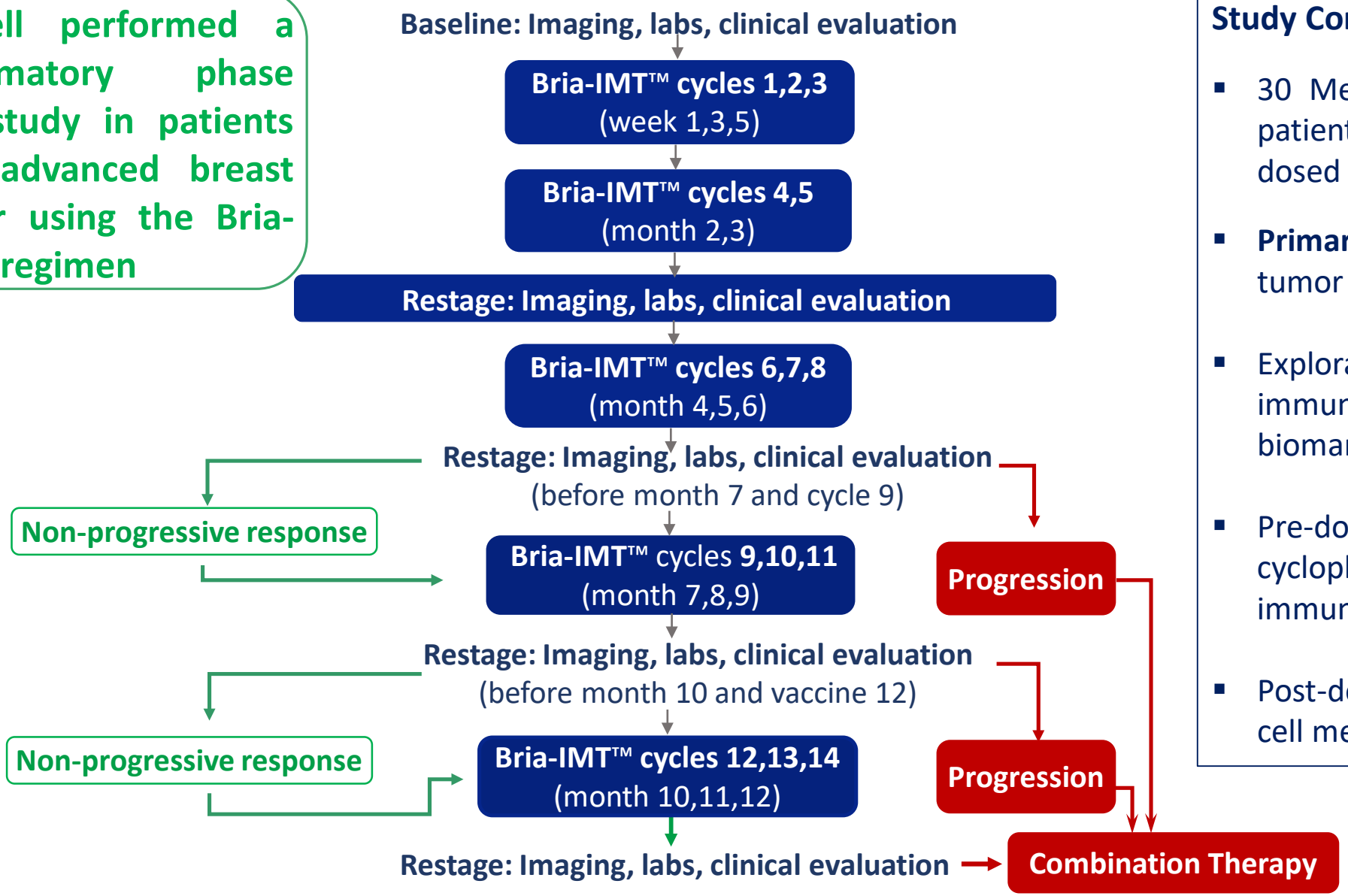
**BriaCell performed a confirmatory phase I/IIa study in patients with advanced breast cancer using the Bria-IMT™ regimen**




**Study Completed:**

- 30 Metastatic Breast Cancer patients screened and 23 dosed
- **Primary objectives**: Safety & tumor response
- Exploratory objectives include immune response to tumor, biomarkers, Quality of Life
- Pre-dose low dose cyclophosphamide to reduce immune suppression
- Post-dose IFN-α2b to boost cell mediated immunity

# Bria-IMT™

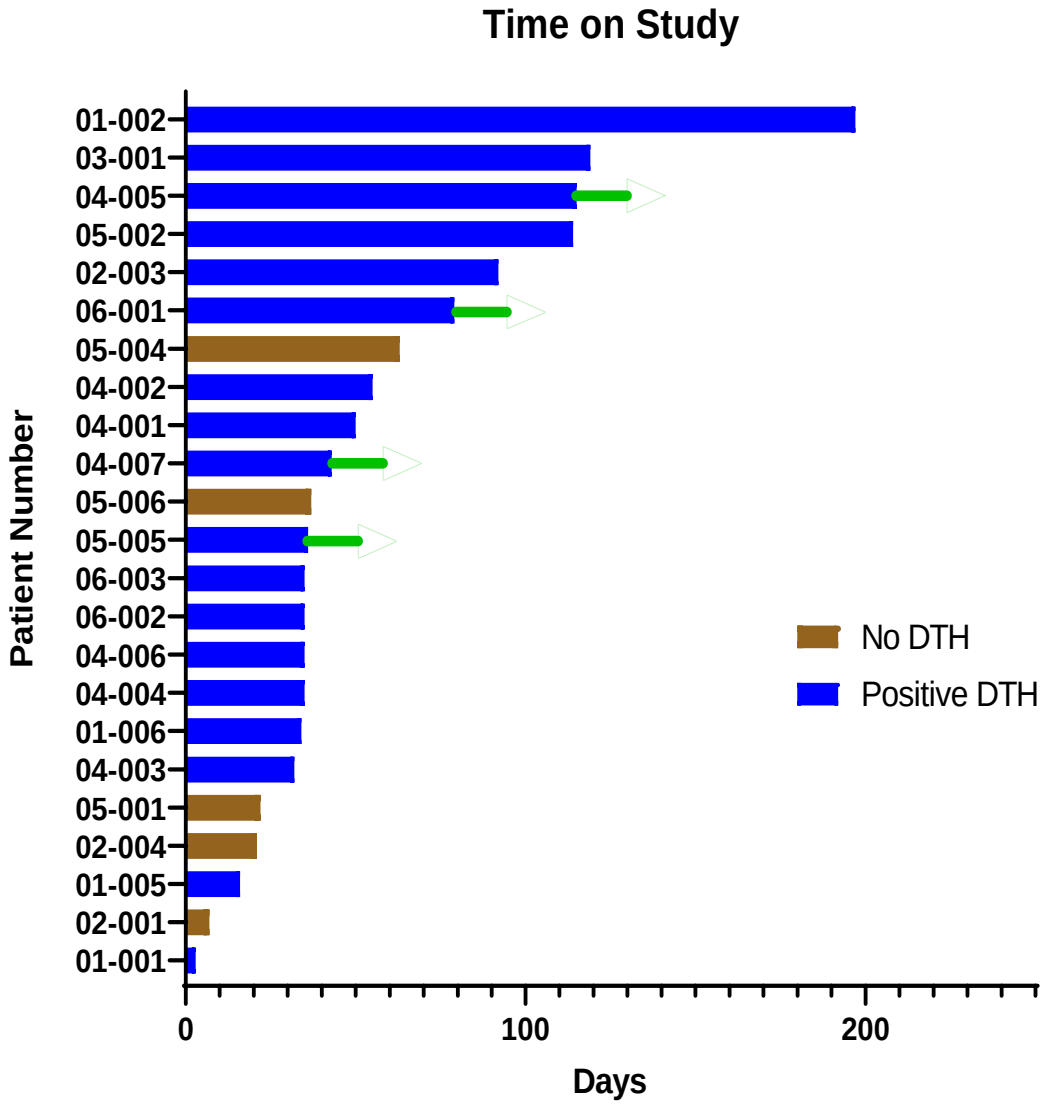
## *Study WRI-GEV-007 – Monotherapy Patient Characteristics*

| Patient Characteristics (23 total) | No HLA Allele Matches (n=6) | 1+ HLA Allele Matches (n=17) | 2+ HLA Allele Matches (n=4) |
|---|---|---|---|
| Age | 55 ± 14 | 60 ± 8 | 68 ± 7 |
| Median Prior Systemic Regimens | 5.5 (range 2-13) | 4 (range 0-10) | 3.5 (range 3-7) |
| % ER/PR + | 67% | 33% | 33% |
| % Her2/neu + | 47% | 41% | 24% |
| % Triple Negative | 75% | 50% | 0% |
| Grade I/II | 2 | 4 | 2 |
| Grade III | 4 | 13 | 3 |

**The patients are heavily pre-treated and generally similar regardless of HLA matching with Bria-IMT™**

# Bria-IMT™

## *Study WRI-GEV-007 – Monotherapy Time on Study*




**Brown bars** indicate patients unable to mount a DTH response

**Blue bars** indicate patients able to mount a DTH response

Arrows → indicate the patients rolled over to combination therapy

**Conclusion: In spite of being very heavily pre-treated (median of 4 prior chemotherapy or biological therapy regimens), patients were able to remain on the Bria-IMT™ regimen for protracted periods of time suggesting clinical benefit. Lack of a DTH response tended to correlate with shorter time on study.**

# Bria-IMT™

## *Study WRI-GEV-007 – Monotherapy Safety Data*

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### Adverse Events seen in 2 or More Patients

| ADVERSE EVENT TERM | Occurrences | Patients |
|---|---|---|
| Erythema | 42 | 11 |
| Induration | 32 | 7 |
| Pruritis | 13 | 7 |
| Abdominal pain | 9 | 6 |
| Fatigue | 8 | 6 |
| Nausea | 8 | 6 |
| Pain, musculoskeletal | 9 | 6 |
| constipation | 5 | 5 |
| Diarrhea | 5 | 4 |
| Flu like symptoms | 5 | 4 |
| peripheral neuropathy | 3 | 3 |
| Urinary Tract Infection | 3 | 3 |
| Abdominal distension | 2 | 2 |
| Anorexia | 2 | 2 |
| Bruising, Facial | 2 | 2 |
| Chills | 2 | 2 |
| Decreased appetite | 2 | 2 |
| Dehydration | 2 | 2 |
| Dizziness | 2 | 2 |
| Dyspepsia | 2 | 2 |
| Erythema multi form | 2 | 2 |
| GGTP Increased | 3 | 2 |
| Hypertension | 2 | 2 |
| Increased Alkaline Phosphatase | 3 | 2 |
| Increased ALT | 2 | 2 |
| Increased AST | 4 | 2 |
| Increased GGT | 2 | 2 |
| Injection site reaction | 3 | 2 |
| Myalgia | 2 | 2 |
| Numbness in hands | 2 | 2 |
| Pleural effusion | 2 | 2 |
| Rash | 3 | 2 |
| High uric acid | 2 | 2 |
| Urticaria | 3 | 2 |
| Vomiting | 2 | 2 |

### Serious Adverse Events

| Serious Adverse Event | Severity | Relationship to Bria-IMT™ |
|---|---|---|
| Fever | Grade 1 | Unrelated |
| Influenza A | Grade 2 | Unlikely Related |
| Palpitations | Grade 2 | Unlikely Related |
| GERD | Grade 2 | Possibly Related |
| Bone pain | Grade 3 | Unrelated |
| Urinary Tract Infection | Grade 3 | Unlikely Related |
| Hyponatremia | Grade 3 | Unrelated |
| Hypercalcemia | Grade 4 | Unlikely Related |
| Worsening of Hypercalcemia | Grade 4 | Unlikely Related |
| Sepsis | Grade 4 | Unlikely Related |
| Pleural Effusion | Grade 4 | Unrelated |
| Respiratory Failure Death | Grade 4 | Unrelated |
| Restrictive Cardiomyopathy | Grade 5 | Unlikely Related |

**Conclusion: Bria-IMT™ was generally safe and well tolerated**

# Bria-IMT™- Activity Dependent on Ability to Develop DTH

**Bria-IMT™ appears to be most effective in patients who match with Bria-IMT™ at HLA loci and who are able to mount a DTH response further supporting our "HLA Matching Hypothesis"**

## HLA Matching and Biological Activity

| Patients | HLA Match | Tumor Shrinkage | Tumor Shrinkage in Immune Responders* |
|---|---|---|---|
| N=6 | ≥ 2 | 50% | 75% |
| N=20 | ≥ 1 | 20% | 27% |
| N=7 | 0 | 0% | 0% |

*Immune response measured by delayed-type hypersensitivity.

- PD-L1 expression on circulating cancer cells & cancer-associated cells in >90% of patients → Strong rationale for combination with checkpoint inhibitors

# Bria-IMT™

## *Current Phase I/IIa Data Supports HLA Matching Hypothesis*

- **Patient 01-002:** 73-year-old woman with breast cancer diagnosed in 1995. Developed liver metastases in 2010, and lung metastases in 2017. Previously treated with 7 rounds of chemotherapy with 8 different chemotherapy agents. Received 5 cycles of Bria-IMT™ over 3 months, then monthly cycles (6 months total). Evaluated after 3 months and 6 months. After 3 months, despite the extensive prior therapy, her scans noted that, "there has been a clear response in the multiple bilateral pulmonary nodules". The response was maintained after 6 months of Bria-IMT™ treatment. **She matches Bria-IMT™ at 2 HLA alleles.**

- The liver tumors were stable to slightly increased at 3 months, and then progressed after 6 months.

