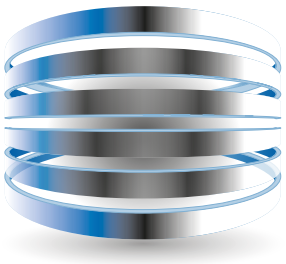


ImaginAb

Round Table

December 2nd, 2021

“Imaging may improve decision making in early I-O clinical trials”

Overview of event &
responses to questions

Challenge • Create • Transform

Forward by Ian Wilson, CEO and President of ImaginAb

ImaginAb is a market leading global biotechnology company, focused on developing next generation immuno-oncology imaging agents and therapeutic radiopharmaceuticals (RPT).

As a market leader, we are very keen to explore the potential benefits that imaging could bring and, as part of this, have launched a series of round table events, in which we have asked leading experts to come together to debate, discuss and answer questions across a range of different subjects.

In our first event, that took place on December 2nd, 2021, we debated how 'imaging may help improve decision making in early I-O clinical trials' and were joined by a number of leading voices in the imaging and biomarker fields. During the hour we explored the world of imaging and biomarker development, and how these may be used to improve decision making in early I-O clinical trials, while also potentially addressing some of the perceived issues that using biomarkers and imaging have.

The hour was split into three components:

1. A keynote talk from Dr. William Williams, President and CEO of BriaCell Therapeutics Corp.
2. A question-and-answer session, in which each of the panelists gave their reaction and thoughts to questions that we either received ahead of the event or during it.
3. Closed the session with remarks from the panel members who summarized what, in their views, where the latest developments in the field of biomarkers, imaging and immuno-oncology drug development.

We have included a transcript to the presentation given by our keynote speaker, Dr. William Williams (CEO and President of BriaCell) along with the answers given by our panel members (Prof. Anna Wu, Dr. Laura Dillon and Dr. Jeff Evelhoch) to the questions raised ahead of, and during the event.

I hope you find the information informative and helpful, and if you would like to find out more about how our CD8 ImmunoPET technology and other imaging agents could help your clinical trials or simply to find out information on future events then please contact me at info@imaginab.com.

Finally, I'd like to thank our key-note speaker, our panel members and everyone who registered and attended for their involvement in making it such a lively and informative event.

Regards

Ian Wilson
CEO & President of ImaginAb

Legal statement

Please note that this is a transcript of the ImaginAb Virtual Round Table event held on December 2, 2021. ImaginAb invited several imaging experts to describe their experiences of working with ImaginAb, or of incorporating ImaginAb's CD8 technology into their cancer immuno-therapy clinical trials.

The round table panel members

Dr Ian Wilson
Moderator

With over 25 years of experience in development of in vivo medical diagnostics and imaging medical devices, Ian is a highly established and influential member of the industry and has built an enviable skill set over the years through a number of significant healthcare roles.

It's this diverse portfolio of skills, along with his aspirational vision of growing ImaginAb to transform the healthcare and biotechnology industry that has led Ian, as president and CEO of ImaginAb, to accelerate its business presence and performance.

Dr William V. Williams
Guest Speaker

Bill is a seasoned biopharmaceutical executive with over 35 years of industry and academic expertise, including significant clinical management in multinational pharmaceutical companies. Bill has served as BriaCell's President & CEO since Nov 2016.

Previously, Bill was appointed as VP of Exploratory Development at Incyte Corporation during 2005 – 2016. He facilitated entry of over 20 compounds into the clinic, including approvals for ruxolitinib (Jakafi) and baricitinib (Olumiant).

As VP of Clinical Pharmacology and Experimental Medicine at GlaxoSmithKline, Bill evaluated numerous molecules in clinical studies in various therapeutic areas. He was involved in new or supplemental drug authorizations for a number of oncology drugs including Bexxar (lymphoma), Hycamtin (ovarian cancer), and Navelbine (non-small cell lung cancer) as well as ibandronate (Boniva) for osteoporosis.

As Head of Rheumatology Research at the University of Pennsylvania, he ran a major research program in receptor biology, collaborated with David B. Weiner, PhD to develop DNA vaccines and was able to bring novel DNA vaccines into the clinic for the treatment of cutaneous T cell lymphoma.

Bill earned his BSc. in Chemistry and Biotechnology from MIT and Medical Doctorate from Tufts University School of Medicine. He has worked in the molecular immunology laboratory of Mark I. Greene, MD, PhD, FRCP, at the University of Pennsylvania, developed novel methods of bioactive peptide design, and collaborated in the study of the activation of the p185/Human epidermal growth factor receptor 2 (HER2) receptor. HER-2 is a protein which is known to promote the growth of cancer cells. Bill is the named author to over 130 peer reviewed publications, over 15 patents and numerous Investigational New Drugs (INDs) and NDAs.

Professor Anna Wu
Panel Member

Anna M. Wu, Ph.D., is professor and chair of the Department of Immunology and Theranostics, co-director, Centre for Theranostics Studies and professor in the Department of Radiation Oncology at City of Hope in Duarte, California. Anna's research interests include engineered antibodies and proteins for targeting, imagining, and therapeutic approaches in cancer and immunology, including the use of SPECT, PET, optical, and multimodality approaches.

Anna also holds the title of research professor, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, where she previously served as professor and vice chair. While at UCLA, she also held positions as director, Cancer Molecular Imaging Program, Jonsson Comprehensive Cancer Centre, and co-associate director, Crump Institute for Molecular Imaging. She is a past chair of the California Breast Cancer Research Council, and fellow and past president of the World Molecular Imaging Society.

Anna is the co-founder and chief scientific advisor to ImaginAb and began her independent research career as an assistant research scientist at Beckman Research Institute of City of Hope and advanced to the position of professor of molecular biology in 2002.

Anna received her A.B. degree in biochemical sciences from Harvard University and a Ph.D. from Yale University in molecular biophysics and biochemistry (MB&B). Postdoctoral studies were conducted at Yale University (MB&B) and at University of California San Francisco in the Department of Biochemistry and Biophysics.

Dr. Jeff Evelhoch
Panel Member

Jeff retired from Merck Research Laboratories in 2000, where he was responsible for the development and qualification of novel biomarkers, use of biomarkers to inform pipeline decisions and the development and deployment of companion diagnostics at Merck.

