



The Future of Cancer Immunotherapy

 info@BriaCell.com  BriaCell.com  1-888-485-6340

**3rd Annual Biologics World Nordic 2020 Conference
Presentation**

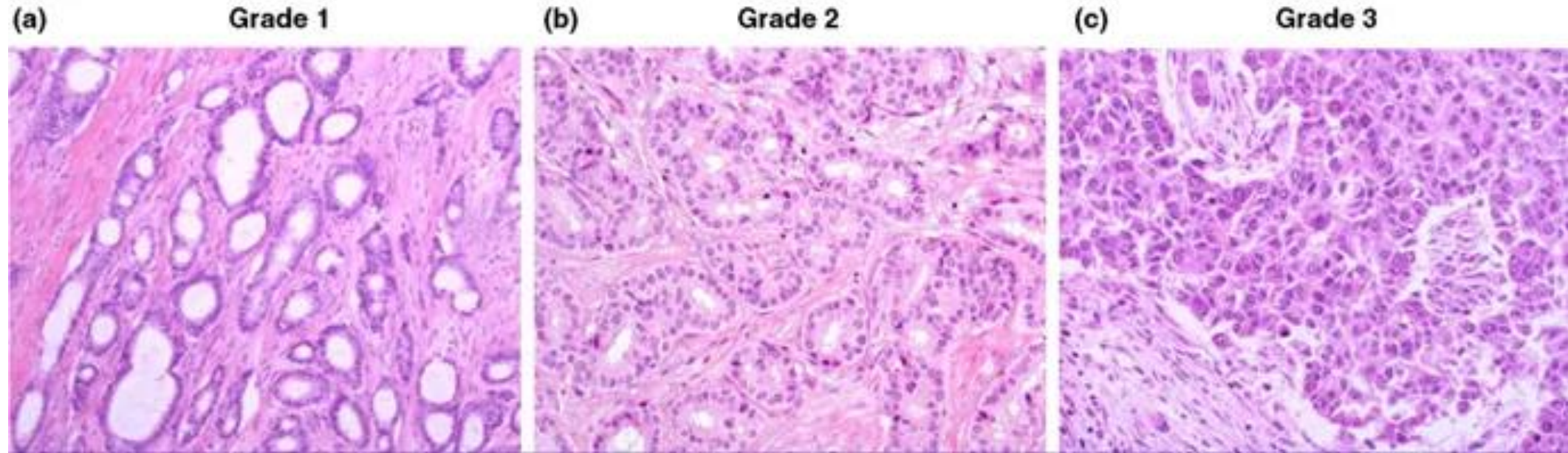
The Problems

- **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 perhaps because 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.

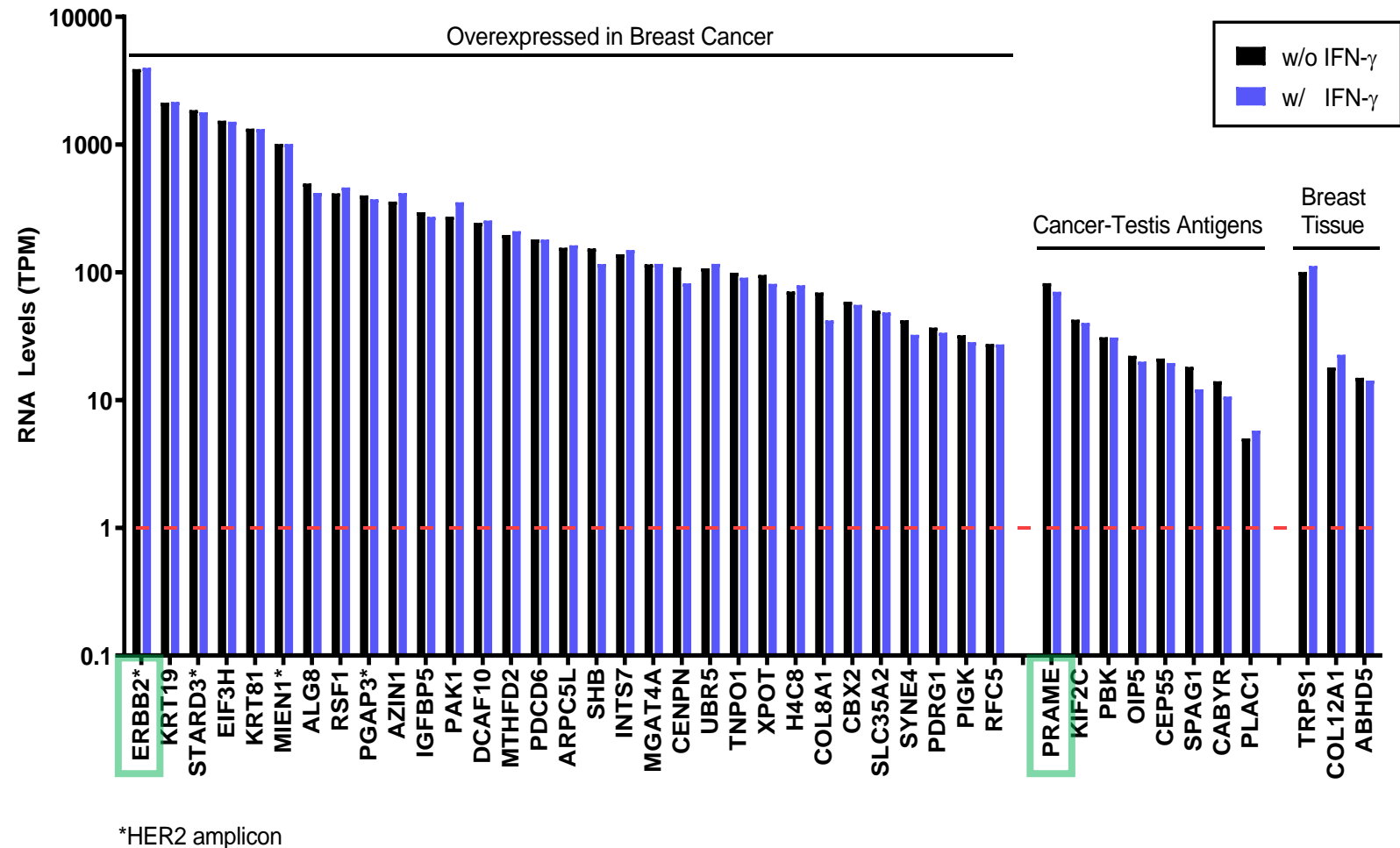


Histological grade of breast cancer as assessed by the Nottingham Grading System. (a) A well-differentiated tumor (grade 1) that demonstrates high homology to the normal breast terminal duct lobular unit, tubule formation (>75%), a mild degree of nuclear pleomorphism, and low mitotic count. (b) A moderately 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%) (Rakha *et al.*, 2010).

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

Bria-IMT™ Expresses Multiple Breast/Cancer related Antigens

- 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.



- Bria-IMT™ expresses at least 22 immunostimulatory genes

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, HLA-F
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

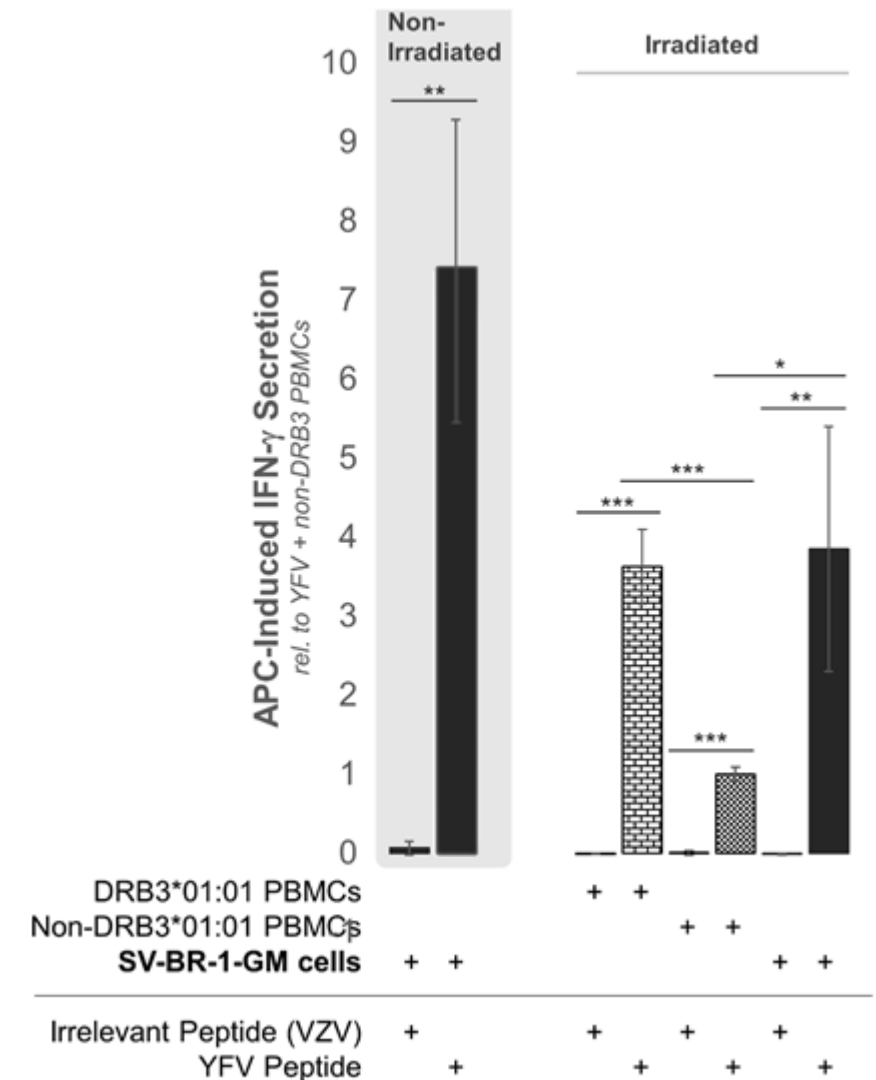
Genes with immunostimulatory roles expressed in SV-BR-1-GM cells. Gene symbols refer to the NCBI designations and HUGO Gene Nomenclature Committee (HGNC) recommendations. Gene symbols, official full names/descriptions, and aliases are indicated as shown on the respective NCBI Gene sites with or without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