- This supports our hypothesis of heightened anti-tumor activity in patients with a matched HLA types.
- Clear path to develop BriaDX™ to select the patients using HLA testing.

| | Tumor Type | Survival (months) | Tumor Response | HLA-A Alleles | | HLA-B Alleles | | HLA-C Alleles | | HLA-DRB3 Alleles | | HLA-DRB1 Alleles | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bria-IMT™** | **Breast** | | | - | **24:02** | **35:08** | **55:01** | **01:02** | **04:01** | **01:01** | **02:02** | **11:04** | **13:03** |
| **Patient 01002** | Breast | Ongoing | Mixed | 03:01 | **24:02** | 15:01 | 51:01 | 03:03 | 14:02 | **02:02** | - | 08:01 | 14:01 |

# Bria-IMT™

## *Patient 01-002 Lung Lesions (16 Cleared, 5 Regressed) (2017)*

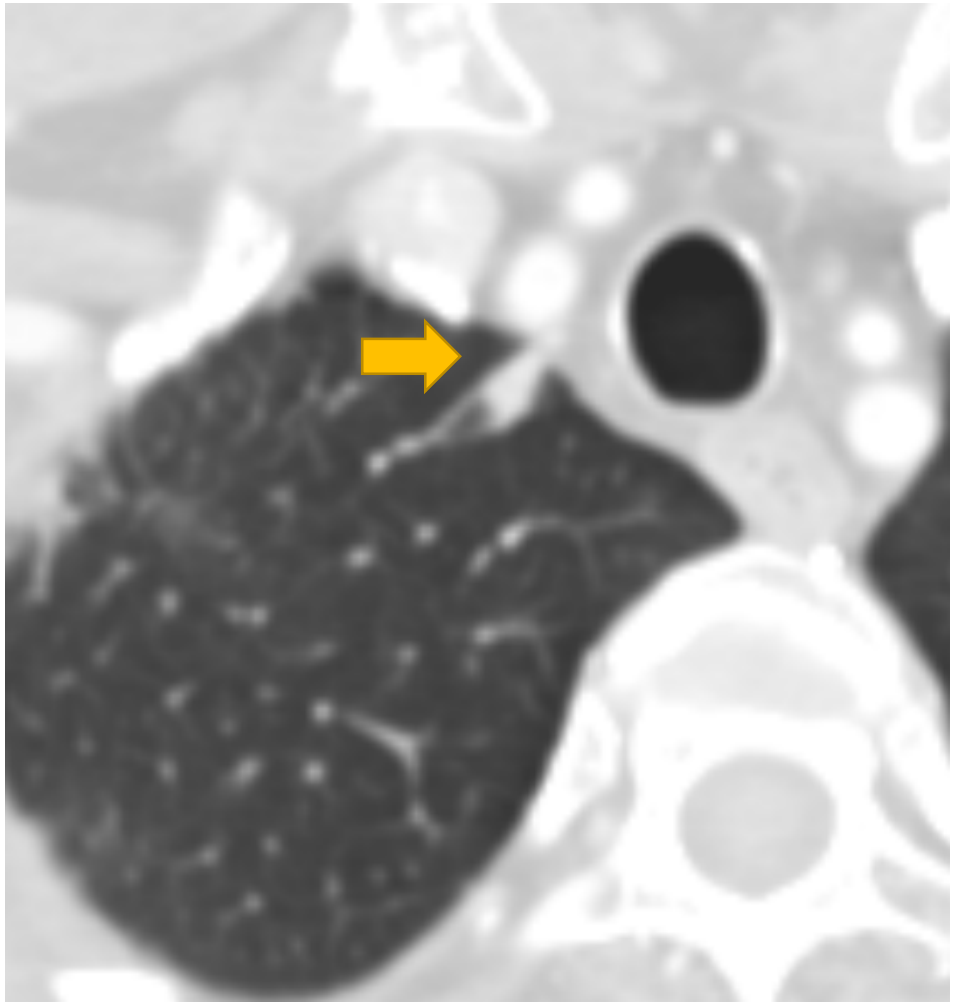
| Pt 01-002 CT Lung Images | | | | | |
|---|---|---|---|---|---|
| | Site | Description | Size mm- Pre-Treatment | Size mm- 3 months | Size mm- 6 months |
| 1 | RLL | | 2.9 | Not Detectable | Not Detectable |
| 2 | LUL | apical pleural based | 3.4 | tiny nodule < 1mm ?scar | tiny nodule < 1mm ?scar |
| 3 | xxx | | 3.9 | Not Detectable | Not Detectable |
| 4 | | | 4.0 | Not Detectable | Not Detectable |
| 5 | RLL | | 4.5 | Not Detectable | Not Detectable |
| 6 | LLL | | 4.9 | Not Detectable | Not Detectable |
| 7 | xxx | | 5.2 | Not Detectable | Not Detectable |
| 8 | RLL | | 5.2 | Not Detectable | Not Detectable |
| 9 | RLL | | 5.6 | Not Detectable | Not Detectable |
| 10 | RLL | costophrenic recess | 5.6 | Not Detectable | Not Detectable |
| 11 | XXX | | 5.8 | Not Detectable | Not Detectable |
| 12 | LUL | | 6.0 | Not Detectable | Not Detectable |
| 13 | XXX | | 6.7 | 1.5 | 1.5 |
| 14 | RUL | | 7.2 | 1.5 | 1.5 |
| 15 | LLL | | 7.6 | Not Detectable | Not Detectable |
| 16 | RUL | Noncalcified Nodule | 7.7 | Not Detectable | Not Detectable |
| 17 | RLL | costophrenic recess | 7.9 | 1.0 | 1.0 |
| 18 | RUL | | 8.2 | Not Detectable | Not Detectable |
| 19 | RLL | | 9.0 | Not Detectable | Not Detectable |
| 20 | RLL | | 9.1 | < 0.1 | < 0.1 |
| 21 | xxx | | xxx | Not Detectable | Not Detectable |

# Bria-IMT™: Remarkable Efficacy in Advanced Breast Cancer

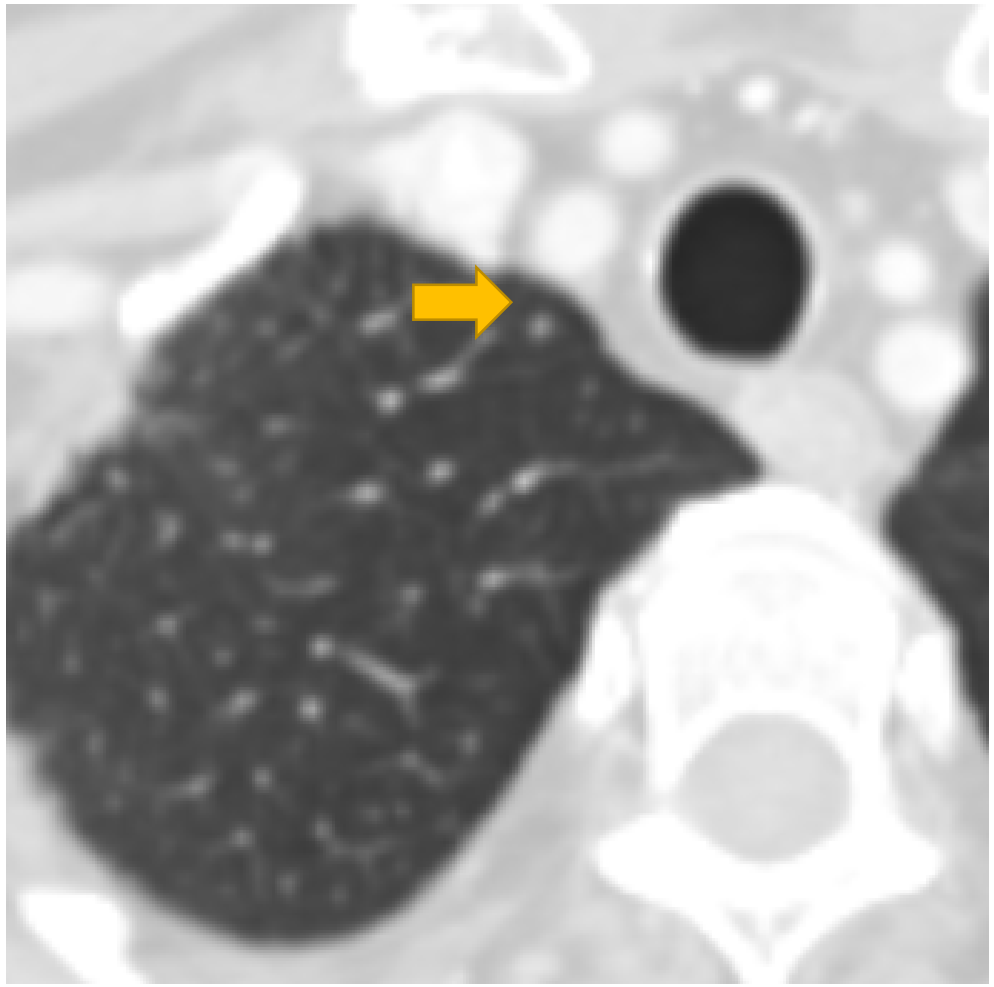
## *Patient 01-002 Lung Lesions (failed 7 prior chemo regimens) (2017)*

**Patient with 20 lung metastases all either disappeared or shrunk to tiny scars – 2 HLA Matches**

**Pre-Treatment**



**Post-Treatment**

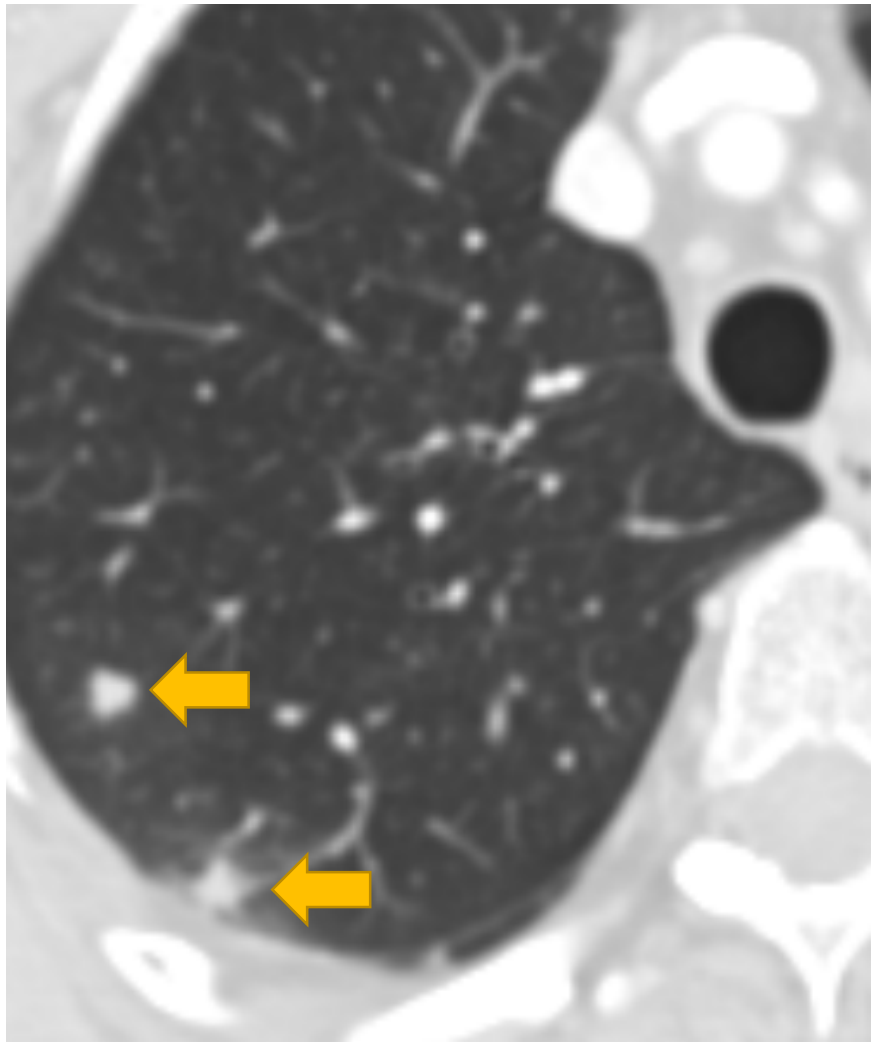


# Bria-IMT™: Remarkable Efficacy in Advanced Breast Cancer

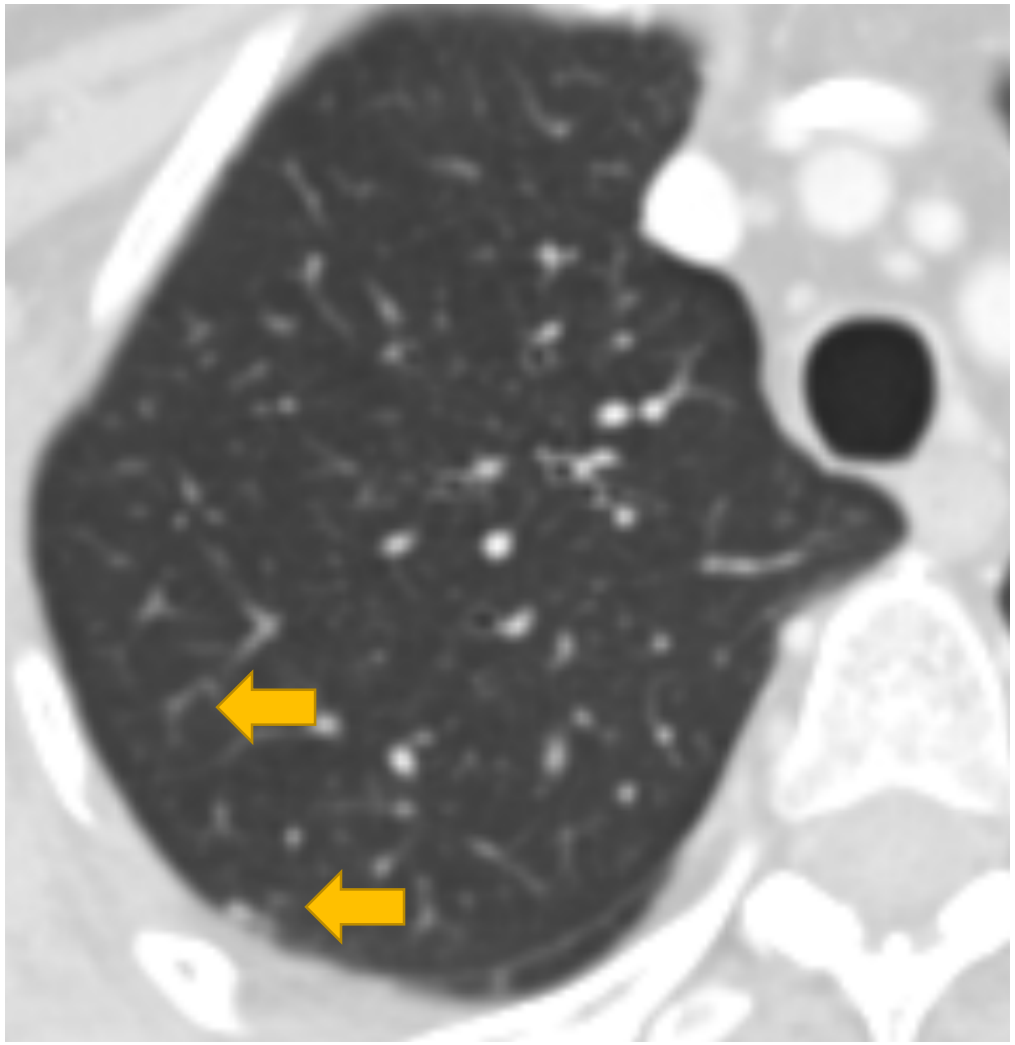
## *Patient 01-002 Lung Lesions (failed 7 prior chemo regimens) (2017)*