Jeff joined Merck Research Laboratories in 2008 as Vice President and Head of Imaging and was named Vice President and Head of Translational Biomarkers in 2015. He joined Merck after four years at Amgen as Executive Director and Head of Imaging Sciences, which followed 2 years at Pfizer Global Research & Development and Pharmacia as Director of Structural Imaging.

Prior to joining the biopharmaceutical industry, Jeff was on the faculty of Wayne State University School of Medicine for 18 years, where he was a Professor of Internal Medicine, Cancer Biology and Radiology. He has a B.S. in Chemistry from West Chester University, received his M.S. and Ph.D. in Analytical Chemistry from the University of California at Riverside and was a postdoctoral fellow at Washington University in St. Louis. Jeff is now a consultant providing expertise in biomarkers and diagnostics.

Dr. Laura Dillon

Laura is the Head of Translational Biomarkers at Parthenon Therapeutics, a precision oncology biotech that is developing therapies to targe immune excluded tumors by reprogramming the tumor microenvironment. She is responsible for designing and implementing the company's biomarker strategy across preclinical and clinical activities, including the use of traditional and novel imaging and omics technologies and analysis platforms.

She has over 15 years of experience in industry, academia, and government. Prior to joining Parthenon, Laura was the Director of Pathology Data Strategy at AstraZeneca where she focused on the development of novel methodologies to extract information from imaging datasets and the implementation of non-invasive bioimaging techniques to advance the drug development pipeline. While at AstraZeneca, Laura served on the Steering Committee of the ImaginAb CD8 Consortium.

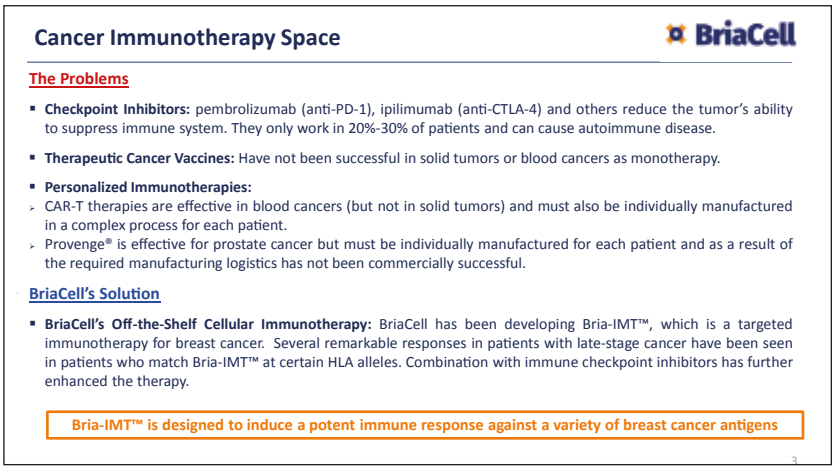
Laura has a Ph.D. in Bioinformatics and Genomics from the University of Maryland.

Keynote talk by Dr. William V Williams[1]

"Developing Novel Therapeutics to Destroy Cancer"

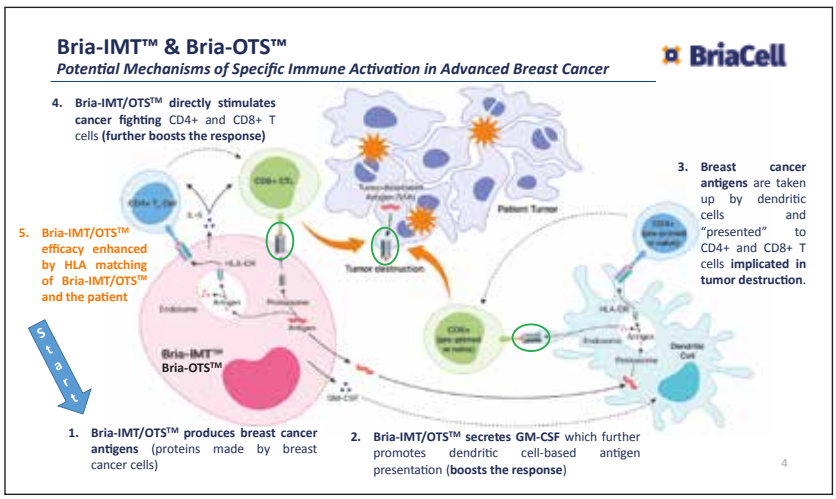
The Cancer Immunotherapy space if you look at it objectively, considering things like Check Point Inhibitors, Pembrolizumab, Ipilimumab, and others, all reduce the tumors', ability to suppress the immune system but they only work in 20 to 30% of patients even in the tumors where they work and in some tumors they don't work, certainly not as monotherapy and they can cause autoimmune disease.

So, a targeted immune response against the cancer would be better and therapeutic cancer vaccines have been tried but have not been very successful either in solid tumors or in blood cancers as monotherapy. Now personalized immunotherapies have emerged, such as CAR-T and Provenge, but they both require a personalized manufacturing approach which is very difficult.



Our solution is the development of targeted immune responses against the tumor using cellular immunotherapies, specifically what we call Bria-IMTTM. We've seen several remarkable responses in patients with late-stage cancer indicating that there is a mechanism of action that we can really capitalize on.

This is the way our therapy works. Bria-IMT is a breast cancer cell line that has features of an immune cell. It has been genetically engineered to produce GM CSF. And so, you can see starting on the lower left, that Bria-IMT produces breast cancer antigens proteins made by breast cancer cells. These would then be taken up by dendritic cells in the lower right, processed and presented to CD4 and CD8 positive T cells in the context of the HLA molecules. These T cells would then be activated, especially the CD8 positive T cells to go and attack the patient's tumor and to become tumor infiltrating lymphocytes were they can really address the issue at hand.