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](#)



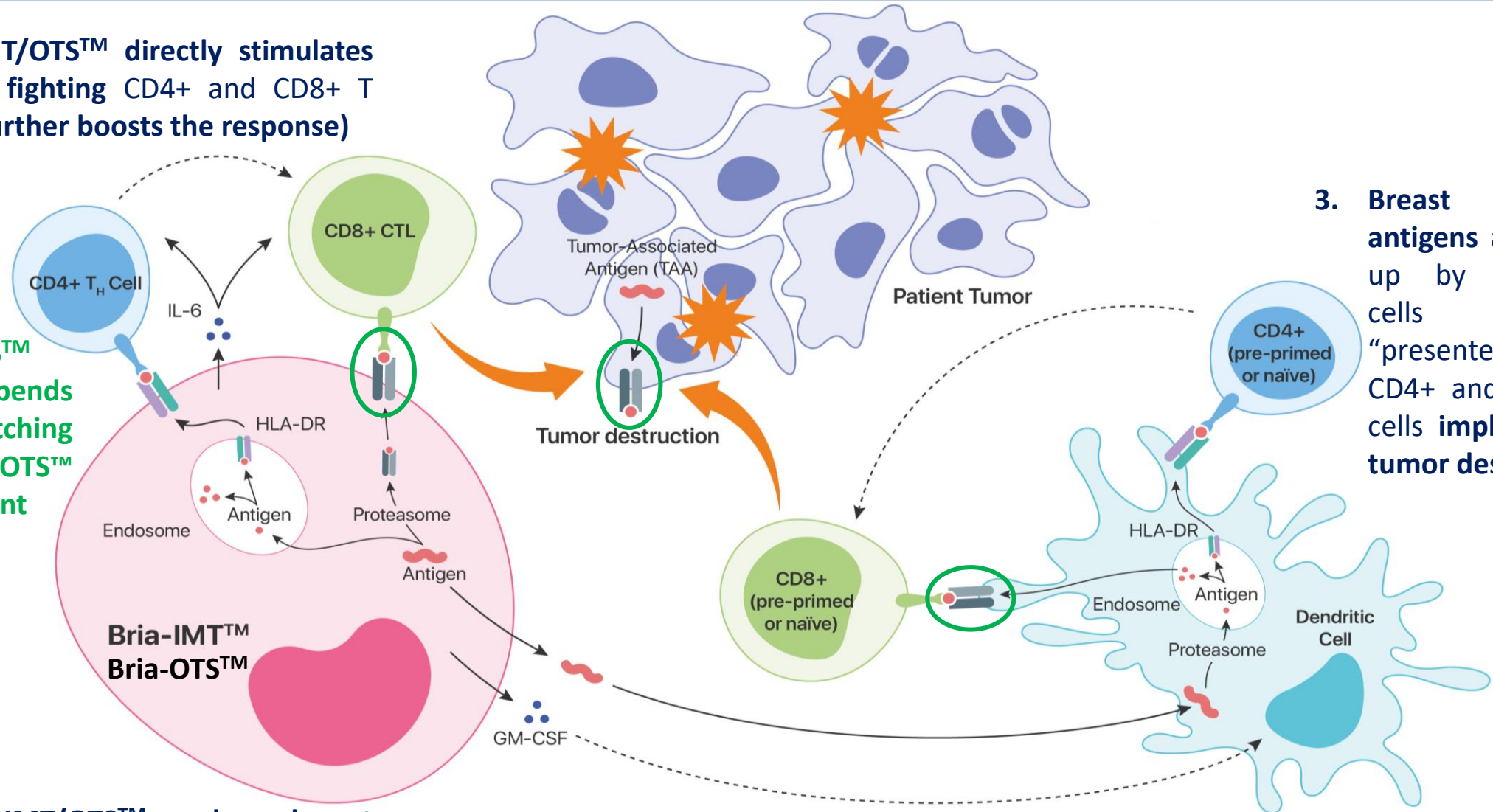
4. Bria-IMT/OTS™ directly stimulates cancer fighting CD4+ and CD8+ T cells (further boosts the response)

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.

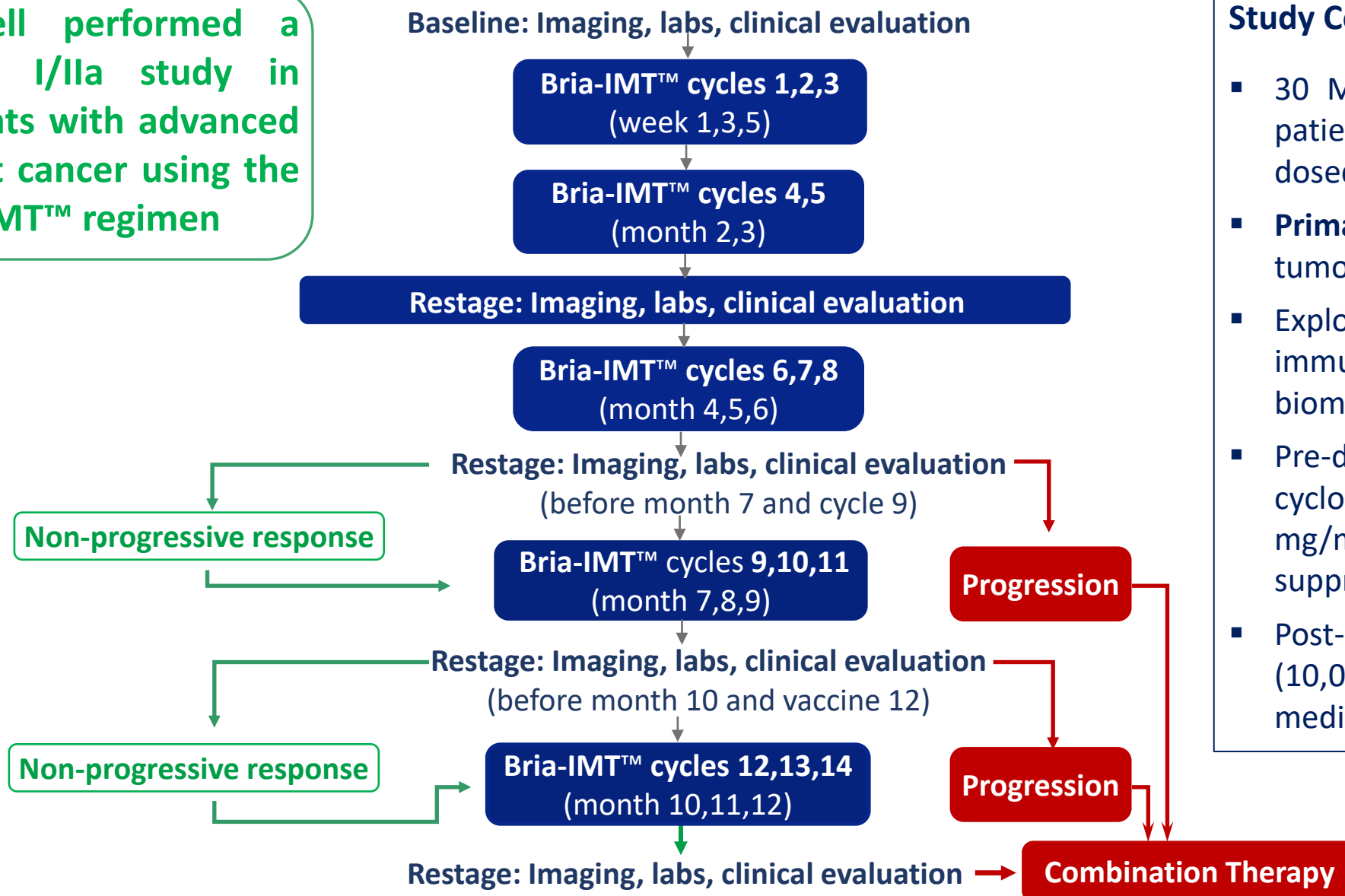
1. Bria-IMT/OTS™ produces breast cancer antigens (proteins made by breast cancer cells)