BriaCell

**Pre-Treatment**



**Post-Treatment**

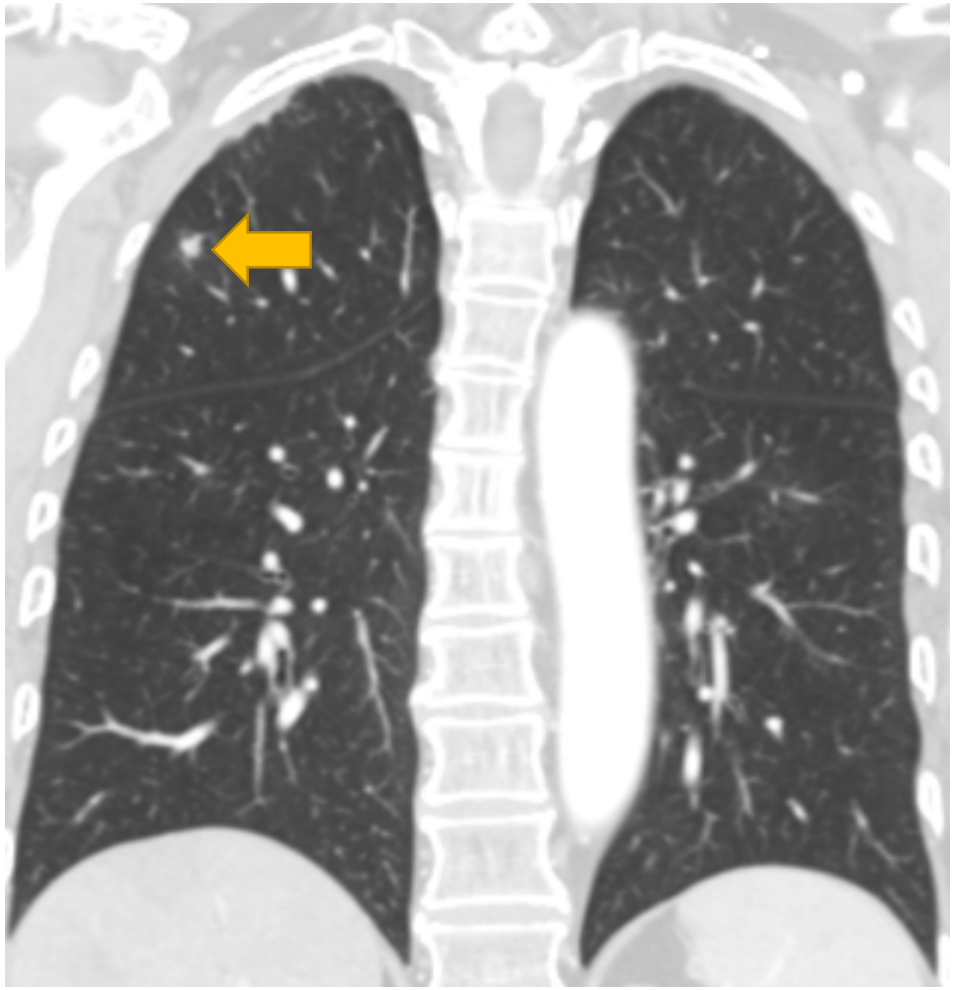


# Bria-IMT™: Remarkable Efficacy in Advanced Breast Cancer

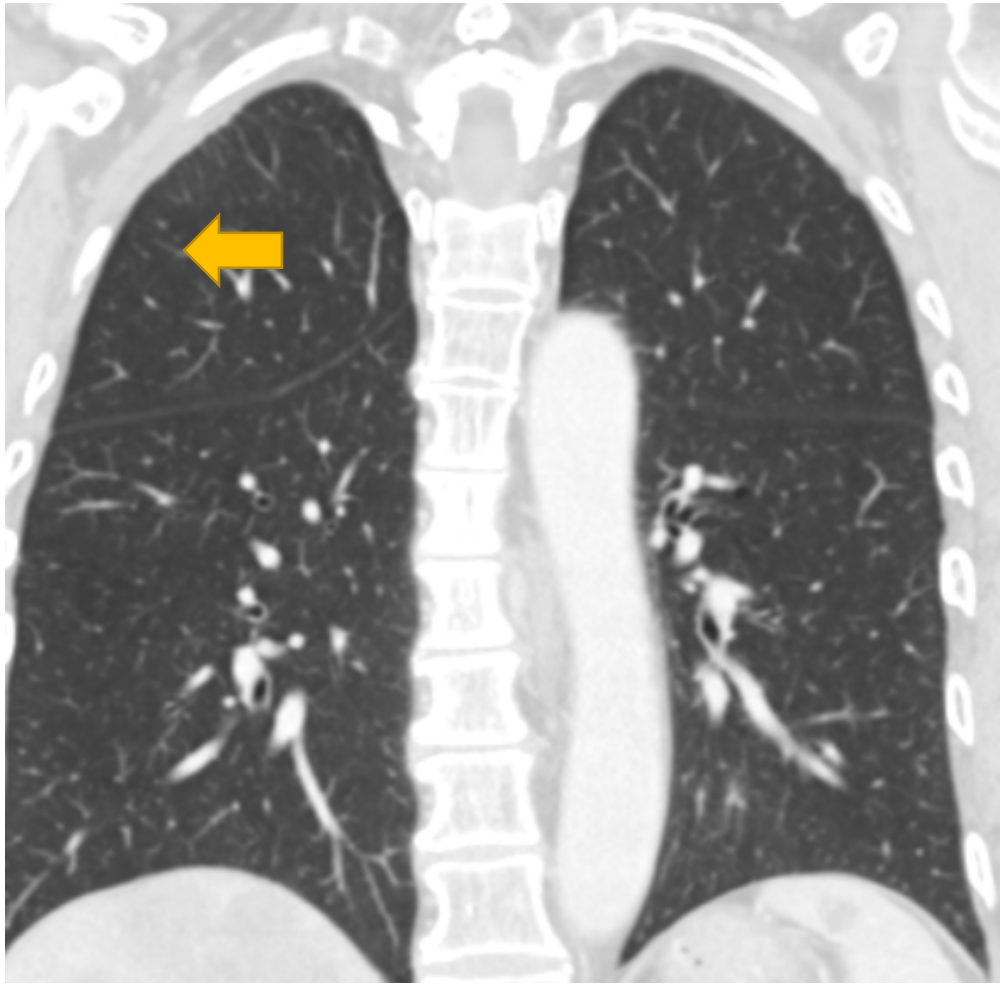
## *Patient 01-002 Lung Lesions (failed 7 prior chemo regimens) (2017)*

BriaCell

**Pre-Treatment**



**Post-Treatment**

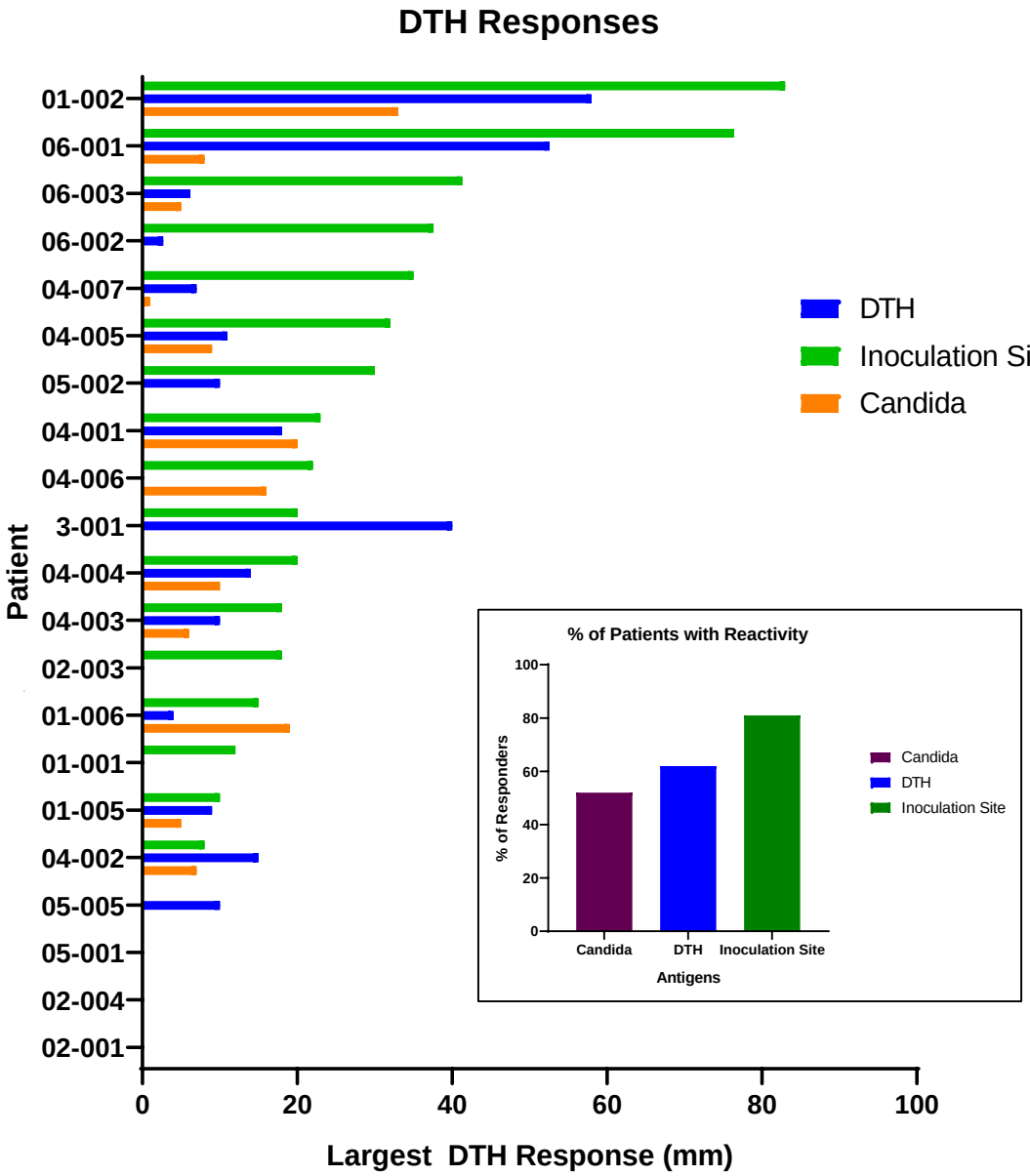


BriaCell

# *Bria-IMT™ Biological Activity Markers*

# Bria-IMT™

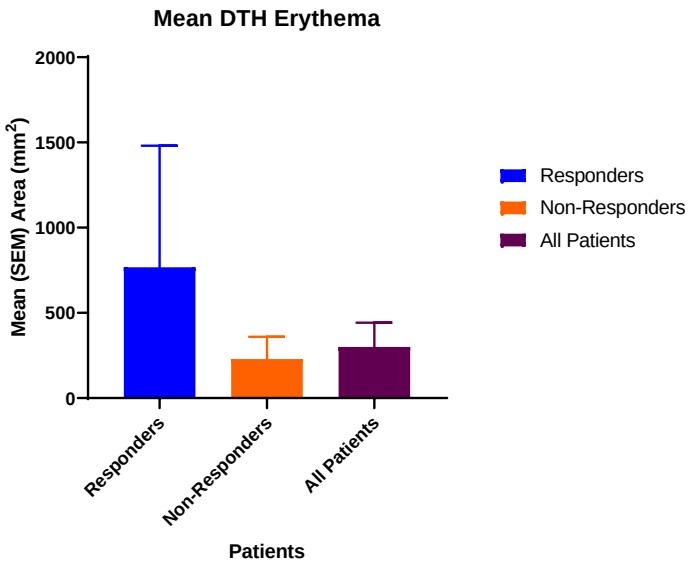
## *Delayed Type Hypersensitivity to Bria-IMT™*

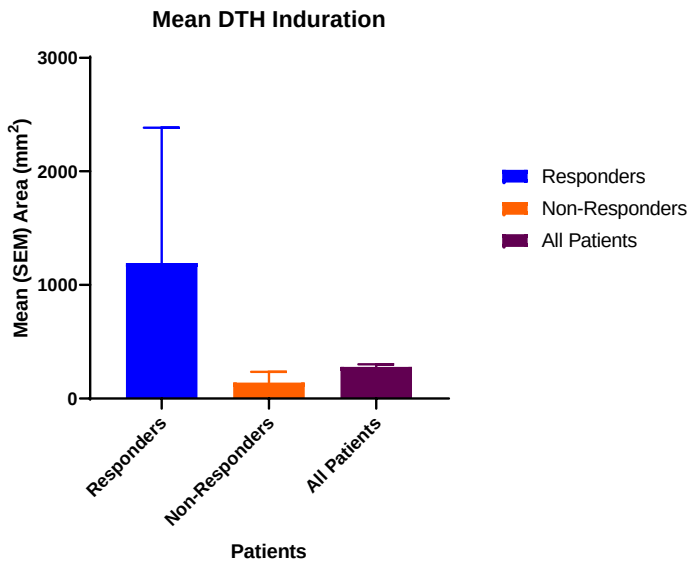


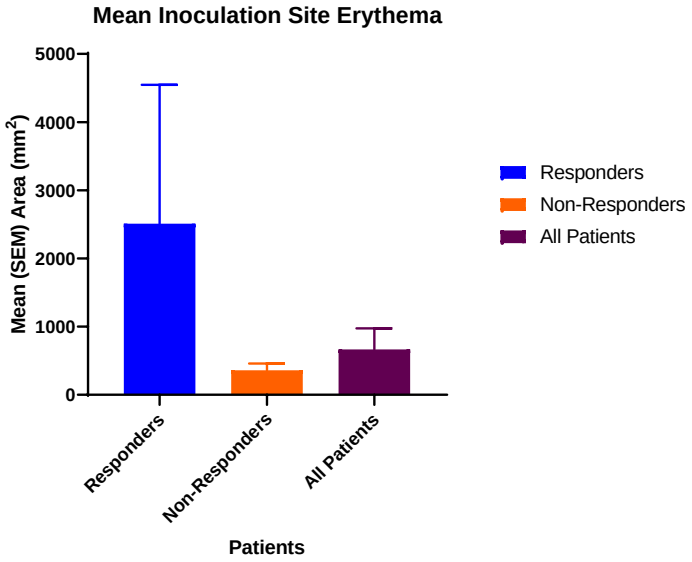

**Rationale:** Delayed-type hypersensitivity (DTH) is a good marker of cellular (T cell) immune responses. Briefly, for each cycle, Bria-IMT™ was injected intra-dermally with 5 x $10^6$ irradiated cells in each of 4 sites in the upper back and thighs. 2 ±1 days later, these sites were assessed for erythema and induration. The largest response (size) for each patient is shown. The insert notes the % of patients able to mount a DTH response (erythema or induration ≥5 mm to the antigen)