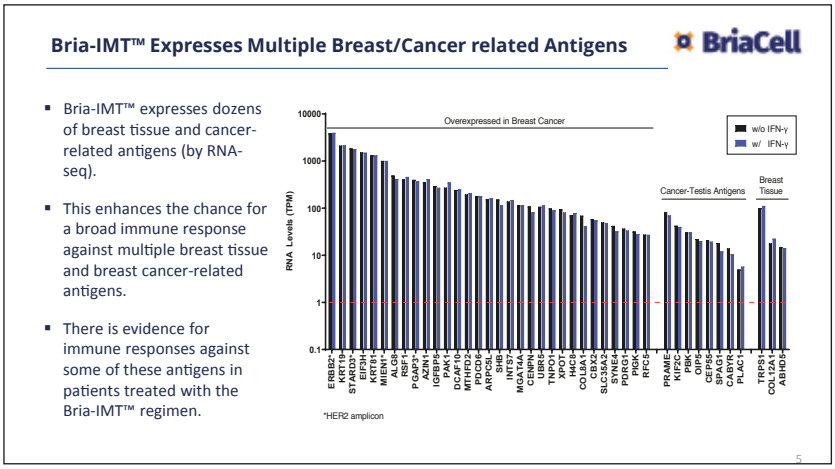


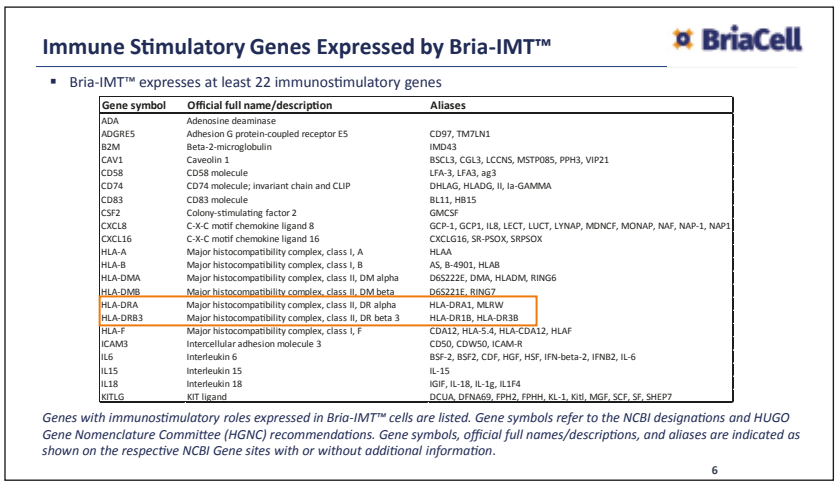
At the same time the Bria-IMTTM cells have been genetically engineered to make GM CSF. This further boosts the dendritic cell response. But what we think is relatively unique about Bria-IMTTM is shown on the upper left. We have shown that Bria-IMTTM can directly stimulate CD4 positive T cells and presumably CD8s in a mechanism that markedly boosts that response.

[1] There are forward-looking statements that accompany the key note talk by Dr. William V Williams. A copy of these can be obtained at info@imaginAb.com

That is how our therapy basically works. The cells are radiated before we administer them to the patient's intradermally. And we usually give them in combination with a couple other drugs namely low dose cyclophosphamide pre-dosed to reduce immune suppression. And then post-dose we follow up with local Alpha interferon inoculations to boost the immune response. In our Mono Therapy studies, we've undertaken cycles every two weeks for the first month and then once a month after that.

You can see here that Bria-IMT expresses multiple breast cancer related antigens. These are proteins that are either overexpressed in breast cancer and there's some Cancer-Testis Antigens which are very good targets for targeted immunotherapies and also a few breast tissue antigens. We believe that these particular antigens are going to be available to prime the immune system with our therapy.

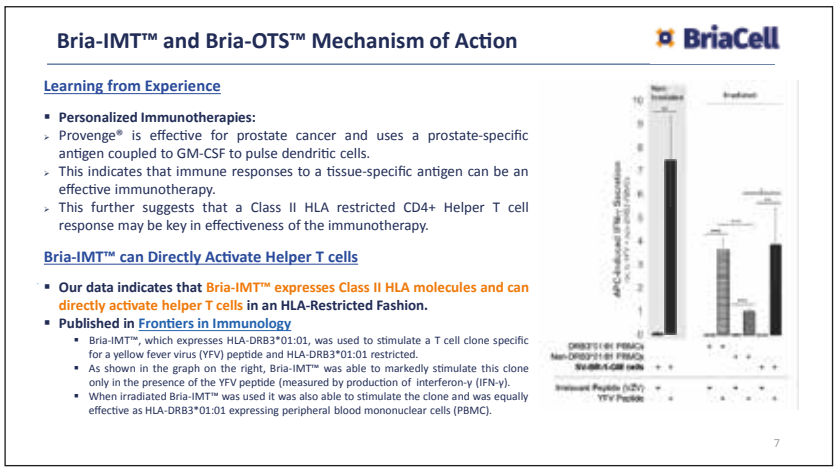




Gene symbol	Official full name/description	Aliases
ADA	Adenosine deaminase	
ADGRE5	Adhesion G protein-coupled receptor E5	CD97, TM7LN1
B2M	Beta-2-microglobulin	IMD43
CAV1	Caveolin 1	BSCL3, CGL3, LCCNS, MSTP085, PPH3, VIP21
CD58	CD58 molecule	LFA-3, LFA3, ag3
CD74	CD74 molecule; invariant chain and CLIP	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

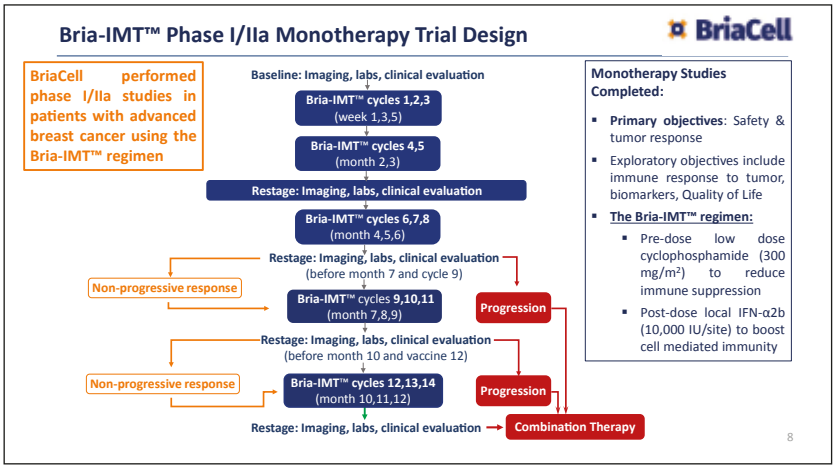
I should also mention that Bria-IMT expresses HLA-DR molecules namely DR Alpha and DR Beta Three which allows our cell line to act functionally as an antigen presenting cell. Some data on that is shown on this slide as presented in a paper by our Former Chief Scientific Officer Markus Lacher.