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



Bria-IMT™ Phase IIa Monotherapy Trial Design

BriaCell performed a 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 (300 mg/m²) to reduce immune suppression
- Post-dose local IFN-α2b (10,000 IU/site) to boost cell mediated immunity

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=5)
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%	47%	67%
% Her2/neu +	17%	20%	33%
% Triple Negative	33%	40%	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™**

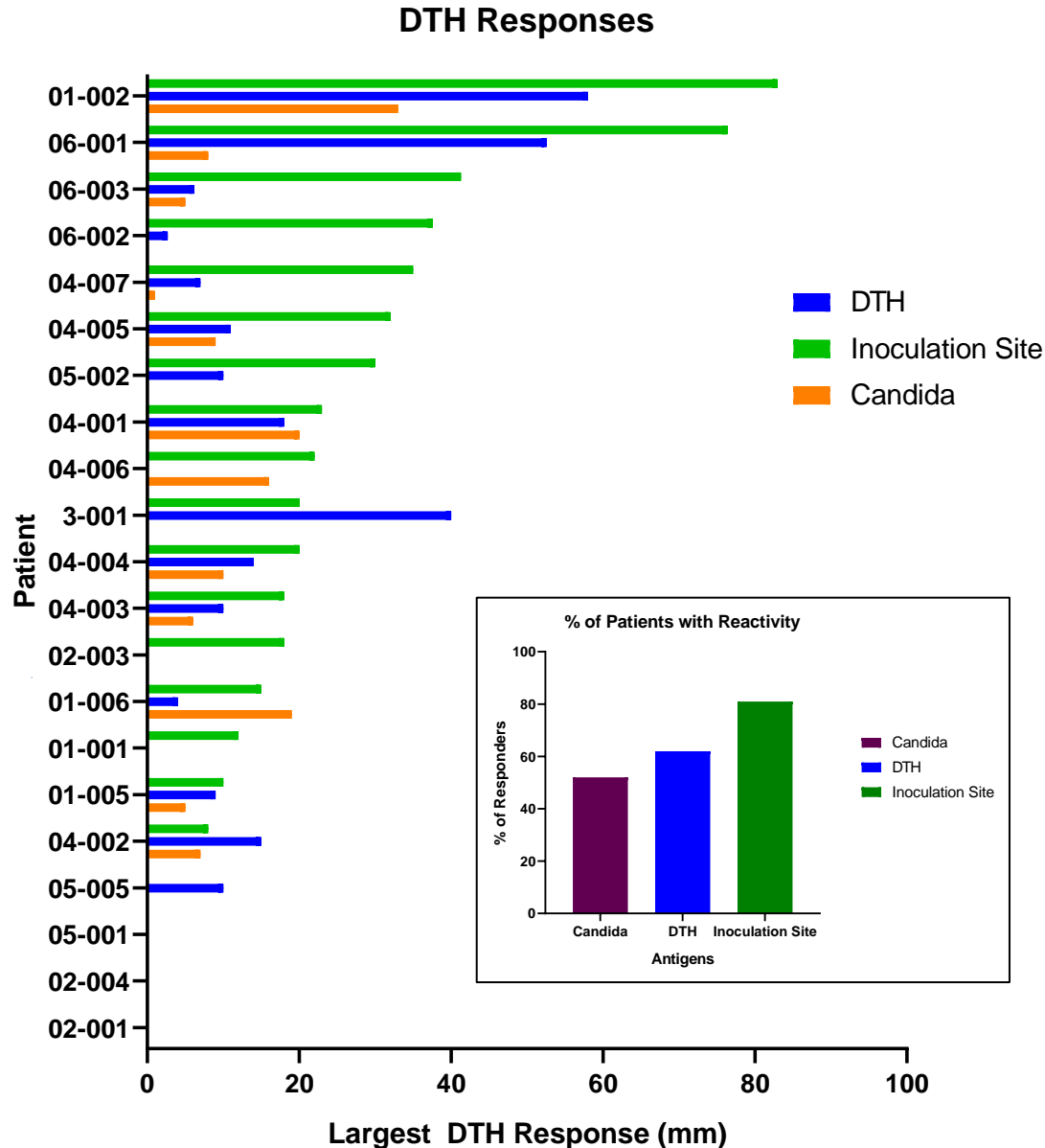
Adverse Events seen in 2 or More Patients

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

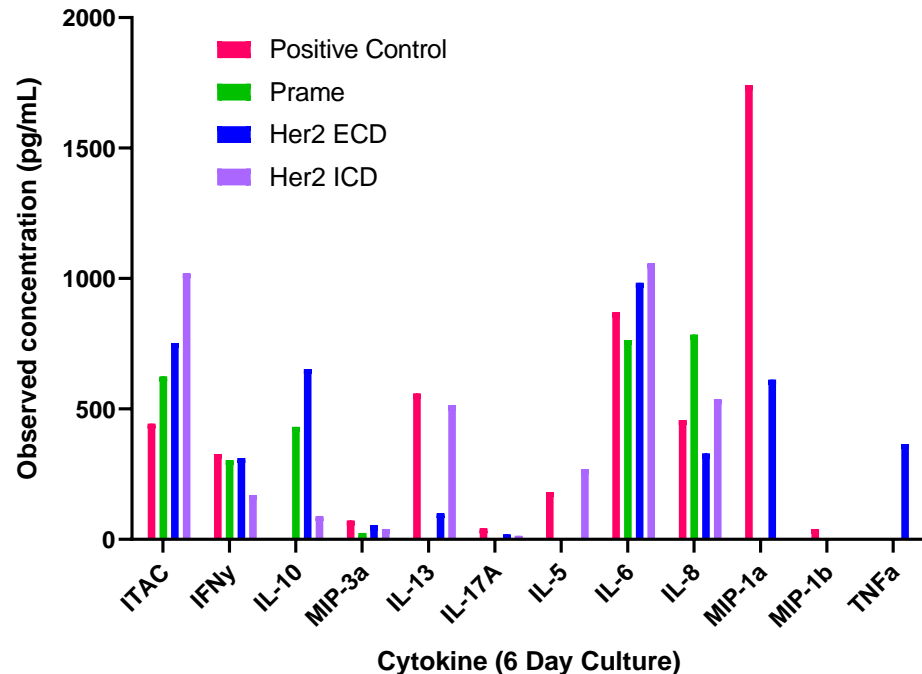
Conclusion: Bria-IMT™ was generally safe and well tolerated



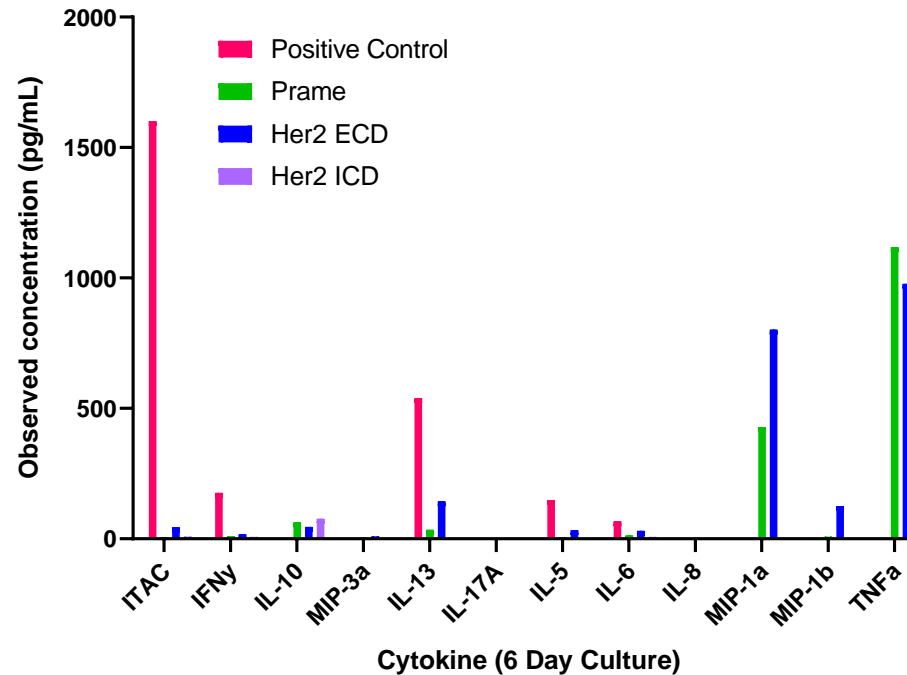
Rationale: Delayed-type hypersensitivity (DTH) is a good marker of cellular (T cell) immune responses. Briefly, for each cycle, Bria-IMT™ was injected intra-dermally with 5×10^6 irradiated cells in each of 4 sites in the upper back and thighs. 2 ± 1 days later, these sites were assessed for erythema 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.