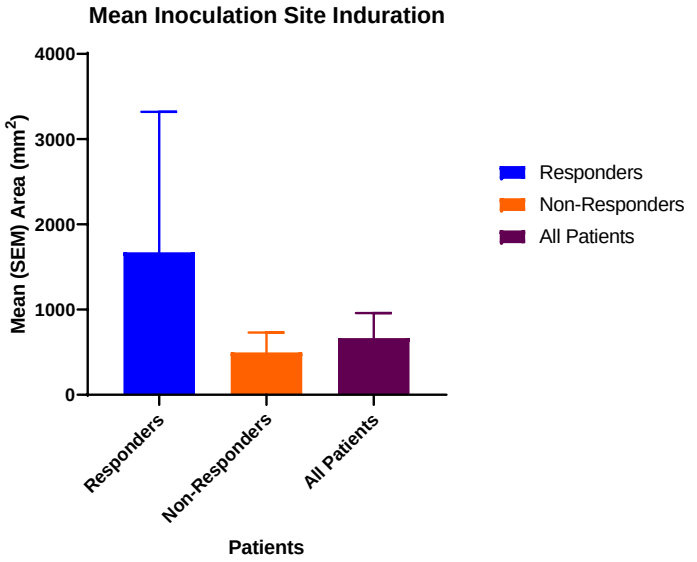
**Conclusion: Many patients developed DTH to Bria-IMT™, some despite anergy to test antigens (Candida), indicating potent immunogenicity of Bria-IMT™. The most robust responses were seen in patients with objective tumor regression.**

# Delayed Type Hypersensitivity to Bria-IMT™ Correlation with Clinical Response



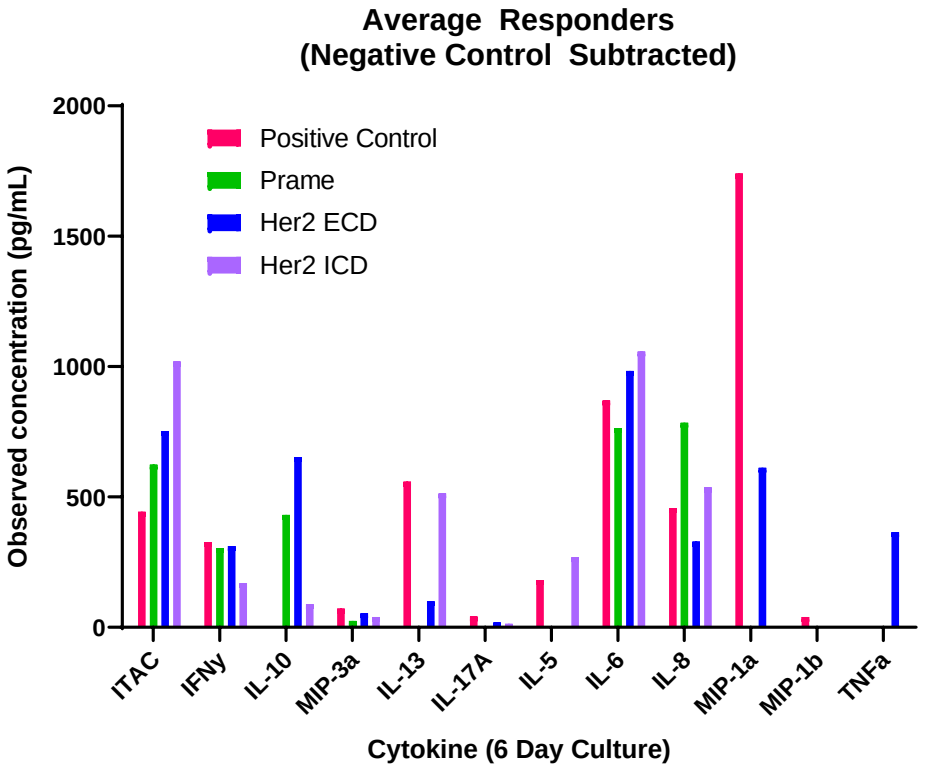



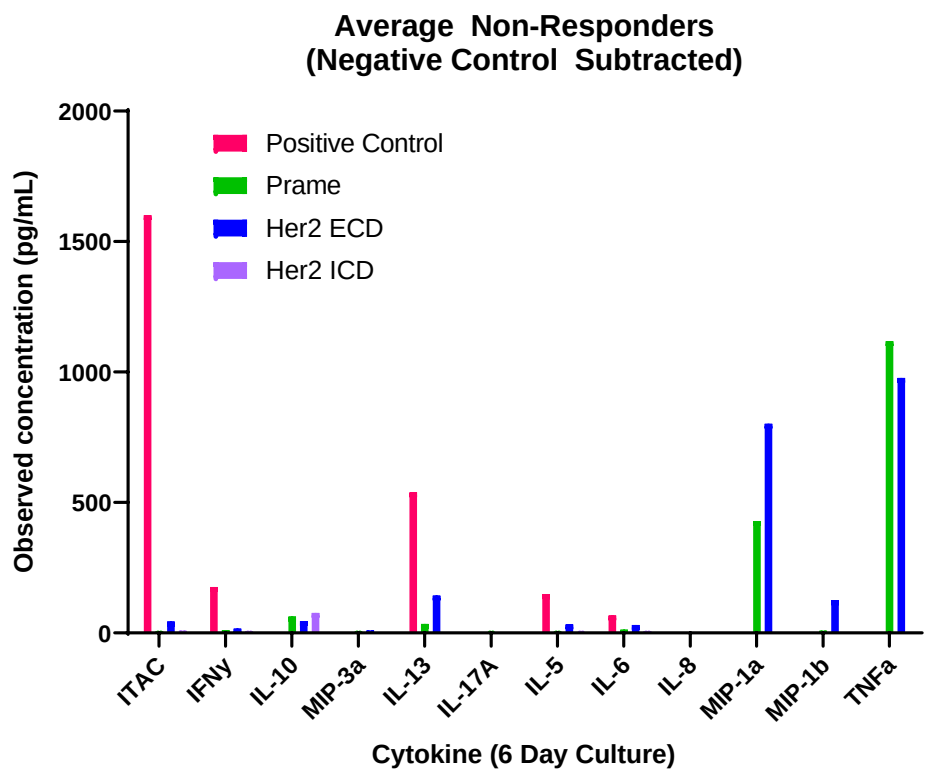




**Rationale:** Generating an Immune Response to Bria-IMT™ is likely to be necessary for anti-tumor activity. This is what we see with Bria-IMT™, and the immune response in responders appears higher than that in non-responders as measured by DTH.

**Conclusion: Patients with tumor shrinkage have more erythema and induration on average compared with non-responders.**

# Bria-IMT™ Treatment Enhances Immune Responsiveness



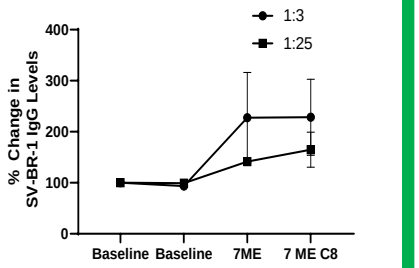



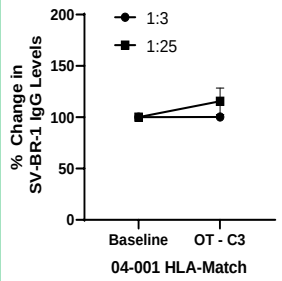

**T cell responses to PRAME (a cancer testis antigen) and HER2/neu peptides (ECD = extracellular domain; ICD = intracellular domain) in patients with and without tumor regression**

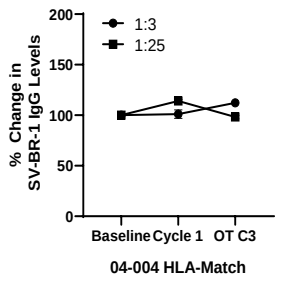
**Working Model -** Tumor regression requires: HLA matching to Bria-IMT™ and the ability to mount a cellular immune response (DTH and *ex vivo* T cell activation)

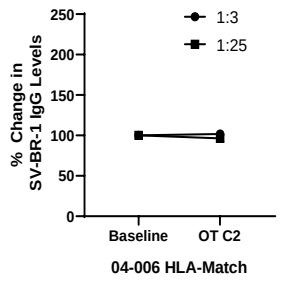
**Conclusion: Responders with tumor regression have a higher propensity to develop T cell responses to the cancer-related antigens PRAME and HER2/neu.**

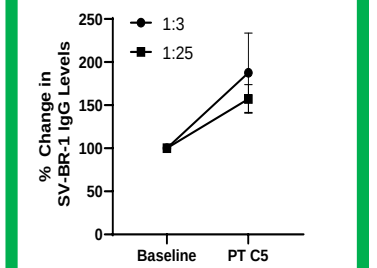
# Anti-SV-BR-1 Antibodies in Patients

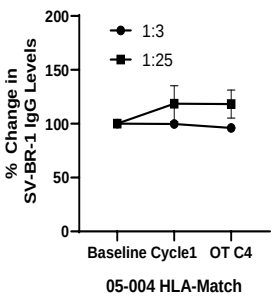


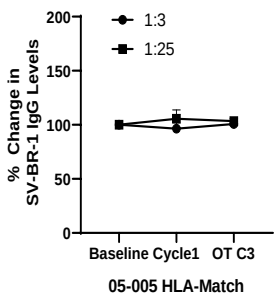



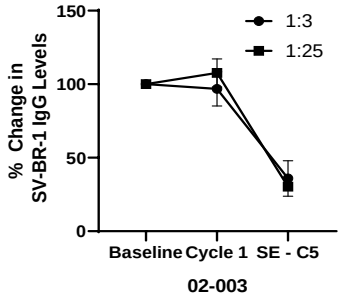



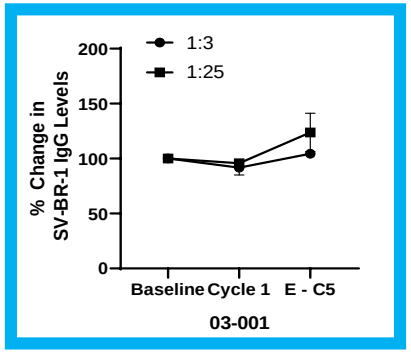



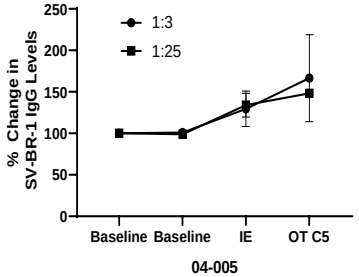



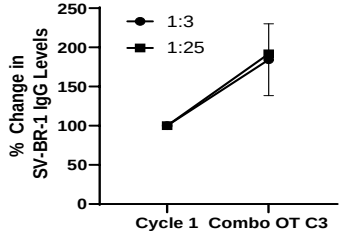

**HLA Match**

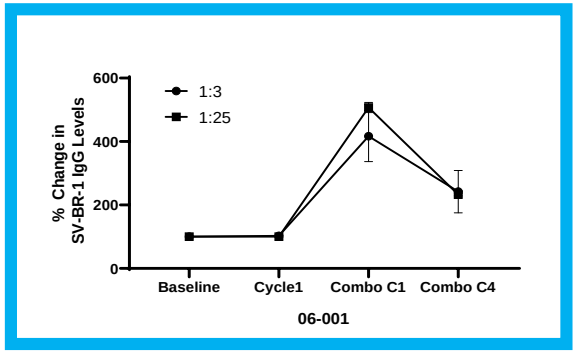
**HLA Mis-Match**




**Anti-SV-BR-1 antibody titers in patient sera.** SV-BR-1 cells were incubated with 1:3 or 1:25 diluted patient sera then stained with fluorescently labeled anti-human IgG and analyzed by flow cytometry. Anti-SV-BR-1 antibodies in all patient sera samples segregated either as HLA matched (≥ 1 allele) or non-HLA matched. Baseline: before treatment with first dose of Bria-IMT™.