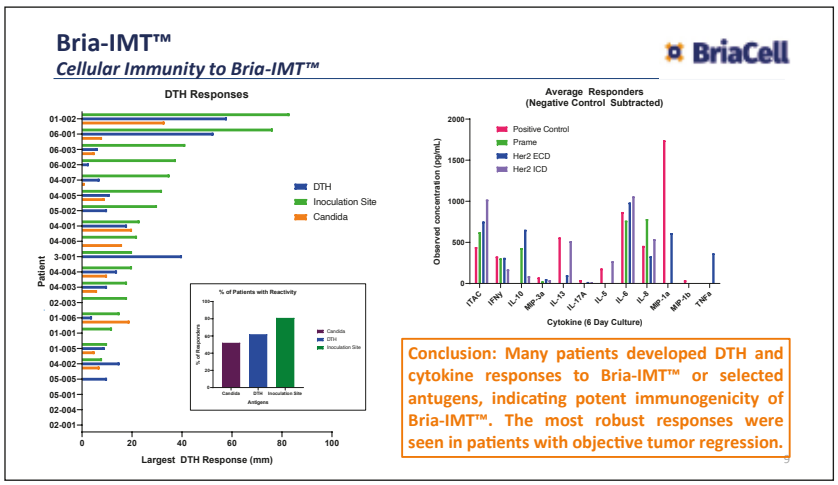
When the Bria-IMT cells were cultured with a T cell clone specific for HLA DR Beta 30101with a yellow fever virus peptide. You can see That in the context of the peptide, the T cell clone is stimulated to make gamma interferon, so this instigates an antigen specific HLA restricted activation induced by our Bria-IMTTM cells and this is even true for the irradiated cells as shown in the panel on the lower right.



We have done a couple of monotherapy studies and the design is basically that the patients come in, get their baseline imaging labs and clinical evaluation. And then they have the cycles I described every two weeks for the first month and then once a month after that. Then we restage the periodically. The prime objectives of course are safety and tumor response, but exploratory objects include tumor biomarkers, quality of life, etc. And I already mentioned the regimen: pre-dose low dose cyclophosphamide, post dose local Alpha interferon. The radiated Bria-IMT cells are inoculated into the patient's intradermally in the upper back and the thighs.

You can see that we induce a very robust immune response shown here on the left by delayed type hypersensitivity in some of the patients. We have two different readouts for the response to the cells. One is that we use a million cells in the forearm to match traditional DTH but then also we measured the inoculation sites. We use a test antigen, Candida, to see if patients are anergic.

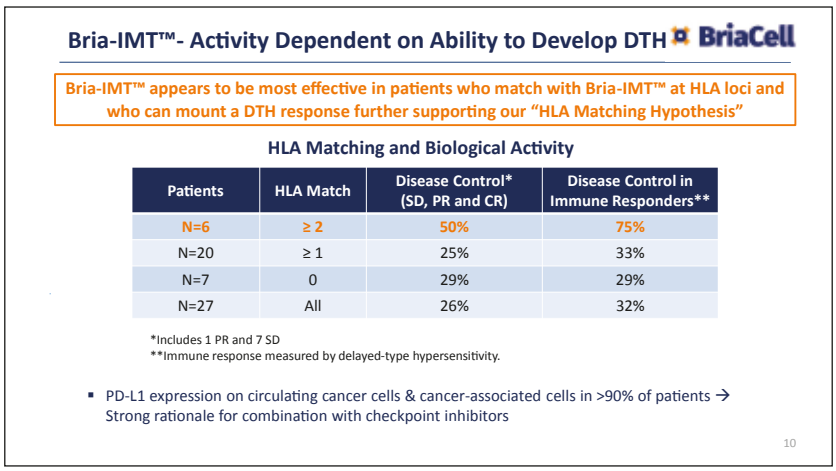




You can see that Bria-IMTTM is a very potent immunogen even in some patients who did not have a response to Candida we were able to induce a response against the cells. But then of course there are some patients who are so advanced that they cannot mount an immune response at all. And we are getting these patients in the late stages of their disease, third line or later.

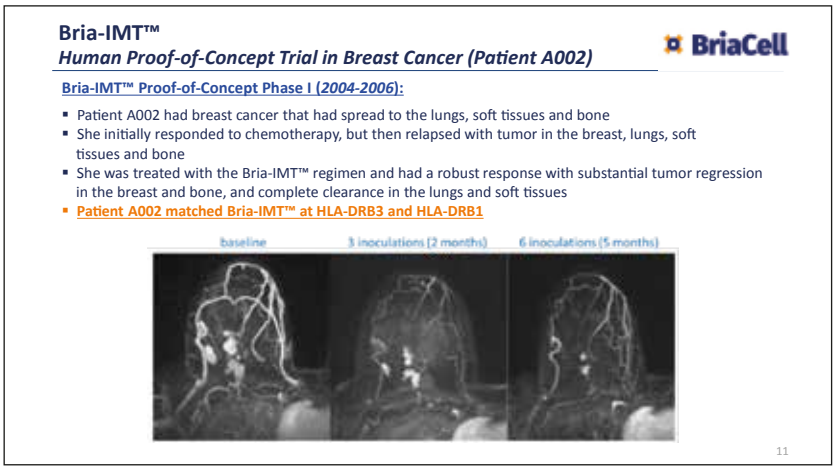
We also looked at some T cell responses in vitro to specific antigens that are expressed by Bria-IMTTM namely overlapping peptides of the Her2 protein extracellular domain and PRAME which is the cancer testis antigen, and we were able to show cytokine production in response to these specific antigens especially in patients who had good clinical responses.