**Average Responders
(Negative Control Subtracted)**



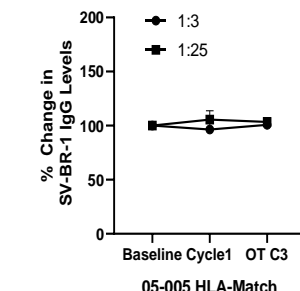
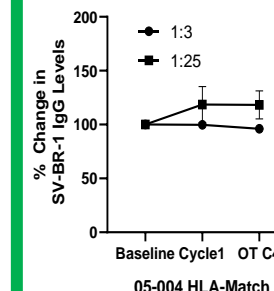
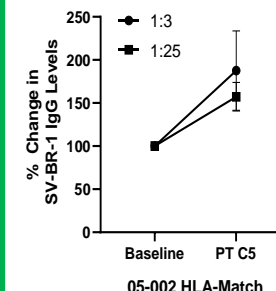
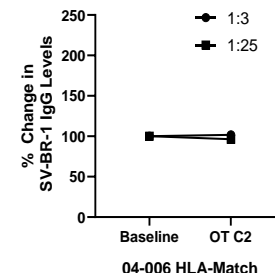
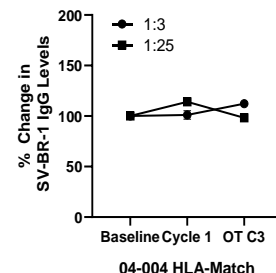
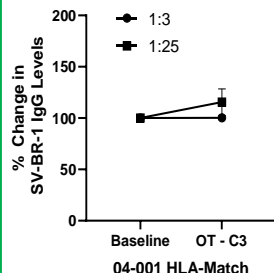
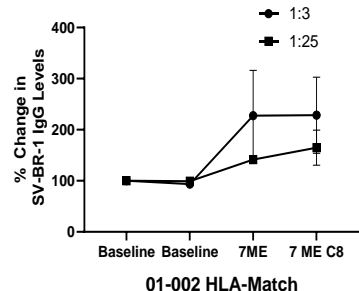
**Average Non-Responders
(Negative Control Subtracted)**



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

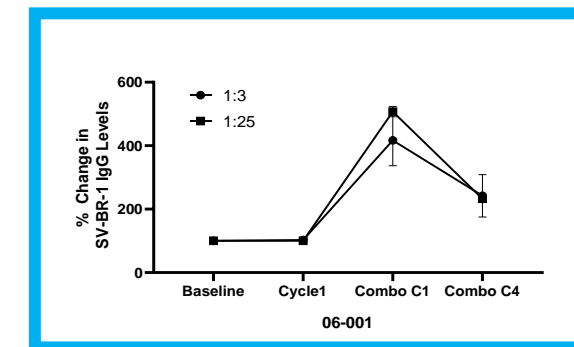
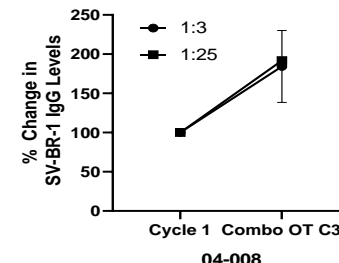
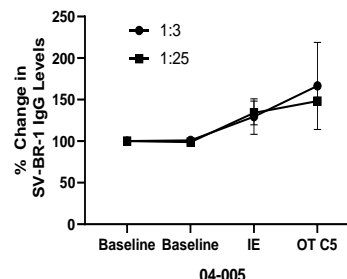
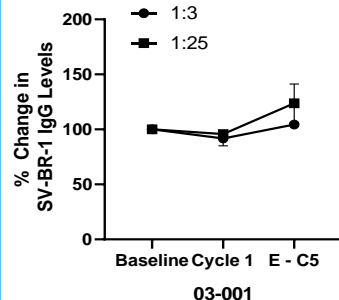
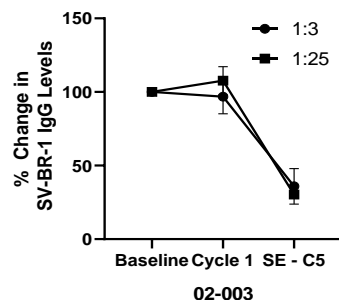
Conclusion: Responders with tumor regression develop T cell responses to the cancer-related antigens PRAME and HER2/neu.

Anti-SV-BR-1 Antibodies in Patients



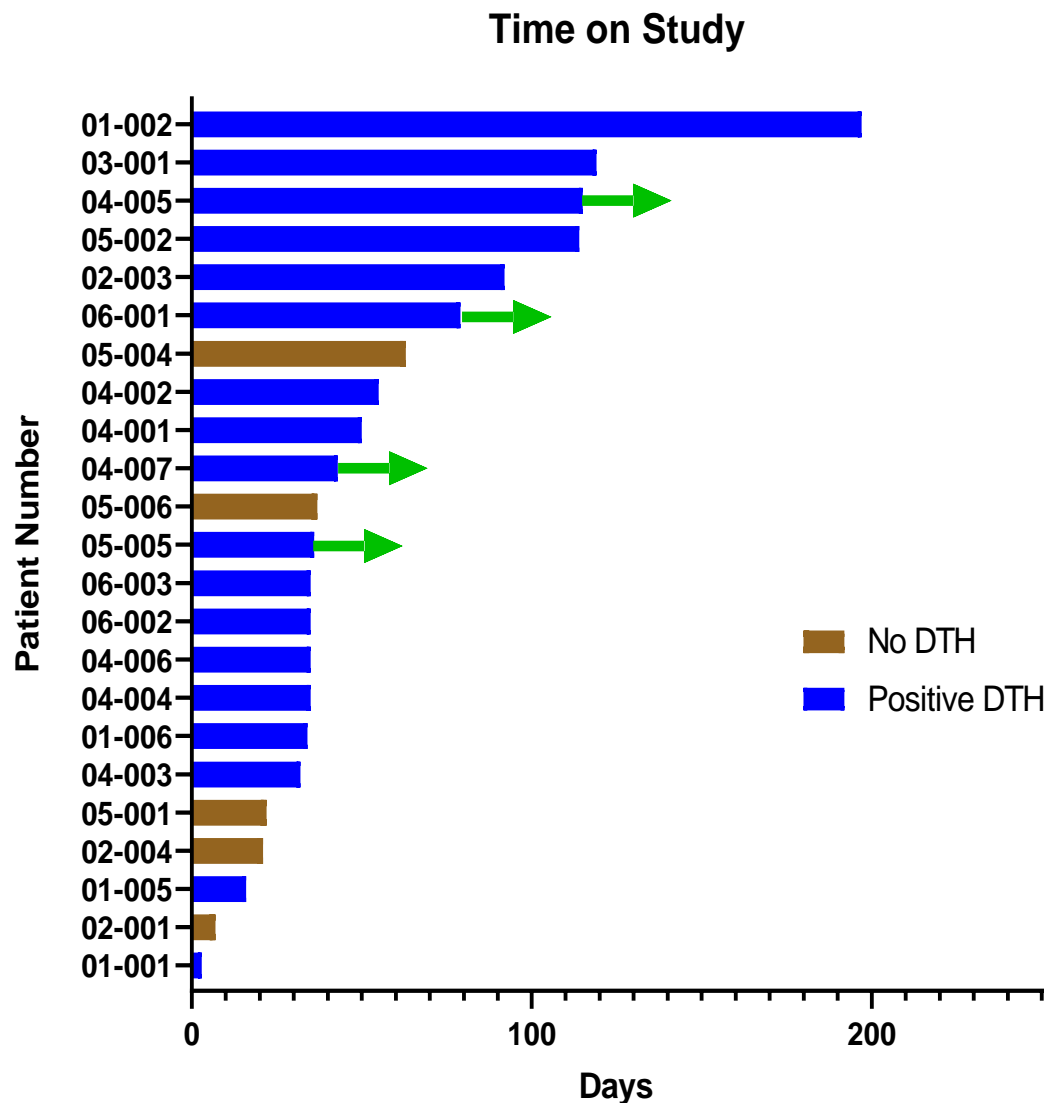
HLA Match ↑

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 indicating activation of the immune system. The best responses are seen in those with tumor shrinkage.