**Conclusions: IgG responses to SV-BR-1 are elicited by Bria-IMT™ treatment.**
**The best responses are seen in those with tumor shrinkage.**

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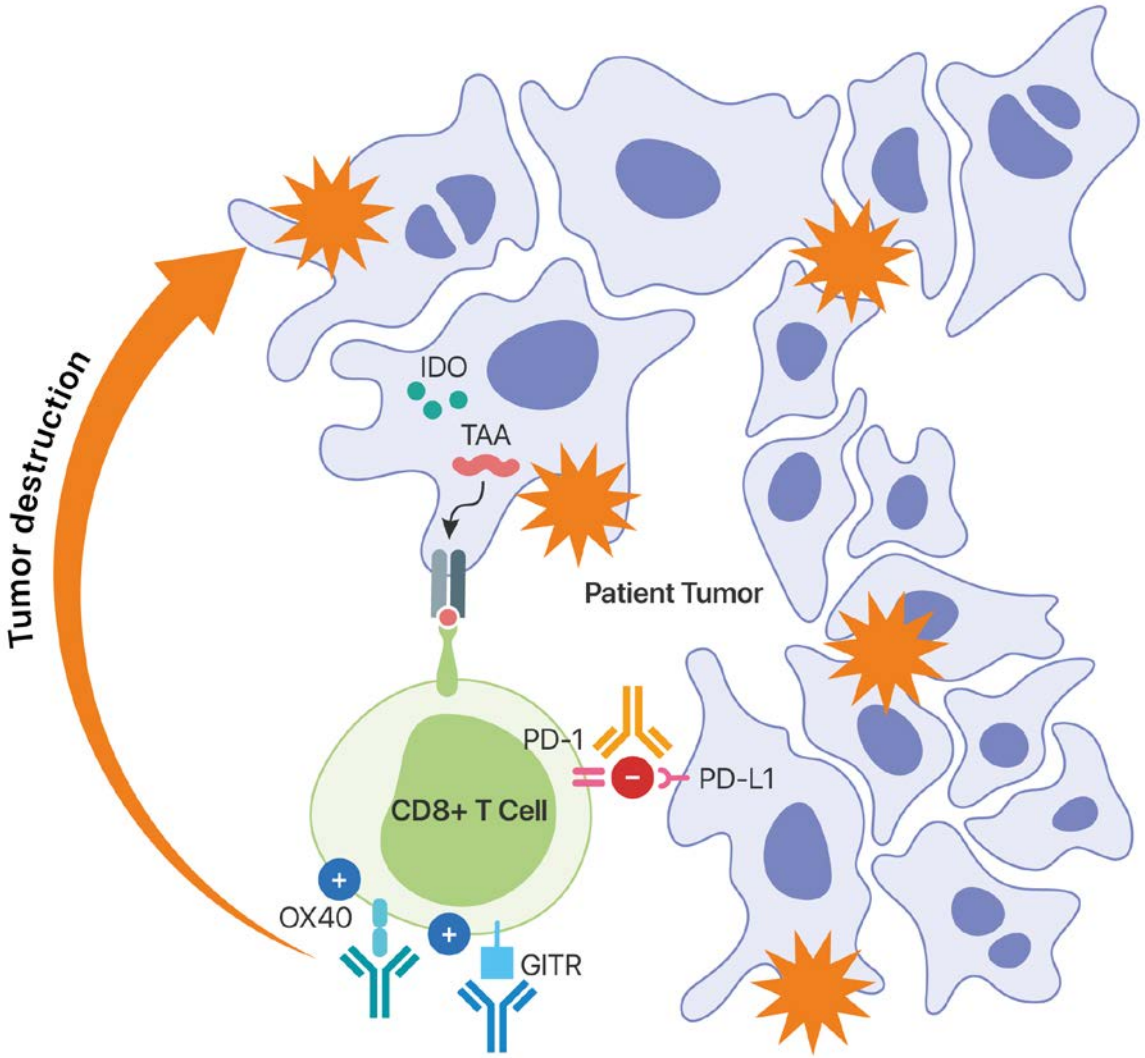
# *Bria-IMT™ Combination Therapy*

# Bria-IMT™ & Bria-OTS™
## *Immunotherapy Combination Considerations*

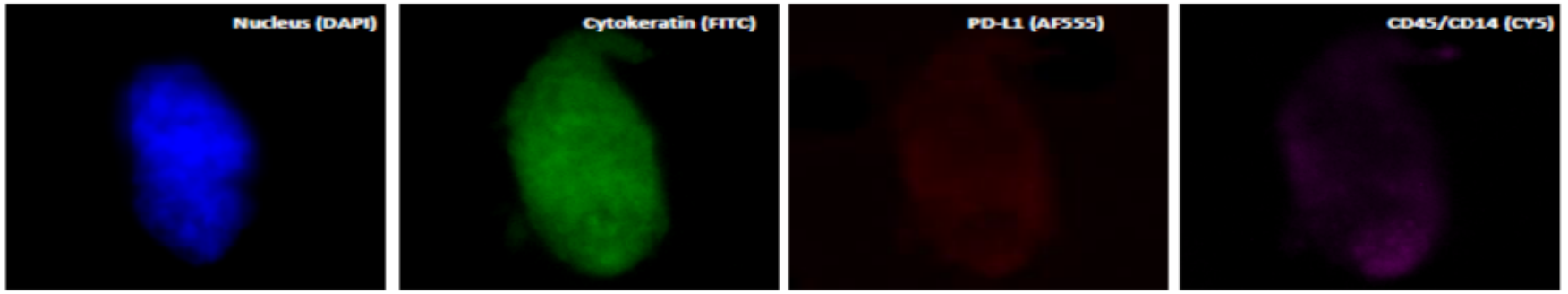
- Bria-IMT™ and Bria-OTS™ should **synergize with existing approved immunotherapies** as well as those still under development
- This includes immune checkpoint inhibitors such as antibodies to PD-1, CTLA-4, GITR and CD73 and IDO inhibitors which **eliminate tumor immunosuppression**
- In addition, **immunostimulatory antibodies** to molecules such as OX40 should **enhance responses** to Bria-IMT™ and Bria-OTS™

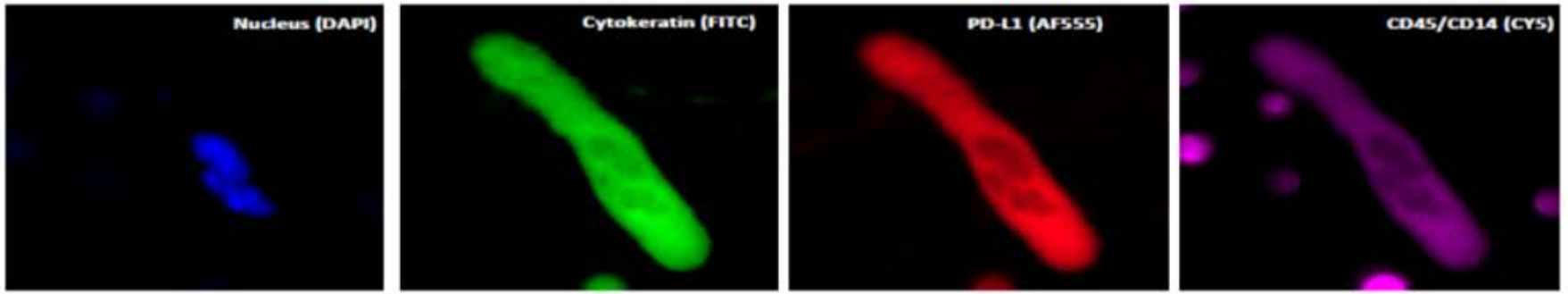


# CTC & CAML PD-L1 expression

- To date, >90% of patients analyzed have had PD-L1 expression on their CAMLs and CTCs
- In Patient 01-002 (monotherapy study) CTCs and CAMLs were analyzed for PD-L1 Expression.
- Mean levels increased from 97 ±7 to 437 ±72 (SEM). Representative Photos are Shown Below

Pre-Treatment PD-L1 Expression Level 105




Post-Treatment PD-L1 Expression Level 815

**Conclusion: Increases in PD-L1 expression in CAMLs are seen during therapy indicating potential synergy with PD-1/PD-L1 inhibition.**

# Anti-PD-1 & Anti-PD-L1 Ineffective as Monotherapy in Breast Cancer

- Brahmer 2012: treated 4 patients with breast cancer (sub-type not specified) – 0 response rate

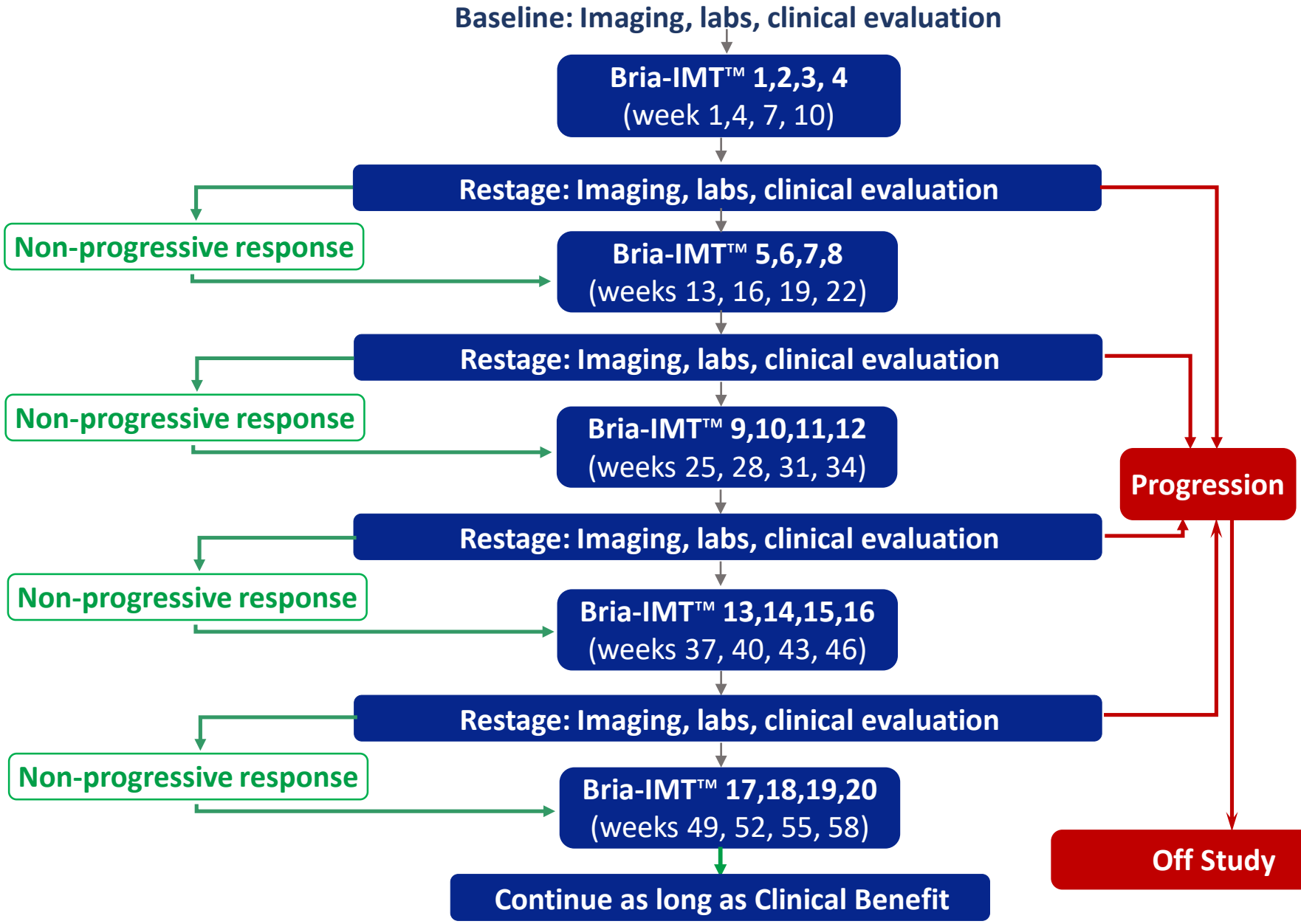
- Nanda 2016: treated 32 patients with triple negative breast cancer (TNBC) with KEYTRUDA®, data on 27, all PD-L1+
  - 18.50% response rate
  - Median time to response 17.9 weeks (range, 7.3 to 32.4 weeks)

- Dirix 2017: treated 168 patients with avelumab (Bavencio)
  - **Response rate of 3%**
  - 5.2% response rate in Triple Negative Breast Cancer (3 of 58 patients)
  - **Response Rate of 1.84%** in other types of breast cancer (2 of 110 patients)

- Patient 06-001 was not TNBC, so the chances this was due to KEYTRUDA® is almost nil

**PD-1 and PD-L1 Inhibitors are Ineffective as Monotherapy in Breast Cancer →**
**Responses seen to Bria-IMT™ Combined With KEYTRUDA® unlikely due to KEYTRUDA® alone**

# Bria-IMT™ Phase I/IIa Combination Therapy Trial




**Currently Recruiting:**

- Treatment in combination with Keytruda® (Merck & Co., Inc.) for PD-L1(+) or PD-L2(+) tumors q3wks x up to 24 cycles, then Bria-IMT™ alone q3wks
- Imaging every 6 -12 weeks
- **First 6 patients have enrolled and safety and tolerability is excellent**
- **Initial efficacy data shows evidence of additive of synergistic activity**

# Bria-IMT™ with Pembrolizumab

- **Eleven patients recruited**
  - **Four rolled over from the "Monotherapy" study**
  - **Seven entered the combination study directly**
- All 11 patients were very heavily pre-treated with a median of 5 prior systemic therapy regimens (such as chemotherapy) prior to enrollment in BriaCell's Combination Study
- Many patients had very weak immune systems as evidenced by meager or absent DTH responses