We dosed a total of 27 patients with this model therapy regimen. If you look at all of the patients about a quarter to a third of them were able to achieve disease control in spite of having been treated, on average, with four prior chemotherapy or biological therapy regimens not counting hormonal therapy.

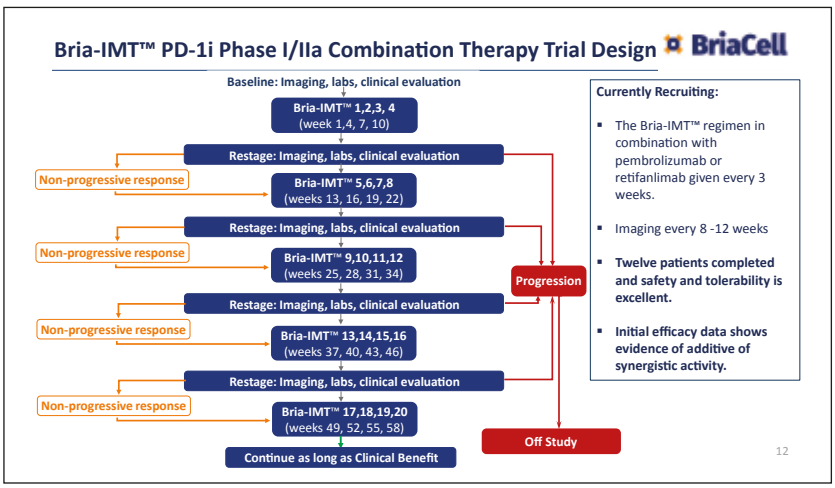


And in those who mount an immune response, our disease control rate is 32%. If you look at those who have no HLA matching with the cell line is it's around 30%, but specifically in those patients who have two or more HLA matches with Bria-IMTTM we see a higher disease control rate especially in immune responders. So, we think that that's a good marker for us to look at in terms of selecting patients to who will most likely benefit from our therapy.

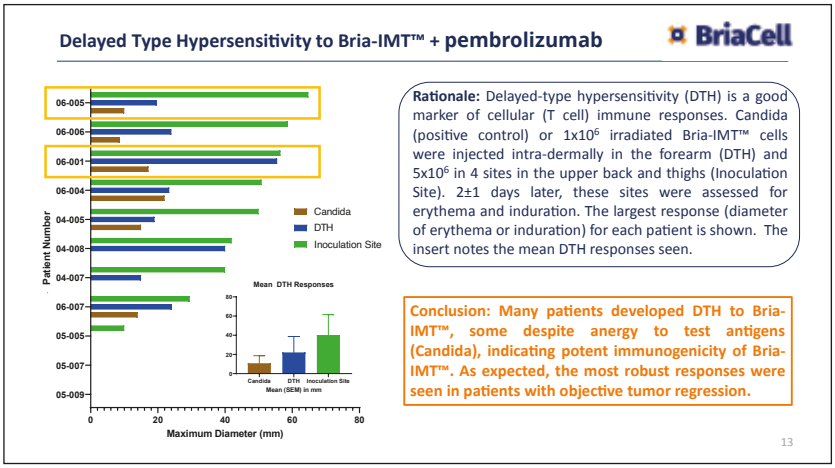
And here's one of the patients that had a very good response. She was a partial responder that had failed prior chemotherapy and had multiple metastasis in the breast as well as the lung, the soft tissue and the bone. You can see these breast lesions markedly decreased with the therapy over five months after six inoculations she had disappearance of a lung lesion and disappearance of soft tissue lesions and improvement in the bone. So again, a Double HLA match and we think a good sign that we have a therapy that works with this regimen.



We then decided to do a combination therapy study in combination initially with Keytruda that has since transitioned over to a combination with retifanlimab which is Incyte'sPD-1 inhibitor and works by the same mechanism as Keytruda. In this case we switched our cycles to every three weeks adding the Keytruda on top of the basic regimen to be given once every three weeks.



Again, we saw some patients who were unable to mount the delayed-type hypersensitivity response but then there were others who had very robust delayed-type hypersensitivity responses. And you can see that again this was even more pronounced compared to the positive control test antigen Candida, so a very potent immunogen.



And we also saw some very good data in regard to Disease Control in this group. Again, they had been very heavily pretreated with an average of five prior regimens, and you can see that with immune responders there is clearly a correlation with HLA matching and those patients who were able to achieve disease control which includes one PR and three stable diseases. So, we believe we're getting some very good immune responses generated. Presumably their immune cells are going to the tumor and attacking the tumor.

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

BriaCell

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.

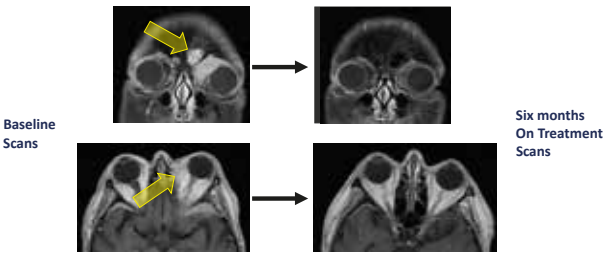
Bria-IMT™ appears to be most effective in patients who match with Bria-IMT™ at HLA loci and who are able to mount a DTH response further supporting our "HLA Matching Hypothesis"

14

Bria-IMT™ + Immune Checkpoint Inhibitor: Remarkable Responder

BriaCell

Tumor behind the left eye causing proptosis completely resolves



Complete resolution of orbital tumor in a heavily pre-treated patient with 2 HLA matches and a grade II tumor supports remarkable activity of the Bria-IMT™ combination regimen, and it is worth noting that checkpoint inhibitors have not proven effective as monotherapy in advanced breast cancer

15

But that's what the ImaginAb technology is going to help us with. I want to mention one particular lady who came in. She'd failed 12 prior regimens and had a large orbital tumor (behind her left eye) which was causing proptosis. She had tumors in the dura matter which is the outside lining of the brain and then she has a tumor in her adrenal gland. And, with the tumors behind her left eye completely resolved, the eye went back in place, and she had improvements elsewhere. Again, she was a double HLA match.