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™ 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	Disease Control** (SD, PR and CR)	Disease Control in Immune Responders***
N=6	≥ 2	50%	75%
N=20	≥ 1	25%	33%
N=7	0	29%	29%
N=27	All	26%	32%

*Includes 4 patients from an initial study in 2004-2006

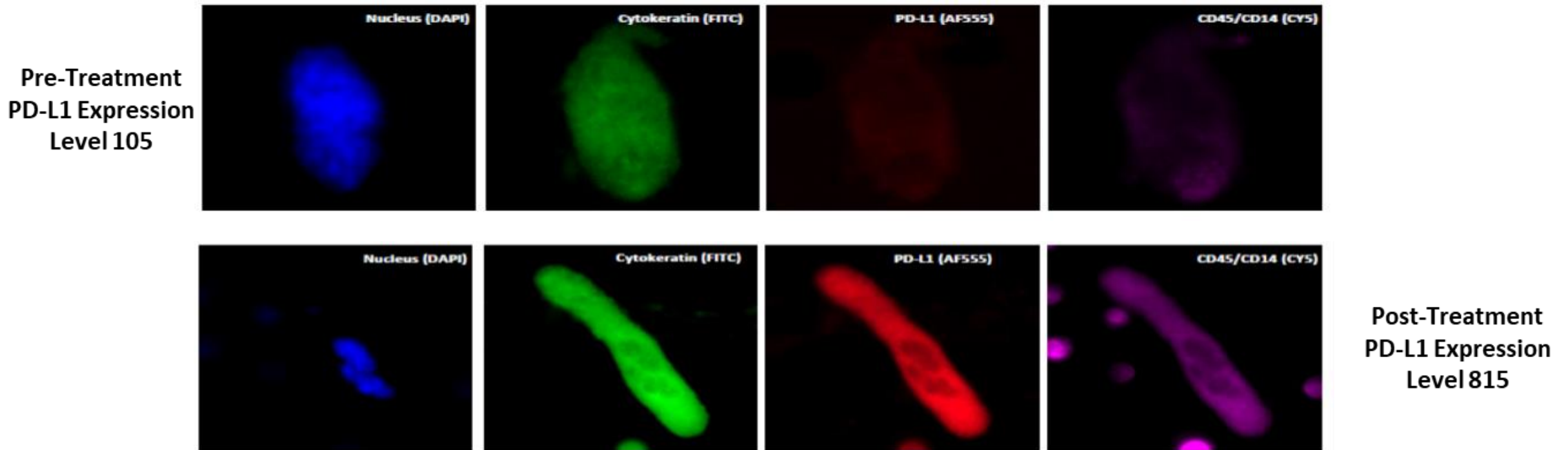
**Includes 1 PR and 7 SD

***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

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



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

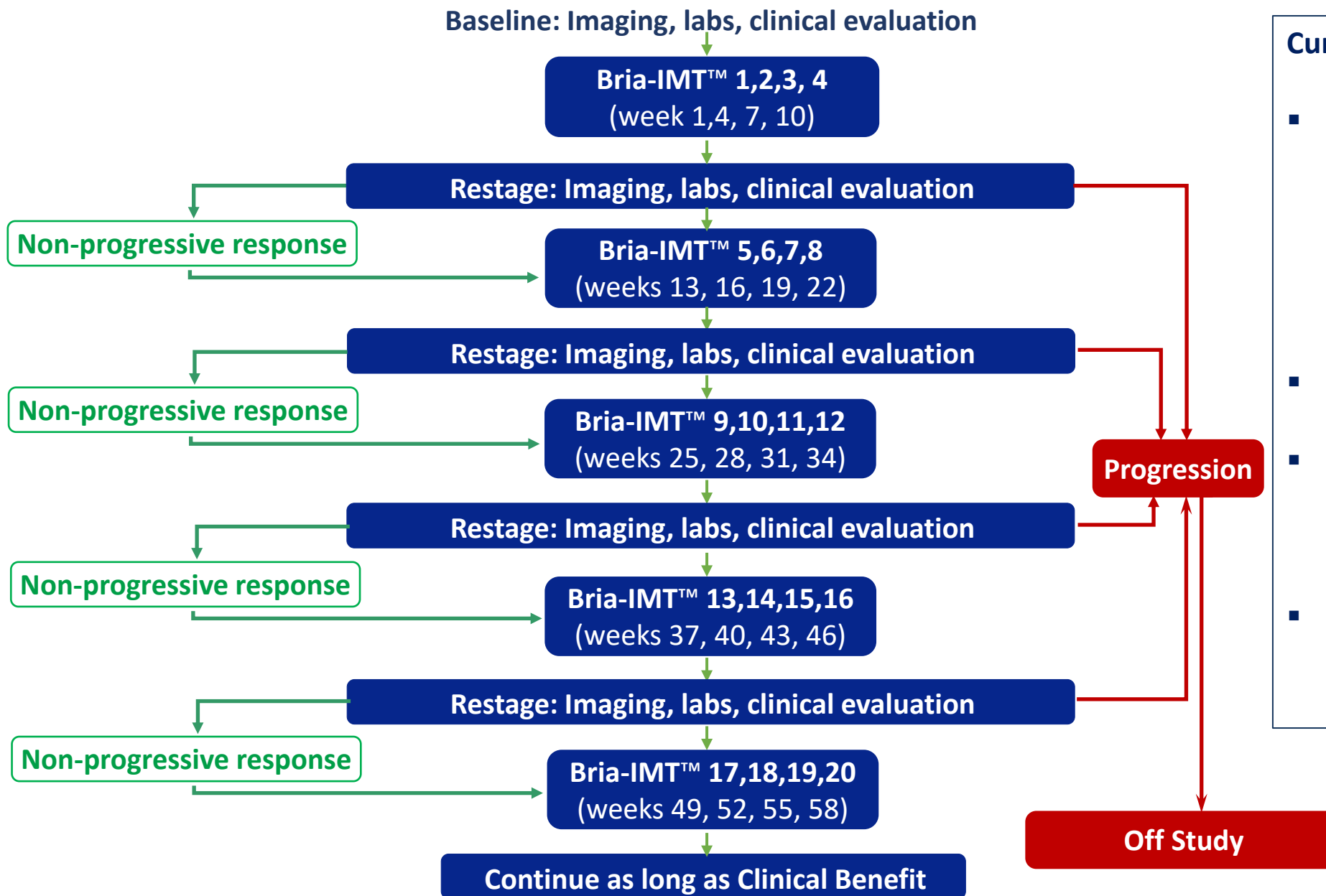
Anti-PD-1 & Anti-PD-L1 Ineffective as Monotherapy in Breast Cancer



- 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)
- Thus, responses in late stage breast cancer with PD-1 or PD-L1 inhibitors rare outside of TNBC

**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**

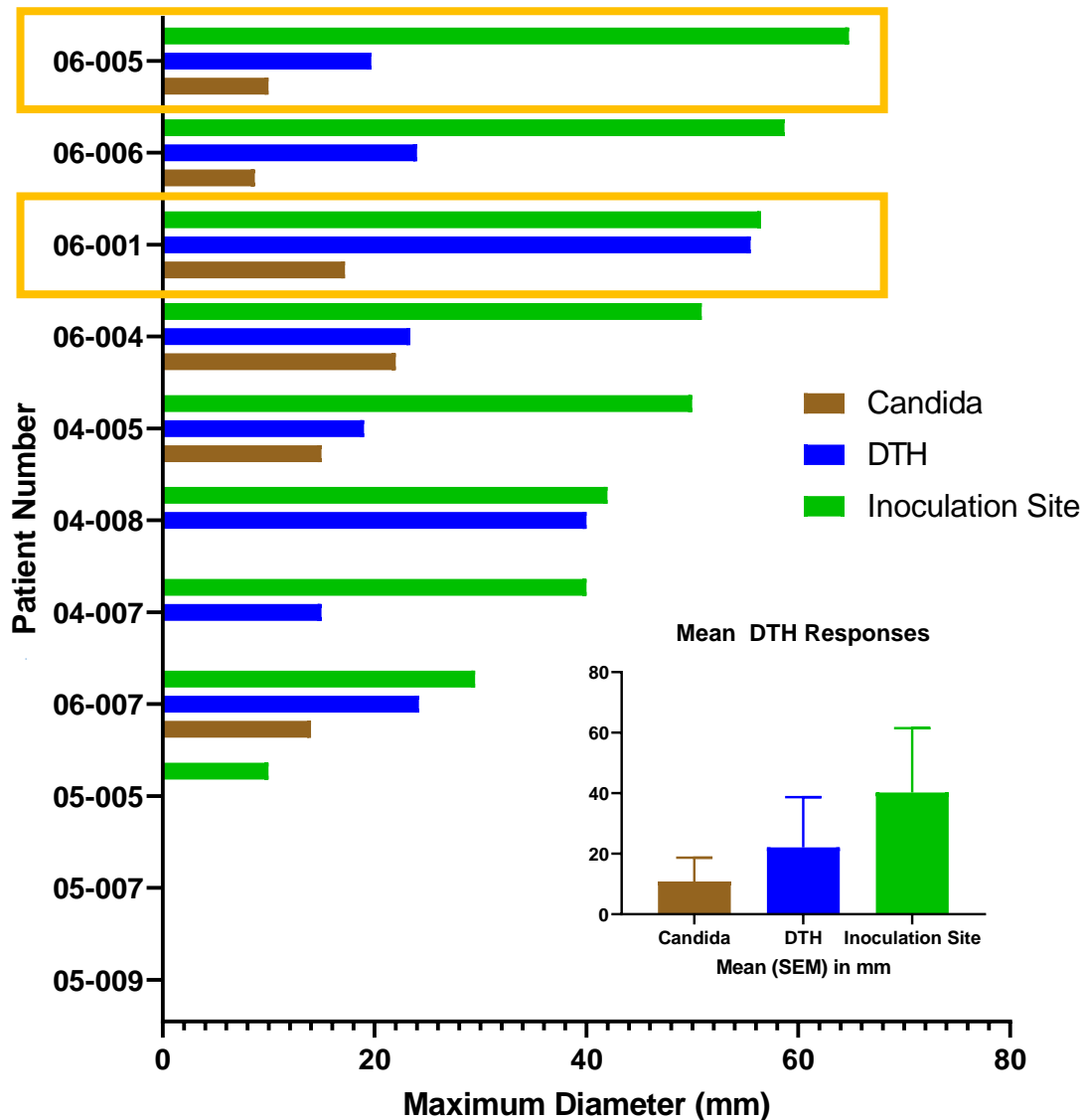
Bria-IMT™ Phase I/IIa PD1i Combination Therapy Trial