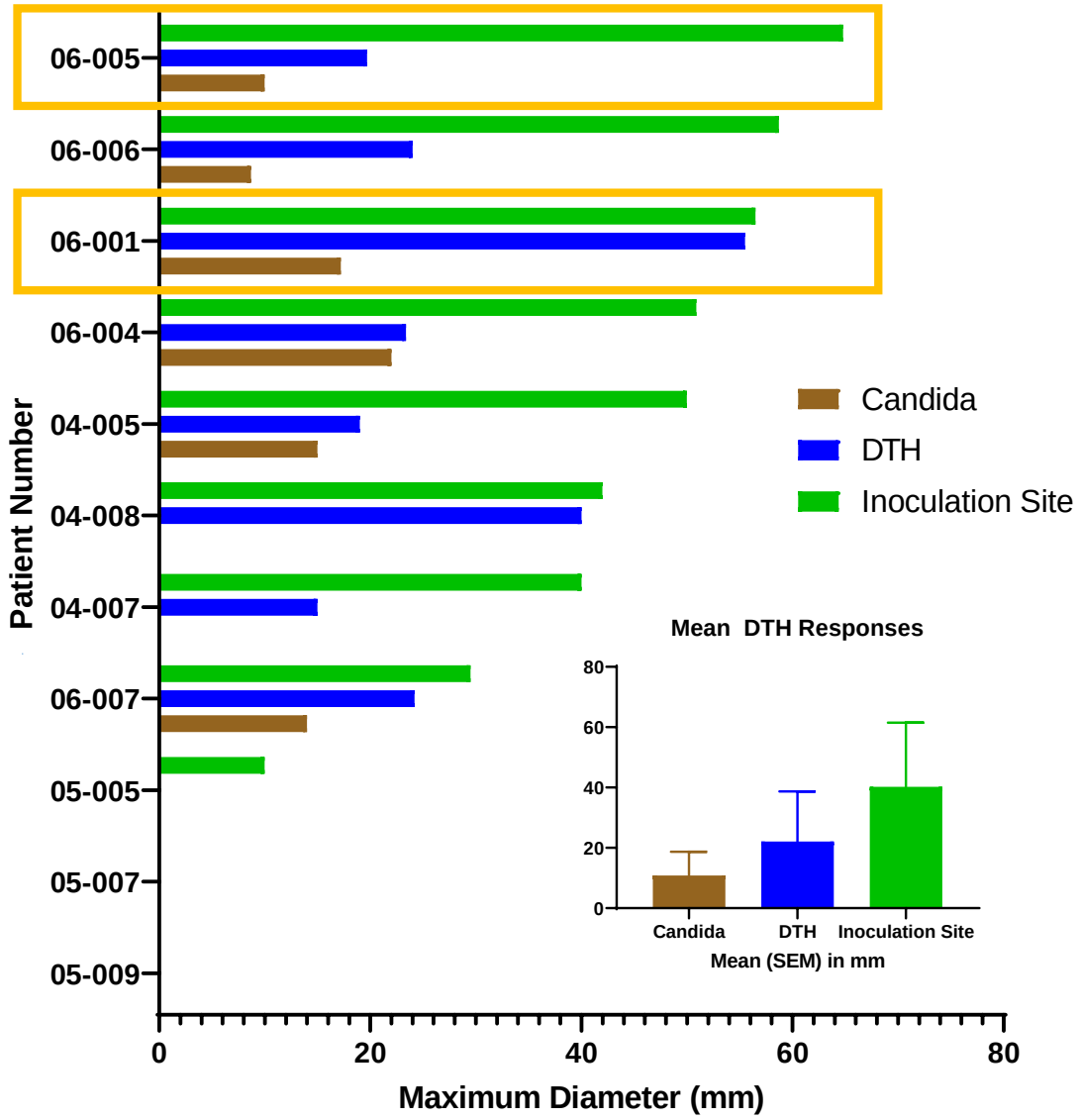
# Bria-IMT™

## *Study BRI-ROL-001 – KEYTRUDA® Combination Patient Characteristics*

| Patient Characteristics (11 total) | No HLA Allele Matches (n=4) | 1+ HLA Allele Matches (n=7) | 2+ HLA Allele Matches (n=5) | All Patients (n=11) |
|---|---|---|---|---|
| Age | 61 ± 11 | 62 ± 9 | 62 ± 12 | 62 ± 9 |
| Median Prior Systemic Regimens | 6 (range 2-10) | 4 (range 1-14) | 4 (range 1-14) | 4 (range 1-14) |
| % ER+ or PR + | 75% | 67% | 50% | 70% |
| % Her2/neu + | 50% | 50% | 50% | 50% |
| % Triple Negative | 0% | 0% | 0% | 0% |
| Grade I/II | 1 | 2 | 1 | 3 |
| Grade III | 3 | 4 | 3 | |

**The patients are heavily pre-treated and generally similar regardless of HLA matching with Bria-IMT™**

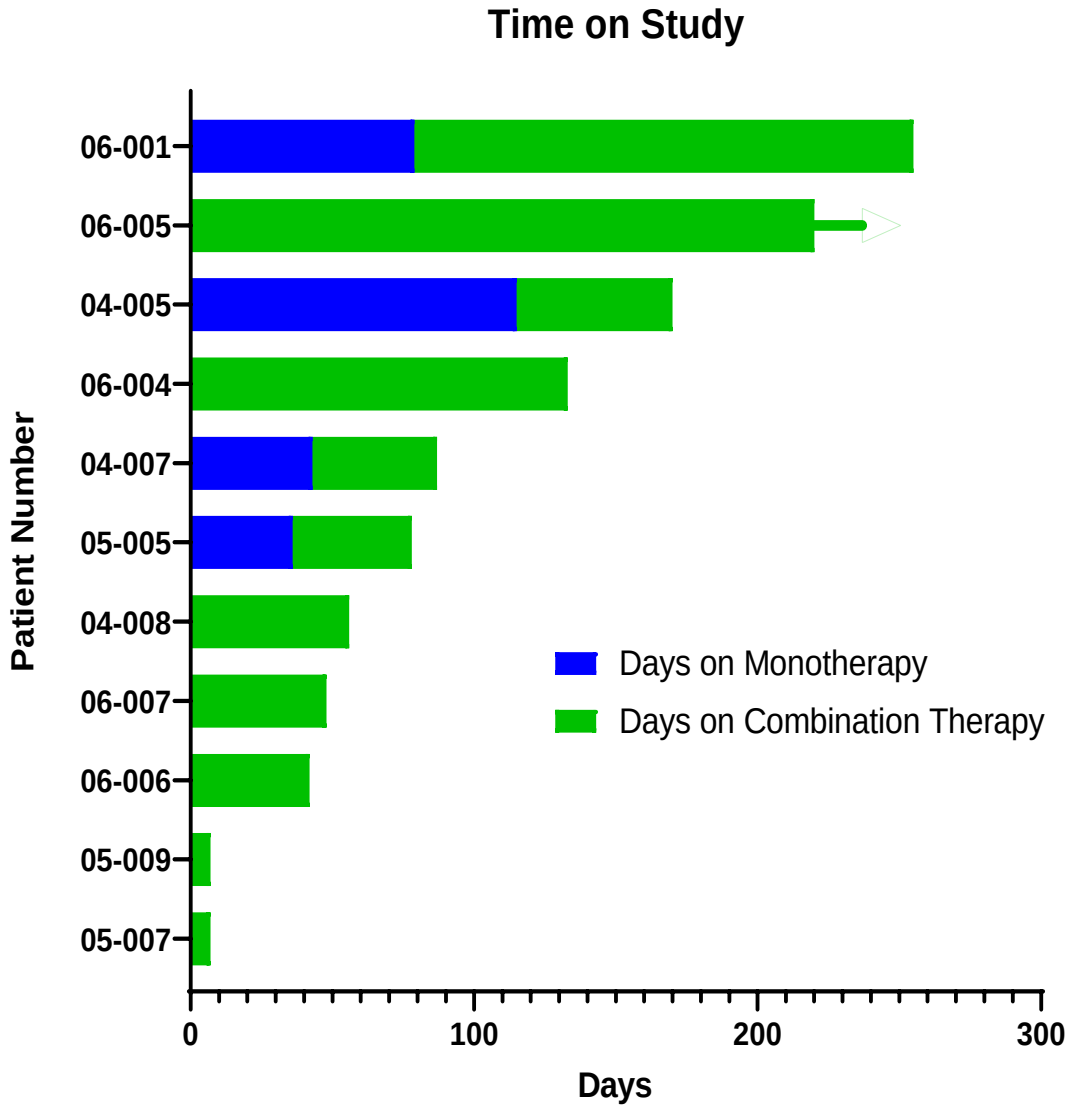
# Delayed Type Hypersensitivity to Bria-IMT™ + KEYTRUDA®




**Rationale:** Delayed-type hypersensitivity (DTH) is a good marker of cellular (T cell) immune responses. Candida (positive control) or $1x10^6$ irradiated Bria-IMT™ cells were injected intra-dermally in the forearm (DTH) and $5x10^6$ in 4 sites in the upper back and thighs (Inoculation Site). 2±1 days later, these sites were assessed for erythema and induration. The largest response (diameter of erythema or induration) for each patient is shown. The insert notes the mean DTH responses seen.

**Conclusion: Many patients developed DTH to Bria-IMT™, some despite anergy to test antigens (Candida), indicating potent immunogenicity of Bria-IMT™. The most robust responses were seen in patients with objective tumor regression.**

# Bria-IMT™ KEYTRUDA® Phase IIa Combination Time on Study




**Blue** indicates roll-over subjects time on Study 1
**Green** indicates time on combination therapy
Arrows → indicate ongoing in the study

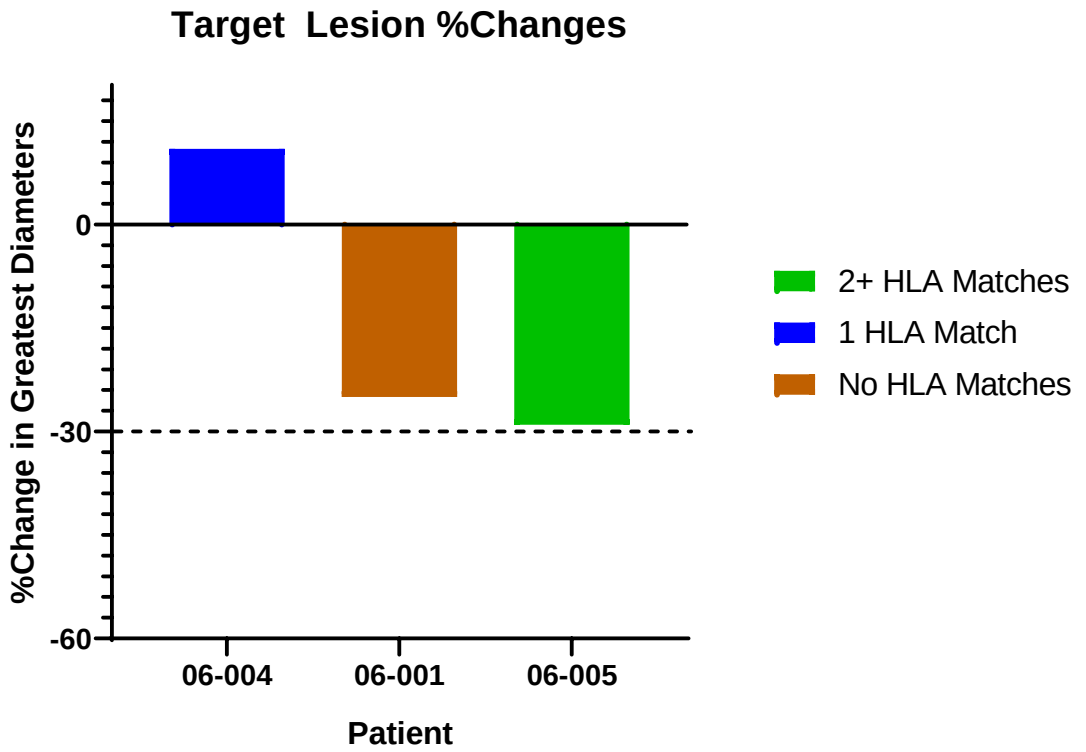
**Results:** To date treatment has been generally safe and well tolerated with no serious adverse events (AEs) or withdrawals from AEs.

**Conclusion: The combination of the Bria-IMT™ regimen with pembrolizumab has been well tolerated.**

# Bria-IMT™ + KEYTRUDA® Tumor Responses and Serum Markers

Tumor Markers in Patients with Follow-up Information

| | 06-001 | 06-004 | 06-005 |
|---|---|---|---|
| Baseline CEA | 167.8 | 0.2 | 139.2 |
| Initial Eval CEA | 48.15 (-68%) | 1.55 | 15.21 (-89%) |
| Baseline 15-3 | 196.5 | 93.4 | 1886 |
| Initial Eval 15-3 | 114.9 (-42%) | 114.4 | 533.7 (-72%) |




- Patient 06-001: ER+/HER2-, Hepatic Metastases, Robust DTH, no HLA Matches with Bria-IMT™
- Patient 06-005: ER+/HER2-, Adrenal and Dural Metastases, Robust DTH, two HLA matches with Bria-IMT™

**The Bria-IMT™ Regimen Combined With KEYTRUDA®: Patients with Robust DTH (06-001 and 06-005) had a Marked Reduction in Tumor Markers and Tumor Size, Suggesting that a Robust Immune Response Correlates with Tumor Regression even Without HLA Matching**

# Bria-IMT™ + KEYTRUDA® Characteristics of Responders

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- **Patient 06-001**
  - 73-year-old woman
  - Ductal adenocarcinoma diagnosed April 2010
  - Stage IV Tumor grade II – Moderate
  - ER+, PR-, HER2-
  - 7 prior chemotherapy regimens with 9 agents + Avastin
  - Did not match at any HLA loci
  - Entered the monotherapy study with 4 liver metastases
  - One of the best immune responders (DTH & Ab)
  - Stable disease on monotherapy (slight increase in tumor sizes)
  - **Reduction in all 4 liver metastases on combination therapy**

- **Patient 06-005**
  - 70-year-old woman
  - Ductal adenocarcinoma diagnosed Dec 2009
  - Stage IV Tumor grade II – Moderate
  - ER+, PR-, HER2 1+
  - 12 prior regimens with 16 agents (13 chemo 3 hormonal)
  - Matched at 2 HLA loci – HLA-C and HLA-DRB3
  - Entered the monotherapy study with adrenal, bone and dural metastases
  - One of the best immune responders (DTH, Ab pending)
  - **Reduction in adrenal (target) and dural metastases**

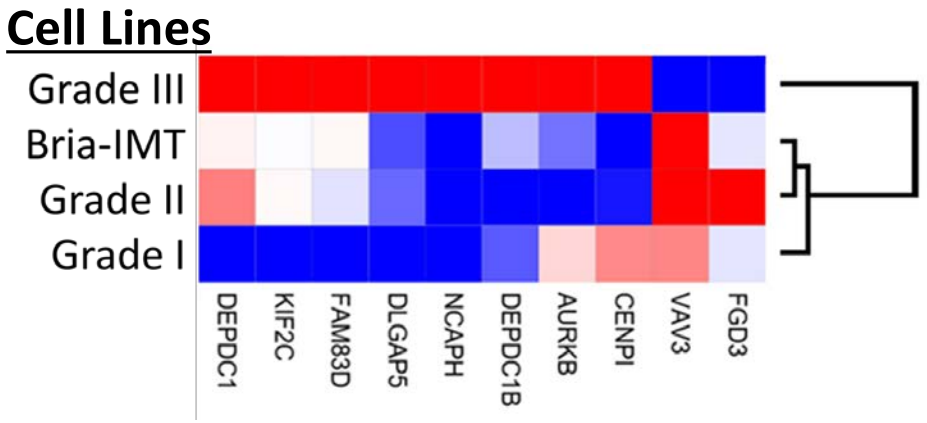
**The Bria-IMT™ regimen in combination with checkpoint inhibition can be effective even in patients who have failed multiple prior lines of therapy**

# Bria-IMT™ in Grade I/II Tumors

## Breast Cancer by Stage of Differentiation

- Breast cancer is classified based on histology into Grade I, II, or III. Also the designations “Luminal”, “Basal A” and “Basal B” (Neve et al., 2006), are used, with Luminal A representing well differentiated (grade I), Basal A moderately differentiated (grade II) and Basal B poorly differentiated (grade III) breast cancer
- Bria-IMT™ is derived from a grade II (moderately differentiated) breast cancer.
- Yao et al. (2005) identified a 9-gene signature discriminating poorly (grade III) from moderately (grade II) differentiated tumors.
- The genes expressed by Bria-IMT™ match best with grade I/II Breast Cancer Cell Lines
  - Cell lines classified as Luminal, Basal A & Basal B, which are believed to correspond best with grade I, II & III, respectively
- Approximately 40% of recurrent breast cancers are grade I/II (~33% grade II and ~7% grade I).