We also saw what we believe is a survival benefit in this study. If you look at patients with third line or later breast cancer their median overall survival is seven to ten months. We saw 12.1 months in spite of the fact that our patients are typically beyond the third line in these studies, with most of them on the average seventh or eighth line in this particular subgroup of patients.

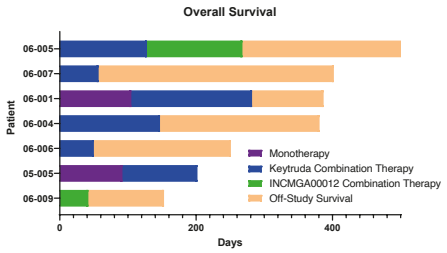
Bria-IMT™ + PD-1i Combination Survival

BriaCell

Median Overall Survival
12.1 months

A recent publication of overall survival in third line metastatic breast cancer in similar patients showed a median overall survival of 7.2 - 9.8 months (depending on treatment)

Kazmi S, Chatterjee D, Raju D, Hauser R, Kaufman PA. Overall survival analysis in patients with metastatic breast cancer and liver or lung metastases treated with eribulin, gemcitabine, or capecitabine. Breast Cancer Res Treat. 2020 Aug 17



We believe the Bria-IMT™ regimen in combination with checkpoint inhibition may have survival benefit in advanced breast cancer

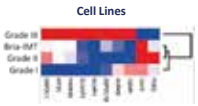
16

Bria-IMT™ in Grade I/II Tumors

BriaCell

Breast Cancer Grade Correlates with Response

- Bria-IMT™ is derived from a grade II (moderately differentiated) breast cancer.
- Genes expressed by Bria-IMT™ match best with grade I/II-derived Breast Cancer Cell Lines
  - ~40% of recurrent breast cancers are grade I/II



Monotherapy Study

5 / 7

Grade I/II patients with immune responses had clinical benefit (5/7 = 71%)

- Patients very heavily pre-treated, median of 7 prior regimens

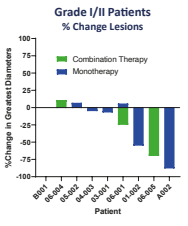
Combination Study

3 / 3

Grade I/II patients with immune responses had clinical benefit (3/3 = 100%)

- Patients very heavily pre-treated with 14-15 prior regimens

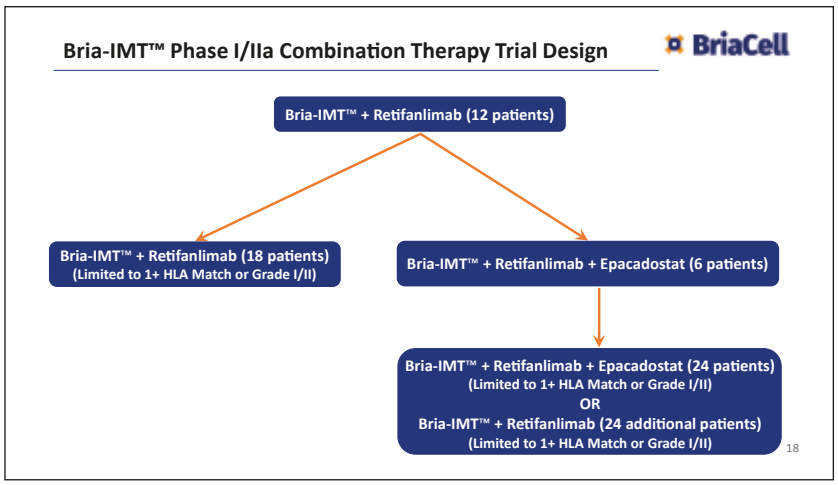
- **Median Overall Survival of 12.5 months**
  - Recent publication in 3rd line patients *(Kazmi S et al Breast Cancer Res Treat. 2020 Aug 17)* showed a median overall survival of 7.2 - 9.8 months



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

17

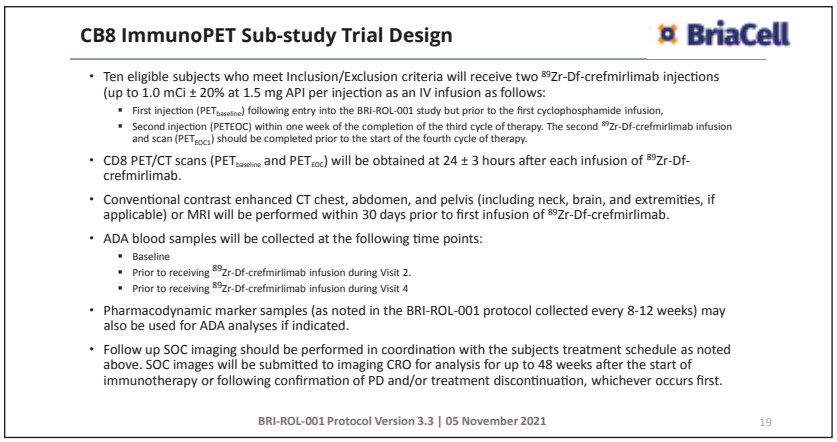
One other subgroup that we're very interested in are patients with grade one or grade two tumors. Bria-IMTTM was derived from a grade two moderately differentiated tumor breast cancer tumor, and it matches genetically most closely with other grade one or grade two breast cancer cell lines. It does not match as well with grade three. Grade one is well differentiated, in other words, it maintains some of the architectural features of normal breast tissue, while grade two is moderately differentiated and grade three is poorly differentiated. So, when we looked at our subgroup of patients, with this particular marker of grade one and grade two in our monotherapy study, 71% had clinical benefit. In the combination therapy study, all three of the patients with grade one or grade two tumors had clinical benefit, a good survival rate of 12.5 months compared to 7 to 10 months for those with typically with third line disease and the tumor size reductions you can see in the lower right whereas others had stable disease.