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	7

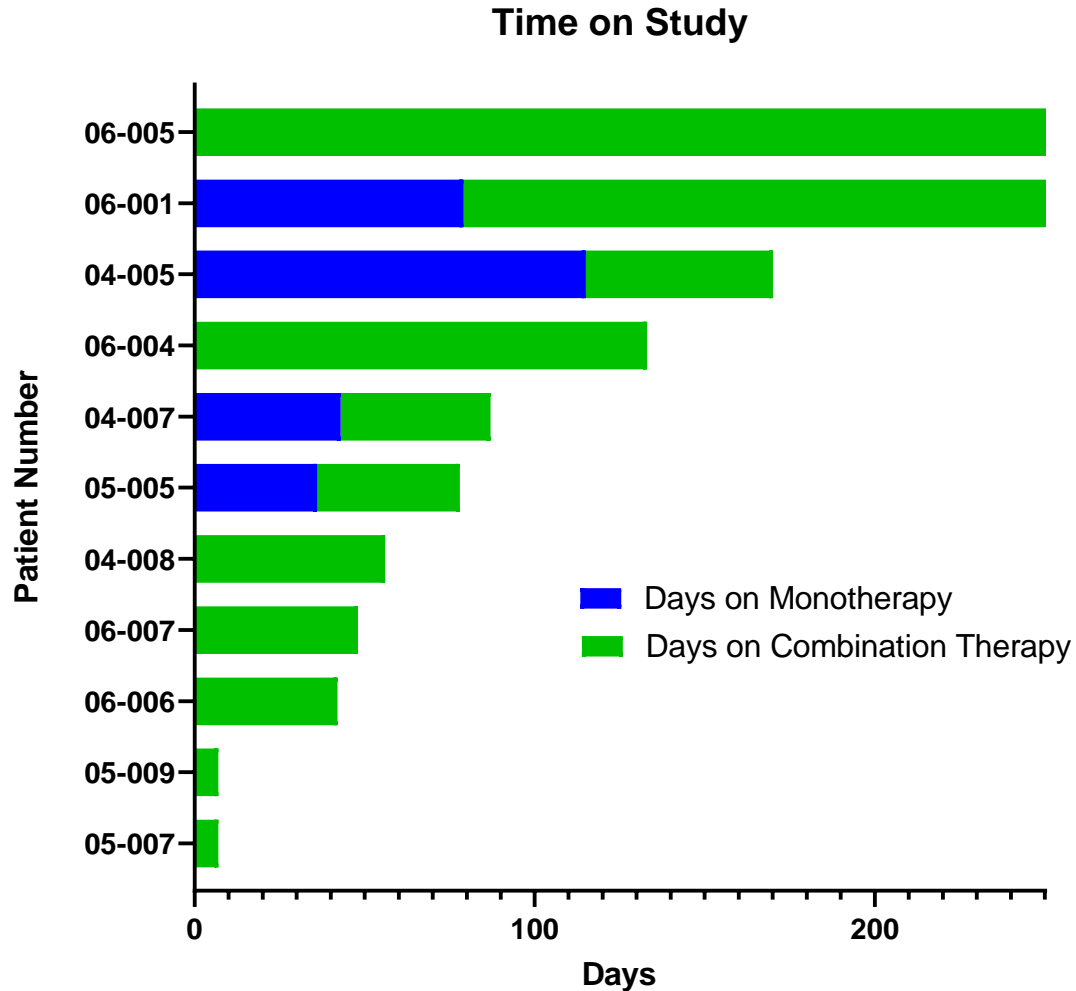
The patients are heavily pre-treated and generally similar regardless of HLA matching with Bria-IMT™

Delayed Type Hypersensitivity to Bria-IMT™ + PD1i



Rationale: Delayed-type hypersensitivity (DTH) is a good marker of cellular (T cell) immune responses. Candida (positive control) or 1×10^6 irradiated Bria-IMT™ cells were injected intra-dermally in the forearm (DTH) and 5×10^6 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.



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 PD1i has been well tolerated.

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

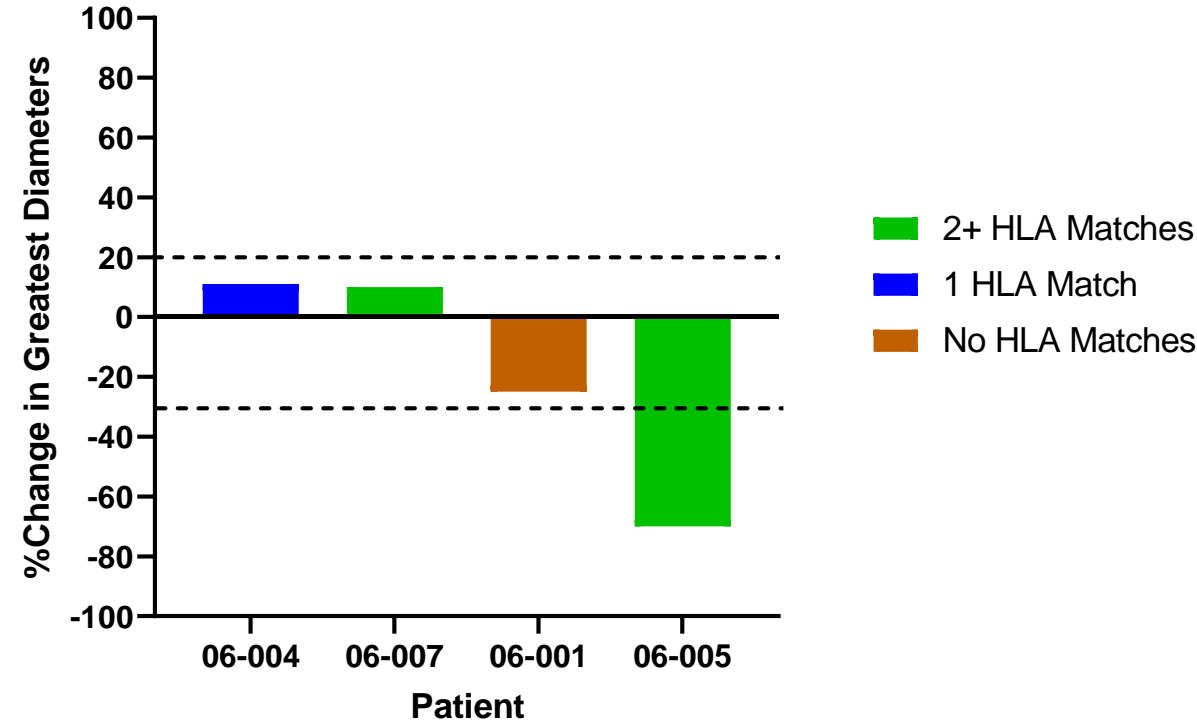
Patients	HLA Match	Disease Control* (SD, PR and CR)	Disease Control in Immune Responders**
N=5	≥ 2	40%	100%
N=7	≥ 1	43%	75%
N=4	0	25%	25%
N=11	All	36%	50%

*Includes 1 PR and 3 SD

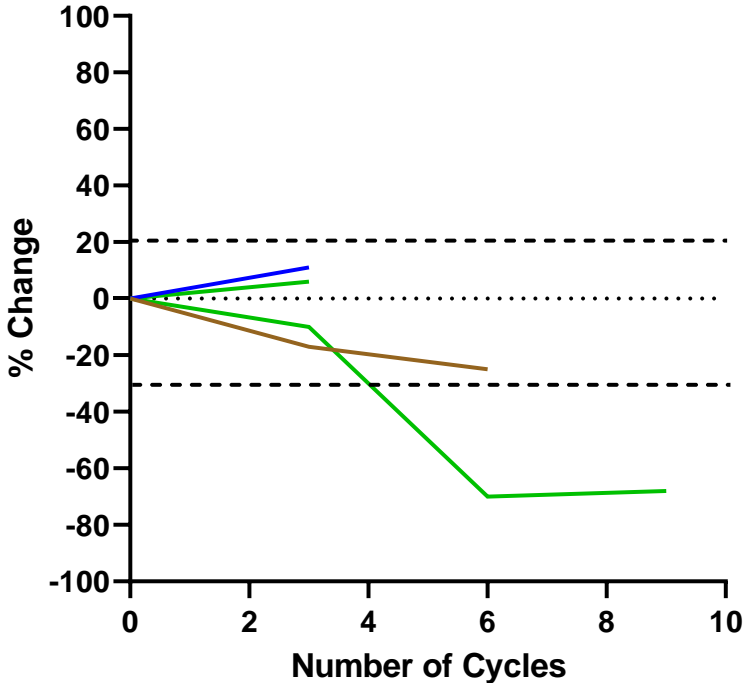
**Immune response measured by delayed-type hypersensitivity.