**Hierarchical clustering of breast cancer cell lines. Bria-IMT™ cells cluster most closely to MDA-MB-468 (grade II).** The MDA-MB-468 cell line represents Basal A (moderately differentiated = grade II), MCF-7 luminal (well differentiated = grade I), and MDA-MB-231 Basal B (poorly differentiated grade III) breast cancer cell types (Neve et al., 2006). Therefore, based on its molecular similarity with MDA-MB-468, **Bria-IMT™ is considered a Basal A and as such a moderately differentiated (grade II) cell line.**




**Bria-IMT™ most closely matches with a Basal A (moderately differentiated = grade II) cell line. This is closely related to a Luminal (well differentiated = grade I) cell line.**


Neve RM, Chin K, Fridlyand J, et al. A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. *Cancer Cell*. 2006;10(6):515-527. doi:10.1016/j.ccr.2006.10.008
Yao F, Zhang C, Du W, Liu C, Xu Y. Identification of gene-expression signatures and protein markers for breast cancer grading and staging. *PLoS One*. 2015;10(9). doi:10.1371/journal.pone.0138213

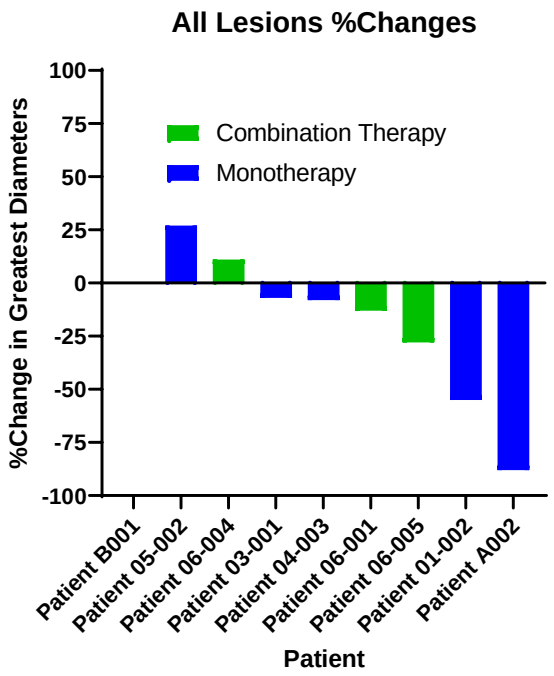
# Bria-IMT™ in Grade I/II Tumors

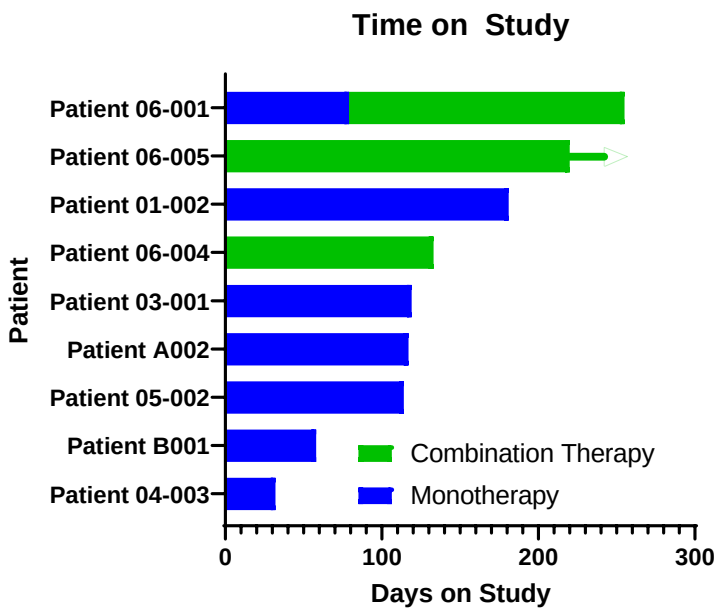
## Breast Cancer Grade Correlates with Response

- The clinical benefit rate in our monotherapy studies for Grade I/II patients with immune responses was 5/7 (71%)
  - Patients very heavily pre-treated, median of 7 prior regimens
- In our combination therapy study with checkpoint inhibitors, all 3 patients with Grade I/II tumors had clinical benefit (100%)
  - All had been very heavily pre-treated with 14-15 prior regimens

Tumor shrinkage seen in most patients with Grade I/II Tumors.

Patients with the greatest tumor reductions had double HLA matches with Bria-IMT™




Extensive time on study especially with combination therapy suggesting clinical benefit

We believe these findings identify a patient population with higher clinical benefit rates

# Incyte Corporation – Clinical Trial Collaboration

## BriaCell & Incyte Collaboration and Supply Agreement

***Non-exclusive clinical trial collaboration to evaluate the effects of combinations***

- The clinical study will focus on (but not limited to) BriaCell's lead candidate, Bria-IMT™, in combination with Incyte's selected compounds for advanced breast cancer.
- Incyte to provide compounds from its development portfolio, including an anti-PD-1 monoclonal antibody (*INCMGA0012*), and an IDO1 inhibitor (*epacadostat*), for use in combination studies with BriaCell's lead candidate, Bria-IMT™.
- **Incyte** is a global biopharmaceutical company focused on discovering and developing novel therapeutics in oncology and inflammation & autoimmunity.
- Incyte has a deep and rich pipeline in immuno-oncology with numerous molecular targets including PD-1, IDO, GITR, OX40, TIM-3, LAG-3, ARG, AXL/MER and PD-L1xCD137

**BriaCell hypothesizes that checkpoint inhibitors, of which Incyte has several candidates, may significantly amplify the tumor-reducing effects of Bria-IMT™.**

# Phase I/IIa Study of Bria-IMT™ with Incyte Compounds

- BriaCell has Initiated the Clinical Study of Bria-IMT™ in combination with Incyte's INCMGA00012 and epacadostat in advanced breast cancer patients who had failed at least two prior treatments.
- Open-label, multi-center study to evaluate the safety and efficacy of the combination in advanced breast cancer patients.
- In the initial stage, BriaCell expects to enroll up to 12 patients with advanced breast cancer.
- The primary endpoint is safety and overall response rate (ORR) and secondary endpoints include duration of response, progression free survival (PFS) and overall survival (OS).
- Additional analysis will include evaluation of potential predictive biomarkers including HLA.
- BriaCell expects to report preliminary efficacy and biomarker findings on up to 30 patients in 2020.
- Initial data on the first patient who transitioned from combination therapy with KEYTRUDA® to the combination with INCMGA00012 shows continued stable disease and **complete disappearance of an orbital tumor** (behind the eye) which had been causing proptosis. She remains on study after 36 weeks of combination therapy. Recruitment is ongoing.

**BriaCell hypothesizes that Incyte Drugs may significantly amplify the tumor-reducing effects of Bria-IMT™.**

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# *Bria-OTS™: Off-The-Shelf Personalized Immunotherapy*

# Bria-OTS™ & BriaDX™
## Personalized *Off-the-Shelf Immunotherapy*

- Bria-OTS™ cell lines are being developed to express both GM-CSF and interferon-α PLUS patient-specific matching HLA types
- Cell lines will be pre-manufactured which express HLA alleles covering/matching with >99% of the overall advanced breast cancer population (double matches in ~90% of the population)
- Using the BriaDX™ companion diagnostic, the off-the-shelf alleles will be matched and selected for each patient prior to treatment
- **RESULT:** Therefore, each patient will have a personalized mix and match of off-the-shelf alleles

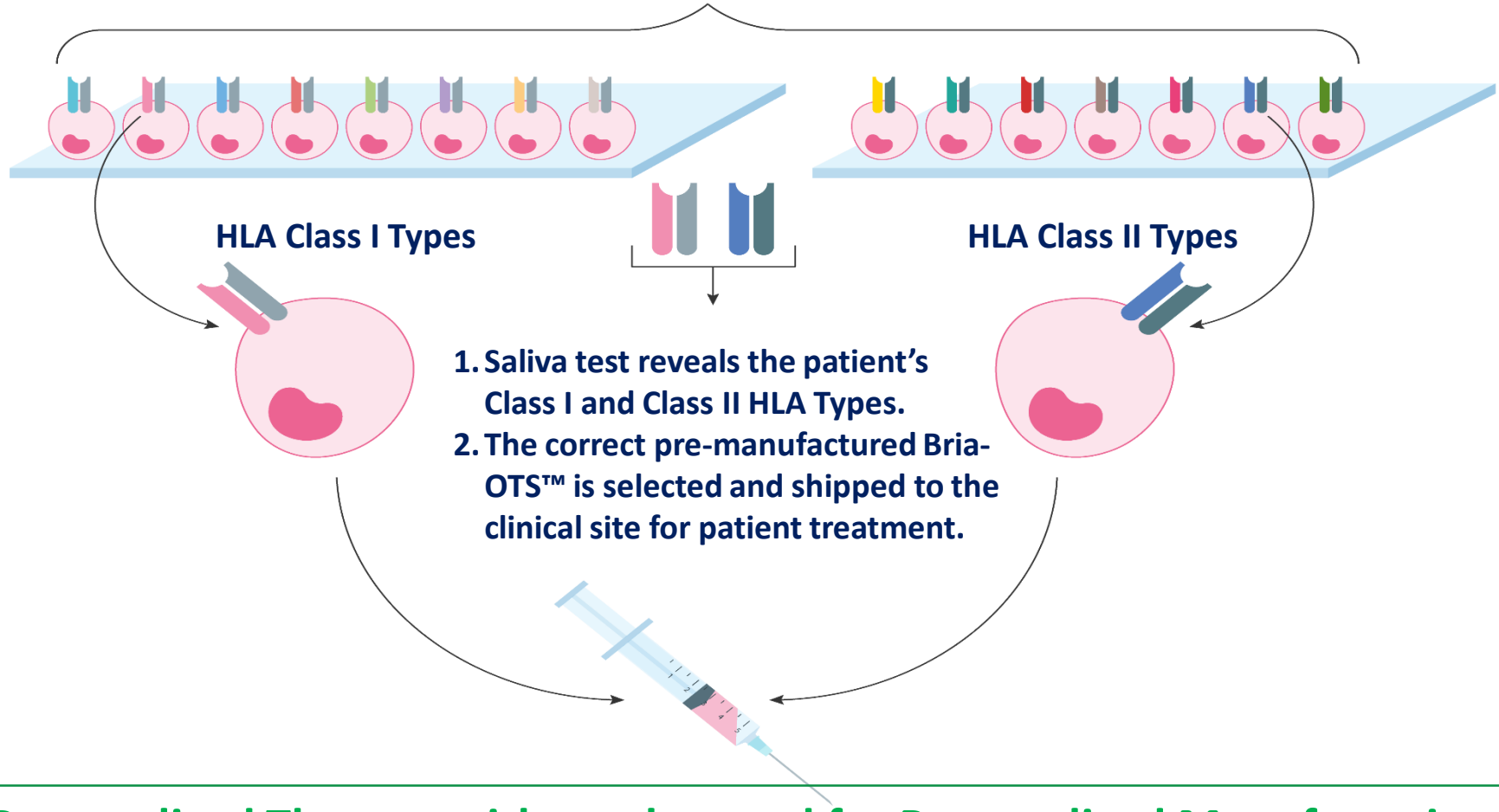
➢ **Personalized therapy without the need for personalized manufacturing**

**Personalized Off-the-Shelf Immunotherapy is cost-effective, saves manufacturing time, and readily available because it is premade.**

# Bria-OTS™ – Off-The-Shelf Personalized Approach

## 15 Unique HLA Types for Tailored Immunotherapies

***A simple test determines the correct "off-the-shelf" immunotherapy to select***




**Personalized Therapy without the need for Personalized Manufacturing**

# Scientific Findings and Clinical Plans

**Bria-IMT™ and Bria-OTS™ (Personalized immunotherapy without the need for personalized manufacturing):**

- Manufactured from Breast cancer cell lines
- Show immune (dendritic) cell characteristics, expresses multiple breast cancer associated antigens, and immune stimulating factors including Class II HLA molecules
- **Directly activate CD4+ T cells (sets them apart from other immunotherapies)**

**Clinical Data of Phase I/IIa Monotherapy Study of Bria-IMT™ in advanced breast cancer: Several patients have responded with marked tumor shrinkage or other evidence of anti-tumor activity. No serious side effects.**

- Bria-IMT™ generates both cellular and humoral immune responses
- Patients with tumor shrinkage matched Bria-IMT™ at least at one HLA locus with high response rates in patients with grade I/II tumors
- Circulating tumor cells or cancer-associated cells express PD-L1 in >90% of patients analyzed suggesting combination with an immune check point inhibitor such as KEYTRUDA® or Incyte's drugs

**Clinical Data of Phase I/IIa Combination Study of Bria-IMT™ with KEYTRUDA® in advanced breast cancer:**

- **Combination study with KEYTRUDA® shows evidence of additive or synergistic activity**
- **Clinical benefit in 100% of patients with grade I/II tumors**

**Phase I/IIa Combination Study of Bria-IMT™ with Incyte drugs in advanced breast cancer Initiated:**

- Collaboration with Incyte and their checkpoint inhibitors underway with initial positive data in the first patient