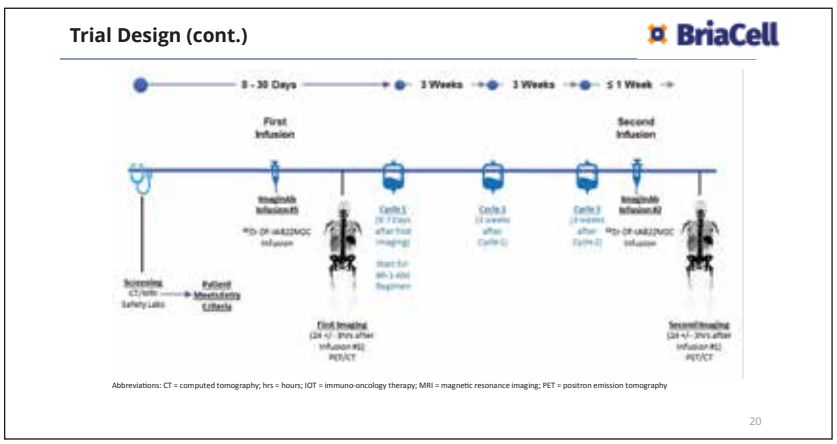


This is our ongoing study right now. We are in combination with Retifanlimab looking at 12 patients, initially to establish safety and then we'll expand that, focusing on the patients with one or more HLA match or with grade 1 or grade 2 tumors because those arethe subsets most likely to benefit. After the initial 12 patients we will expand the double combination in 18 patients, focusing on those most likely to benefit and in parallel with that expansion group, we're going to look at a triple combination, adding Epacadostat in collaboration with Incyte, who are providing both Retifnlimab and Epacadostat for the study.

And then we'll either expand the triple combination or further expand the double combination depending on how the data looks.

This of course is where The CD8 ImmunoPET Study comes in. We're doing a sub study in 10 eligible patients where they will be treated with our combination therapy. Then they'll also have the CD8 ImmunoPET imaging done at baseline and then after their third cycle of therapy. And we'll also be looking at pharmacodynamic marker samples throughout this to evaluate safety, but the basic design of the study is shown here. The patients will be screened if they meet entry criteria. They will be in the phase 2A part of the study and will have their baseline imaging with the ImmunoPET technology. Then they'll receive three cycles of therapy, and then we will repeat the CD8 ImmunoPET imaging to look for tumor infiltrating lymphocytes.





We're very excited about this work and getting this study going. Our patients are very heavily pretreated and were very hesitant to do biopsies. It's certainly something that does not encourage them to come into our study, so CD8 ImmunoPET technology allows us to look for tumor infiltrating lymphocytes non-invasively and in a way that you can avoid skip lesions. Sometimes if you do biopsy, you can miss the tumor infiltrating lymphocytes, so this is going to be very beneficial to us in our clinical program.

Question and Answer Section

Question

Based on your experience, what is the greatest value or benefit for incorporating CD8 imaging into I-O clinical trials or research?

Answer by Dr. William Williams:

I think that there's a tremendous advantage to be gained from this, namely that you can find out if the therapy is working the way it ought to. All of these immune-oncology therapies basically work by causing immune cell infiltration into the tumor so that the tumor can be attacked by the immune system. And our therapy does, in some ways, target CD4 cells, but one of the things that we've noticed, and I think it's a general feature of the immune system, is that all of the responses tend to travel together. In our patients where we've seen CD4 responses, we see an antibody response, so presumably there is also a CD8 response. So, it's a great marker for an immune response in general with the cells getting into the tumor. I think the CD8 ImmunoPET technology creates a tremendous amount of potential and also the fact that it images the entire tumor and not just a little piece of it so you can really see what's going on.

Answer by Dr. Jeff Evelhoch:

I'll answer from the perspective of trying to find drugs to combine with checkpoint inhibitors.

As Bill pointed out in his talk, many of the patients do not benefit from the checkpoint inhibitors and I think 30% is a generous estimate. But we know if we can activate those tumors' immune system, then more patients will have more chance to benefit from the checkpoint inhibitors.

Monotherapy studies with checkpoint inhibitors are pretty much completed now and the focus is on what can you combine with the checkpoint inhibitor to activate the tumor and benefit more patients. There are several examples out there with chemotherapy where it clearly provides a benefit, but we very much want to get away from the toxicity associated with the chemotherapies.

Therefore, the ability of the CD8 PET tracer, to identify agents which can activate tumors provides a really important mechanism for screening in early studies. It can provide evidence for the pharmacodynamic effect of activation of the tumor, taking a cold tumor and turning it hot, which then may benefit from treatment with check point inhibitors. If you look for those agents which can activate more of the tumors than others, then you know that's where you're going to want to invest and try to move forward fast to see if it has benefits.

Answer by Dr. Laura Dillon:

For me the greatest value really is in the 'whole-body assessment' that we get from ImmunoPET and being able to evaluate multiple tumors each in their entirety. Bill has already talked about how it is valuable to be able to look at the whole tumor instead of biopsy, but there are more tumors throughout many of the patients' bodies who we're seeing in our clinical trials. So using it in the context of a clinical trial allows us to monitor the CD8 infiltration across multiple lesions at multiple time points, see how they are changing in response to treatment, and then be able to pick up on pharmacodynamic responses even if we're not seeing response at the whole patient level - a clinical response that we can actually identify - we could see if there's something happening in terms of the tumor microenvironment.

Answer by Professor Anna Wu:

I'd just like to expand upon what Laura said, the ability to image the whole body, so you can look at intra-tumoral as well as inter-tumoral variations and heterogeneity. And the fact that you don't have to do invasive biopsies. Once patients have advanced disease, we really can't go in and biopsy everything. But to treat the patient we need to understand what's going on in the whole patient. And I think there's also a lot to be learned by, at the same time, keeping an eye on what's happening in the immune tissues - spleen, draining lymph nodes, bone marrow, etc. as we might learn some interesting things about how the immune system is working, especially with some of these novel therapies.

Question

Do you think CD8 PET in general can help you determine whether a tumor is hot or cold or excluded, or is that something that you think about from a clinical development point of view or how you annotate these tumors?

Answer by Dr. William Williams:

Our goal is to turn cold tumors hot. And so, the CD8 infiltration, it is kind of the definition of a hot tumor, so if you see that at baseline then you know that you've already got an immune response going on which then of course you now have the opportunity to further boost and also to take the foot off the brakes with something like the checkpoint inhibitor in combination.