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

Target Lesion Best %Changes

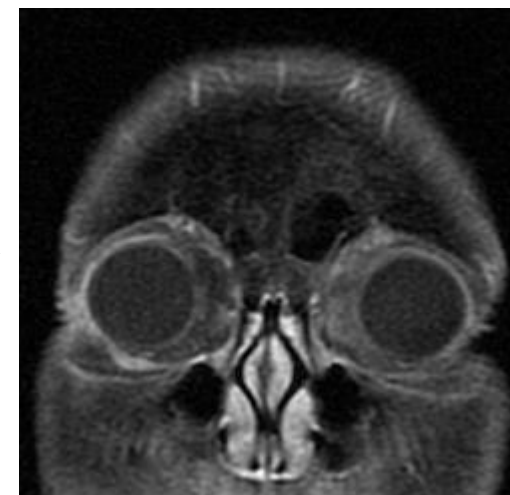
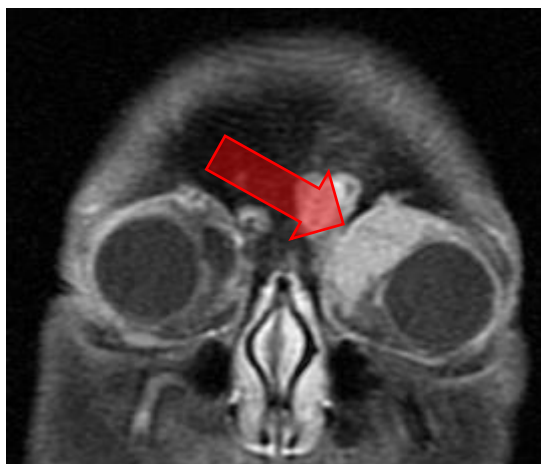


Spider Plot Target Lesions PD-1i Combination

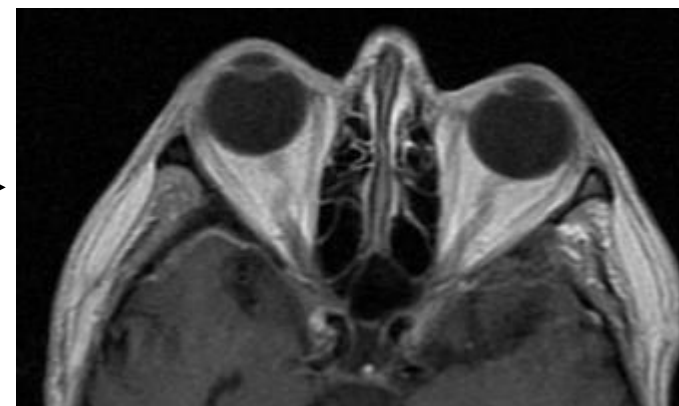
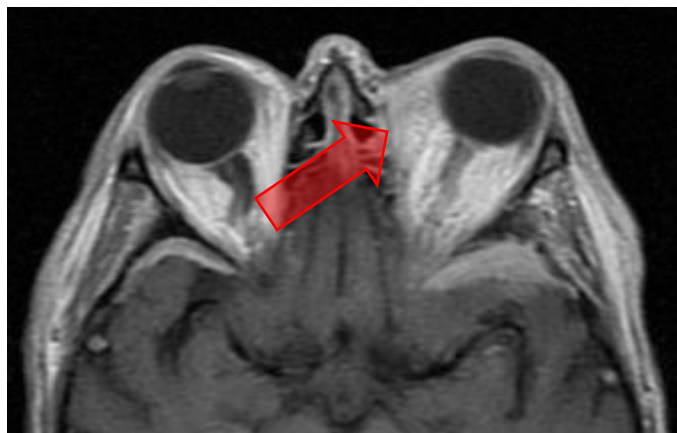


Tumor behind the left eye causing proptosis completely resolves

**Baseline
Scans**



**Six months
On Treatment
Scans**



Complete resolution of orbital tumor in a heavily pre-treated patient with 2 HLA matches and a grade II tumor supports remarkable activity of Bria-IMT™

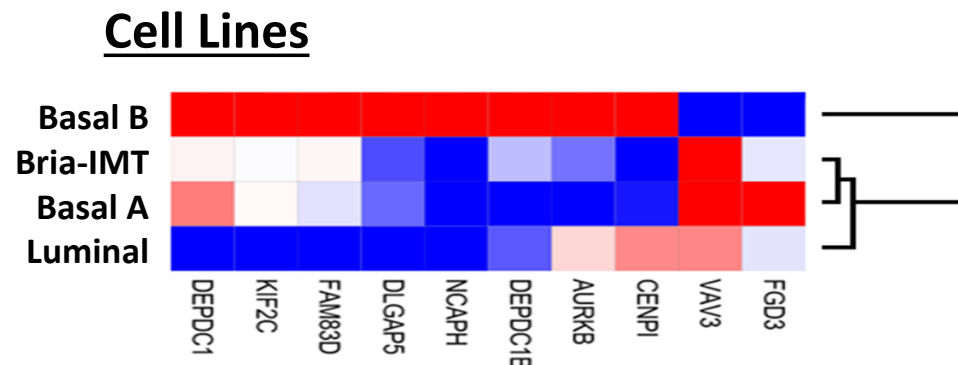
Breast Cancer by Stage of Differentiation

- Breast cancer is classified based on histology into Grade I, II, or III. Also the designations “Luminal A”, “Luminal B”, “HER2+”, “triple negative (including “claudin-low”)” are used, denoting increased aggressiveness in this order (Dai et al., 2017).
- Breast cancer cell lines are similarly classified, with the MCF-7 cell line classified as “Luminal”, the MDA-MB-468 cell line as “Basal A”, and the MDA-MB-231 as “Basal B” (Neve et al., 2006) or “claudin-low”.
- Grade to some extent correlates with aggressiveness: MDA-MB-468 is considered less aggressive than MDA-MB-231 but more aggressive than MCF-7.
- SV-BR-1-GM clusters most closely with MDA-MB-468 and as such may represent a lower grade than MDA-MB-231, perhaps Grade 2.
- **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.

The MDA-MB-468 cell line represents Basal A (less aggressive than Basal B/claudin-low), MCF-7 luminal (less aggressive than Basal A), and MDA-MB-231 Basal B (claudin low). Therefore, based on its molecular similarity with MDA-MB-468, **Bria-IMT™ is considered a Basal A and as such potentially a moderately differentiated (grade II) cell line.**



Bria-IMT™ most closely matches with a Basal A cell line and a Luminal cell line. Basal B (often corresponding to poorly differentiated = grade III tumors) appears distinct

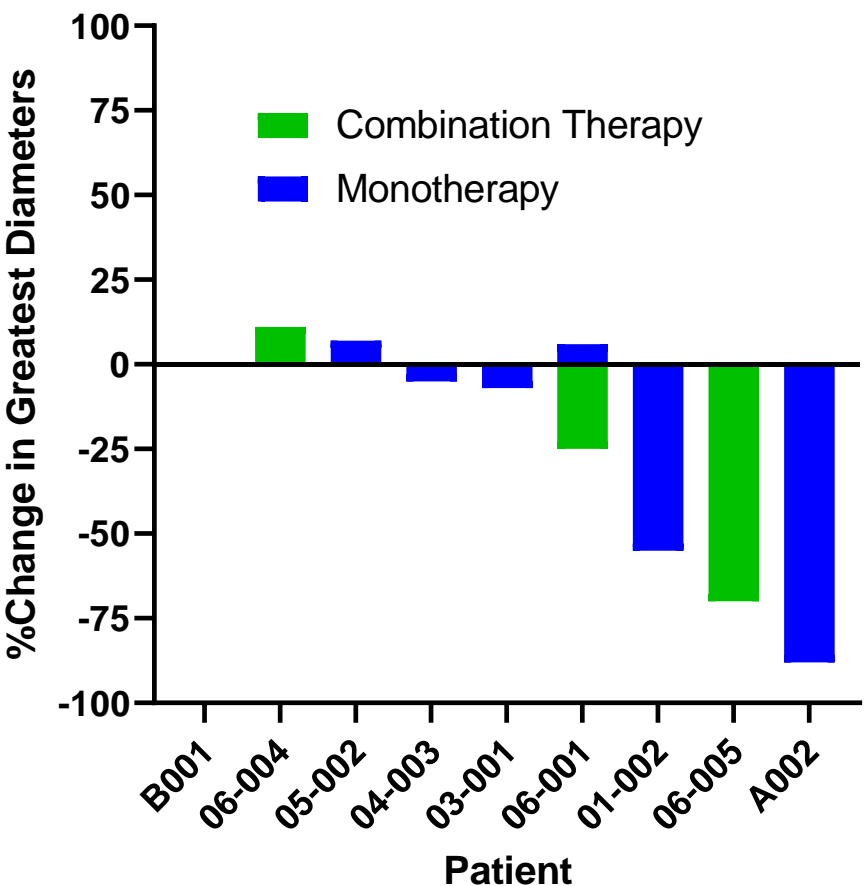
Breast Cancer Grade Correlates with Response