**Planning to Initiate Phase I/IIa of Bria-OTS™ in in advanced breast cancer:**

- Bria-OTS™ cell lines express multiple HLA alleles to match >99% of the breast cancer population

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*The Future of Cancer Immunotherapy*

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# Appendix

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# *Small Molecule Program (PKCδ Inhibitor)*

# In the Pipeline: Protein Kinase C delta (PKCδ) Inhibitors

## Growth Opportunity: Early-Stage Preclinical Program

- **30% of all human malignancies** display activating RAS mutations
  - Another 60% showing over-activity of Ras-signaling pathways
- Ras has been termed “undruggable” (no one has been able to make a Ras inhibitor drug)
- BriaCell’s novel, proprietary **PKCδ inhibitors** have shown activity against multiple **RAS transformed tumors**
  - Lung cancer, Melanoma, Breast cancer, Neuroendocrine cancer, Pancreatic cancer, Colorectal cancer
- This target has an **attractive safety profile** based on in vivo studies and knock out mouse studies
- PKCδ inhibitors should qualify for an **accelerated clinical development plan and regulatory pathway**
- Could be in clinic within **24 months.**

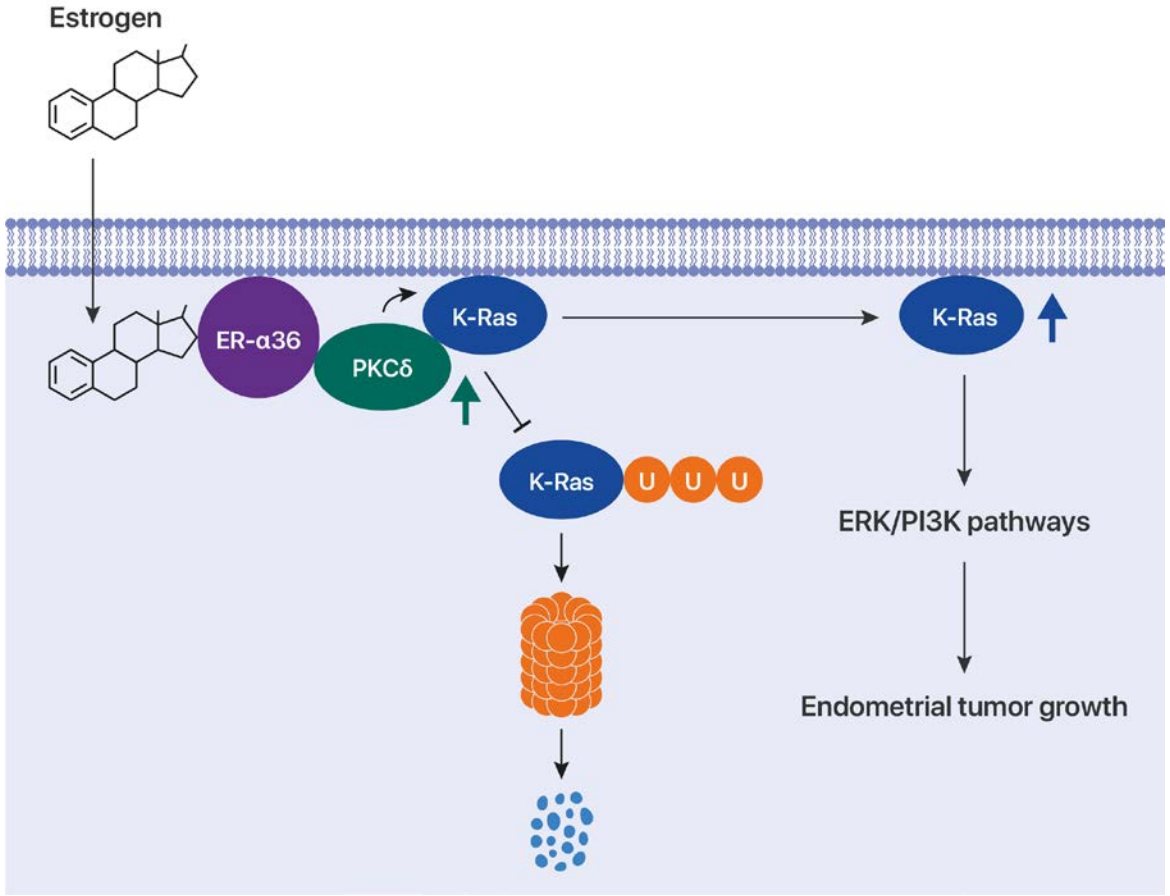
- **Cost-Effective Additional Shot-on-Goal and additional partnership opportunities**

# Protein Kinase C delta (PKCδ) Inhibitors

## Early-Stage Preclinical Program

- **30% of all human malignancies** display activating RAS mutations with another 60% showing over-activity of Ras-signaling pathways.
- BriaCell's novel, proprietary **PKCδ inhibitors** have shown activity against multiple **RAS transformed tumors**.
- This target has an **attractive safety profile** based on in vivo studies and knock out mouse studies.
- PKCδ also has potential activity as an **immunotherapeutic** by blocking TGFβ signaling.
- PKCδ inhibitors are applicable to specific niche tumor types which provide an **accelerated clinical development plan**.
- Could be in clinic within **24 months**

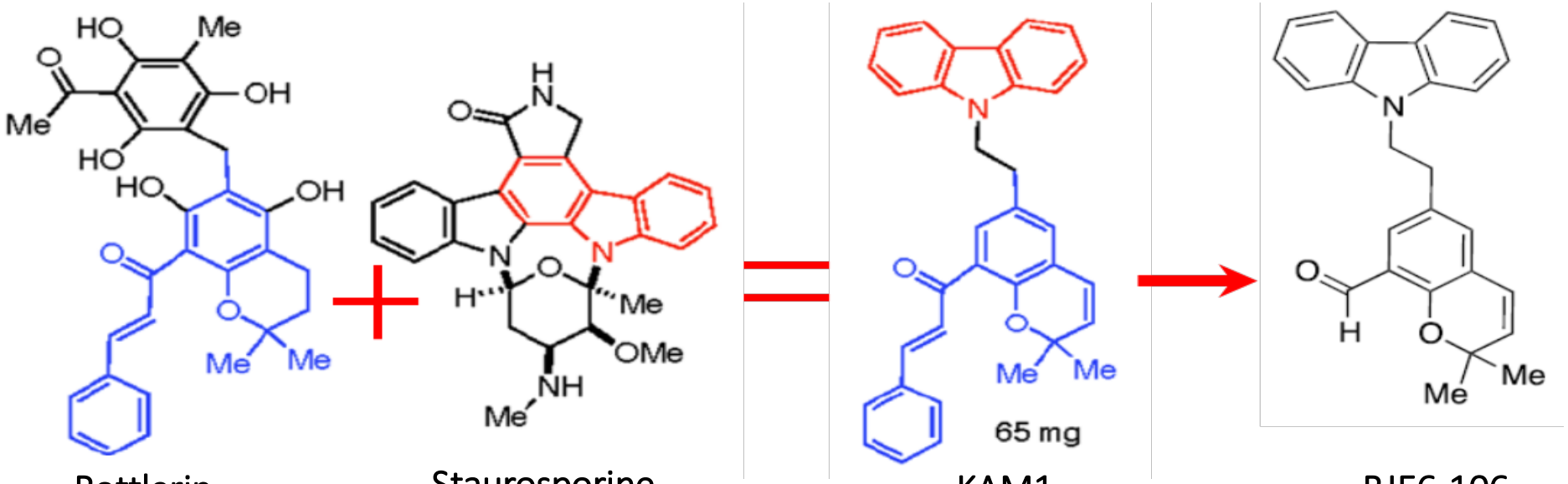
➢ **Tremendous upside potential and attractive to large pharma companies.**




Activated PKCδ inhibits RAS degradation which in turn stimulates tumor growth.

*Koo et al Oncotarget 6:21328, 2016*

# Protein Kinase C delta (PKCδ) Inhibitors

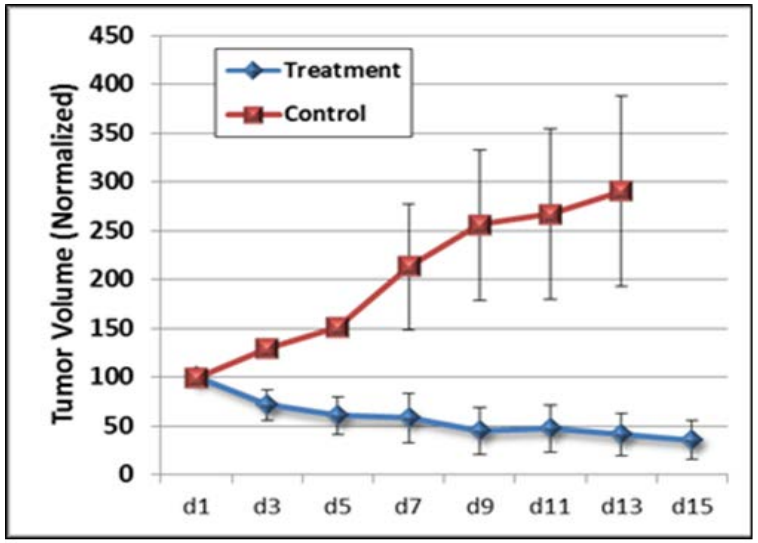



Rottlerin Staurosporine KAM1 BJE6-106

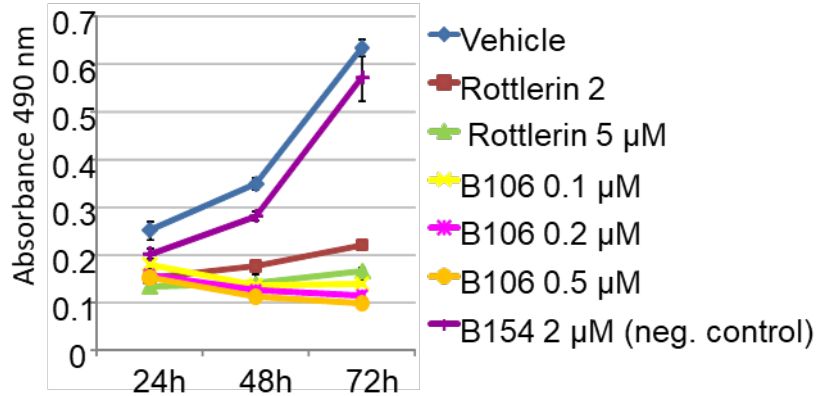
| Generation | PKC-δ $IC_{50}$ | PKC-α $IC_{50}$ | PKC-δ/ PKC-α Selectivity Ratio |
|---|---|---|---|
| 1 | 3 μM | 75 μM | 28-fold |
| 2 | 2 μM | 157 μM | 56-fold |
| 3 | 0.05 μM | 50 μM | 1000-fold |

- Structural aspects of first generation inhibitor rottlerin and staurosporine (pan-PKC activator) were combined to create second generation inhibitor KAM1
- Third generation inhibitors such as BJE6-106 have improved potency and selectivity.
- Fourth generation inhibitors under development to optimize drug-like characteristics.
- PKCδ inhibitors lack endothelial cell cytotoxicity & PKCδ deficient mice develop normally and are fertile
- **Potentially no marked intrinsic toxicity by inhibiting PKCδ**

# PKCδ Inhibitors Block Growth in Various Cancers

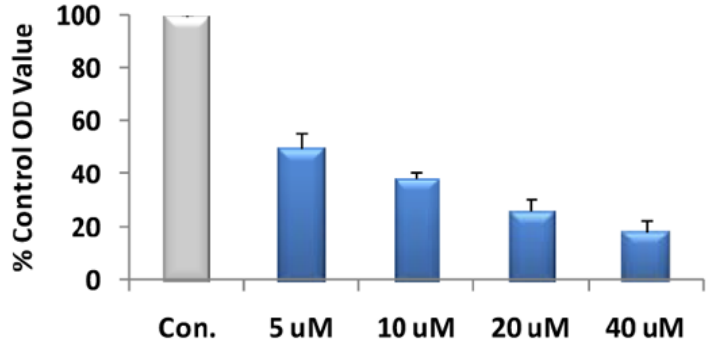



PKCδ inhibitor reduces tumor burden in a human **lung cancer** model (lower is better)



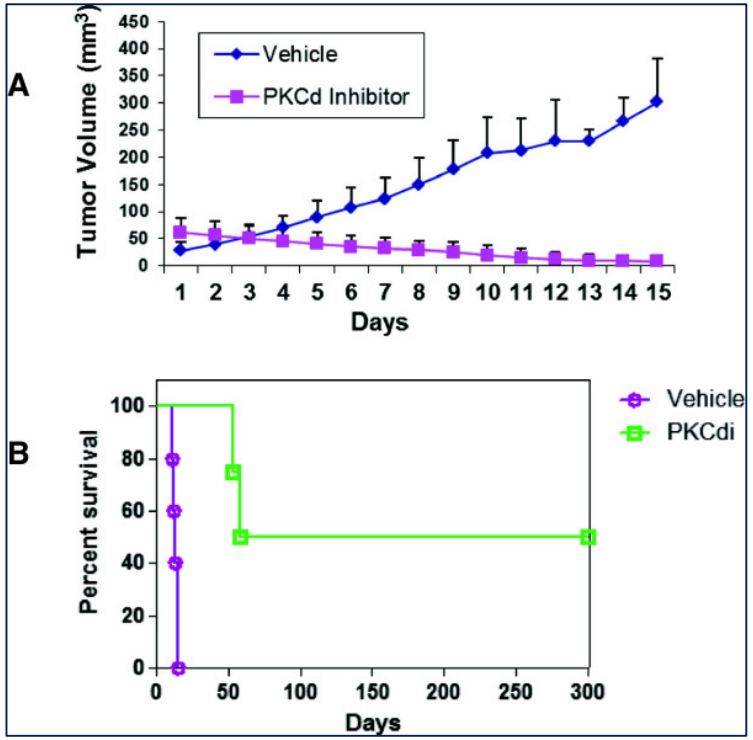

PKCδ inhibitors block growth of **melanoma** cells (lower is better)

PKCδ inhibitors inhibit growth of **neuroendocrine tumor** cell lines (lower is better)




PKCδ inhibitors decrease tumor size and improve survival in **pancreatic cancer** model

(A) lower is better
(B) higher is better)



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## Thank You