- 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 5 prior systemic 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 9-12 prior systemic regimens

Patient Characteristics	Monotherapy Studies (n=8)	Pembrolizumab Combo Study (n=3)	All Patients (n=10)
Age	64 ± 2 (median 62)	67 ± 9 (median 70)	64 ± 7 (median 62)
Median Prior Systemic Regimens	5 (range 0-13)	10 (range 9-12)	8 (range 0-13)
% ER/PR +	86%	100%	89%
% Her2/neu +	0%	33%	11%
% Triple Negative	14%	0%	11%
Grade I	1	0	1
Grade II	7	3	9
Immune Responders	7	3	9
Disease Control	63%	100%	70%
Disease Control in Immune Responders	71%	100%	78%

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

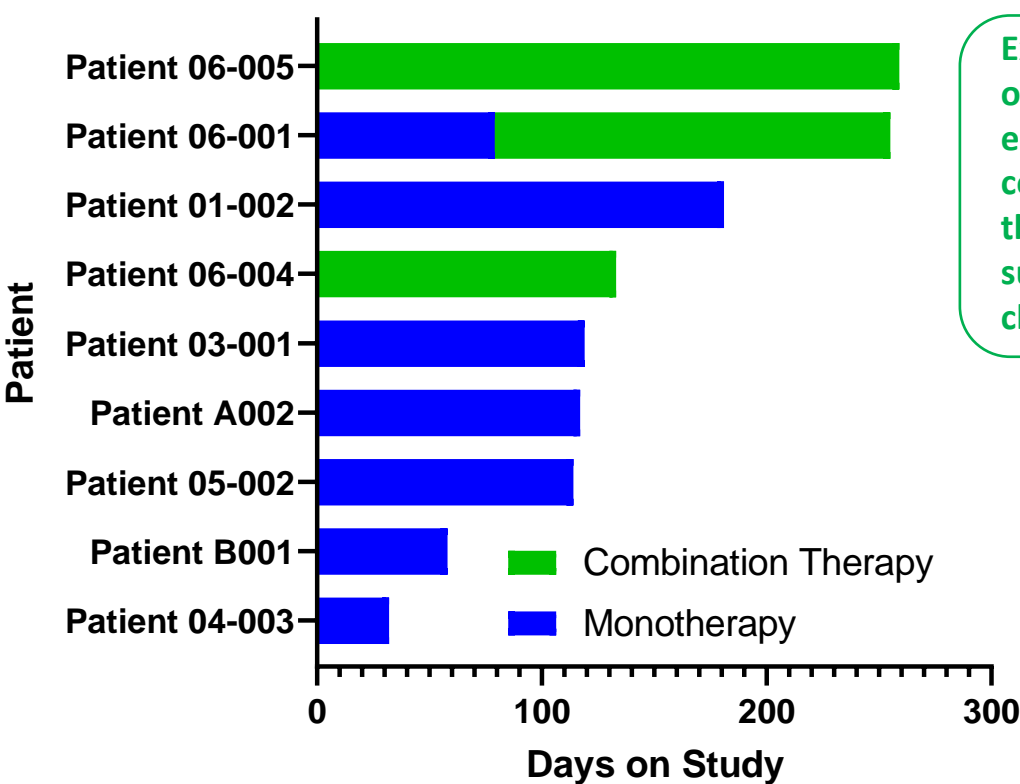
All Lesions %Changes



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

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

Time on Study



Extensive time on study especially with combination therapy suggesting clinical benefit

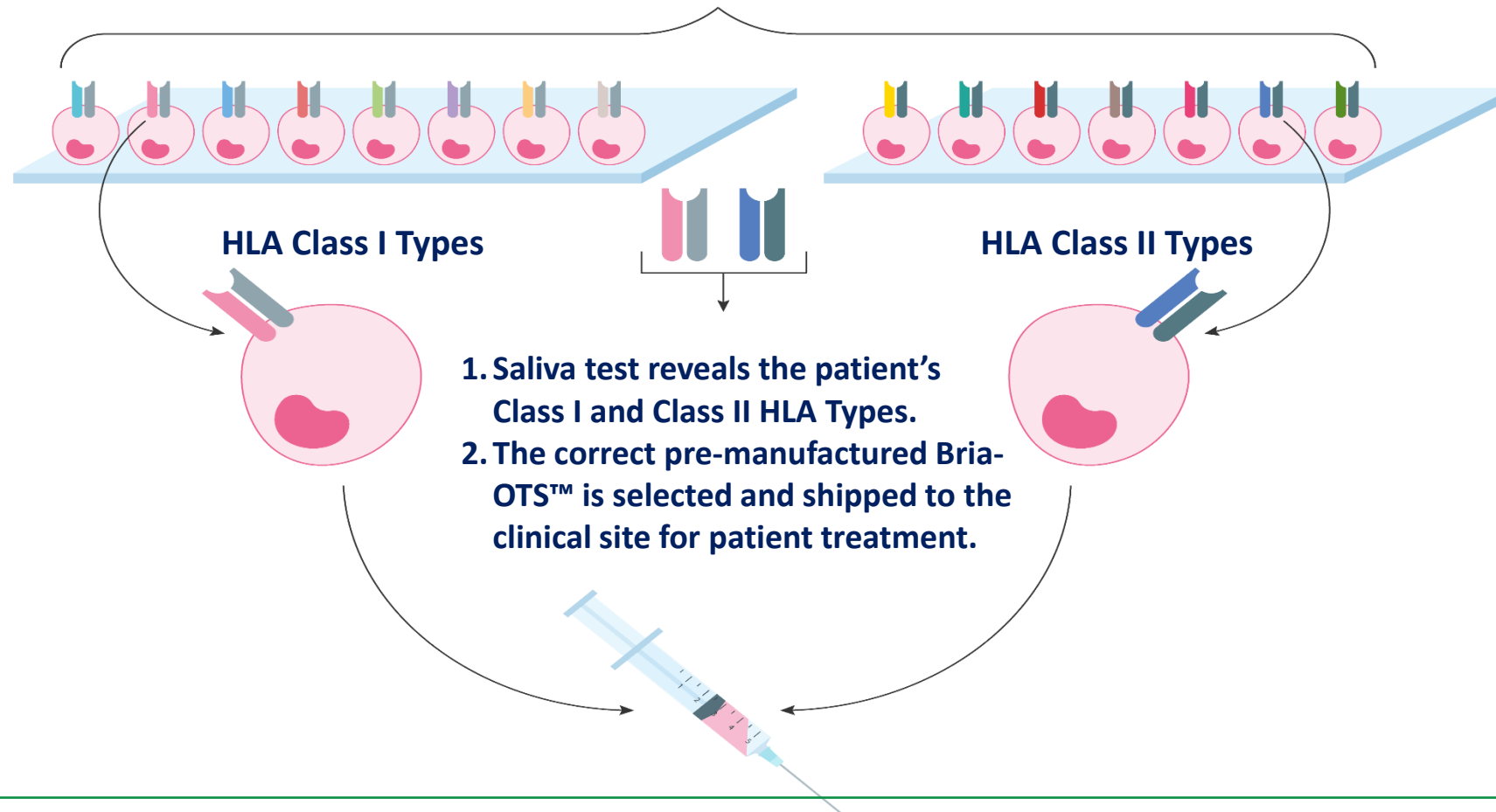
We believe these findings identify a patient population with higher clinical benefit rates

- 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.

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

- Bria-IMT™ is a breast cancer cell line with features of an antigen presenting cell genetically engineered to express GM-CSF
- The Bria-IMT™ regimen has been used by itself to treat 27 patients with advanced breast cancer
- In spite of being heavily pre-treated, disease control rates ranged from 26% to 75% depending on HLA matching and immune response
- Bria-IMT™ in combination with PD1i is able to induce effective anti-tumor immune responses in selected patients.
- Patients with Grade I or II breast cancer have higher response rates with disease control seen in 63% - 100% of patients in the two studies
- Bria-OTS™ cell lines are being developed to express both GM-CSF and interferon- α PLUS patient-specific matching HLA types
- The goal is to develop a personalized therapy without the need for personalized manufacturing
 - This approach should be applicable to multiple tumor types

Bria-IMT™ and Bria-OTS™ should pave the way for the next generation of personalized off-the-shelf immunotherapies for cancer



The Future of Cancer Immunotherapy

 info@BriaCell.com  BriaCell.com  1-888-485-6340

Thank You