But if you do your ImmunoPET Study up front and there's nothing there, then you know that you're going to have to induce an immune response and actually go in and get the tumor infiltrating lymphocytes in there. It helps in both cases, because you can see a cold tumor turn hot and the hot tumor turn hotter with this technology.

Question

In your opinion, when is the best time to implement CD8 imaging into your clinical development cycle? So, in so many words, when should you start thinking about it, and which clinical trials do you think it's best suited to implement CD8?

Answer by Dr. William Williams:

We're using it in a Phase I-IIa study, but we are limiting it to the Phase IIa part. And the reason is very simple, The Phase I part is to establish safety. In my opinion, if I don't know if my drug is safe yet, I don't really want to spend the money to do additional imaging studies. It just doesn't make any sense.

But as soon as we clear that early hurdle, which usually just takes a few patients, then I think that's really the time to get in there because you can see mechanistically if your drug is working the way it ought to. We should be working by inducing tumor infiltrating lymphocytes including CD8 cells, and we want to see very early on, if we're capable of doing that, at least in some patients.

And that's why I think it's very appropriate to go in very early with this. On the other hand, it can also be used later, because then you can correlate the patients who are developing an effective immune response and CD8 infiltration into the tumor with other biomarkers that may help you to select which patients are most likely to benefit from your therapy. So, I would say coming in early, but then sticking with it is probably a good idea if that's feasible.

Answered by Dr. Jeff Evelhoch:

I would agree that one of the primary places to focus on, as I mentioned in my response to the prior question, is in early development. And as Bill pointed out, since Phase I is with a small number of patients it's difficult to get meaningful information out of it, so once you've identified the dose that you want to expand on, it does make sense that's where you want to get the information.

However, I would hope that the clinical trial designs evolve because I think the tracer can also provide useful information on what is the right dose, when those rising doses are being evaluated in terms of safety, you're looking for responses, but responses are hit or miss, and you can sometimes be very misled as to what dose. And often you end up going forward with the highest dose that you can, which may not be optimal, and you may be wasting resources and be risking possible side effects. So, I would hope that as programs evolve, not only are you looking at what is the maximum dose, but you're also looking at where you are higher than you need to be.

Answer from Dr. Laura Dillon:

I'm really in favor of introducing the CD8 imaging during the latter half or so the dose escalation, so once you think you're at a dose where in fact there could be some activity. This is in line with what I spoke about before, in that sometimes you could see a pharmacodynamic activity evident in some tumors but not all tumors so this is where that whole body data really becomes extremely important as you know far more compared to what you would get with just a biopsy.

This is the approach we're taking at Parthenon. It's my expectation that incorporating the CD8 ImmunoPET early in our trial will help us to pick up on PD responses even if we're not seeing something otherwise. I'm excited to use the CD8 imaging this way, to help us understand the heterogeneity in response within lesions, which will give us increased confidence in proceeding with our dose escalation and our dose selection.

It can also be used to inform our patients selection strategy to guide further development and the design of our future trials.

Answer from Professor Anna Wu:

At City of Hope, we're a Phase II site, but we're also looking into some investigator-initiated studies as well, with one example being to add CD8 ImmunoPET into existing standard of care radiation therapy to see what is happening.

This is a really hot field these days in considering the effect of radiation therapy on inducing immune responses and how it can be monitored and capitalized on it. As you can see, there is a lot of interest in bringing CD8 imaging into new treatment areas.

Question

Can you comment on differences in binding kinetics in your engineered Ab fragments? Is the speed of clearance affecting the amount of fragment binding to the site? (I am thinking on the effectiveness of using fragments to deliver therapeutics).

Answer from Professor Anna Wu:

In terms of targeted radiopharmaceutical therapy, this has been a long-standing interest of mine and is one of the reasons I developed the minibody fragments. We were working on targeted delivery of radioisotopes, and I think the minibody has some key features. The ones we work with our very high affinity, they're a single digit nanomolar or lower so they bind very well, they target fast, and they clear fast.

In the field, those of you who do drug development, and understand pharmacokinetics, you know it's always a balance between exposure and clearance. But if you are working with radiopharmaceutical therapies, you have a drug that's active all the time, so we've got to look at not only how much is getting into the tumor but where it's going if it's not. You need to consider potential bone marrow toxicity or does to the liver or kidney. You have to look at the whole picture over time and that's where we like the potential of the minibody because it targets fast, but it clears via the liver which is relatively radio resistant. And the concept there is that we minimize toxicity to bone marrow and to kidney which is more radiosensitive. Therefore we are able to deliver more effective levels of activity to tumor, so it's an area that we've been long interested in and continue to work on.

Question

Considering your time with Merck (Jeff) and AstraZeneca (Laura), when did you become confident of incorporating CD8 into your trials? And Laura, as you were part of the CD8 Consortium[2], could you reflect that involvement in your response?

Answer from Dr. Jeff Evelhoch:

I think when we first gained an interest in really pursuing and incorporating them in clinical trials is when we saw the preclinical results that showed the ability to see the CD8 tracers and then being able to identify tumors that had been activated.

I think what really sealed the deal for the clinicians, was when they saw the first human results and saw that just looking at the images, it made sense where the tracer went and they thought you were imaging CD8. Then, when you looked at the comparison between tumors and biopsies, and found it was as good as you could expect for any comparison between an agent that's imaging the whole tumor and a biopsy that's looking at the small part of the tumor. I think that was what really sealed the deal and put on the gas in terms of getting the agent into our clinicals trials.

Answer from Dr. Laura Dillon:

I was confident in the technology after viewing some of the clinical data that was shown as part of the CD8 Consortium[2] and also from ImaginAb's own data. This allowed us to see the variability within and between tumors assessed by CD8 PET.

And it was clear to me that we're really missing a lot by relying on biopsies, where again you're looking at a single tumor and not even that whole tumor but just a small piece of that one tumor. Don't get me wrong, I don't think we've solved the world with CD8 PET imaging, and there's still a lot of opportunity to learn how to better utilize the data, especially regarding what normalization may be necessary to compare the data between subjects and compare tissues in a single subject, as well as how to interpret the data. It's great to have this wealth of data from all these different tumors, but tumors sometimes respond differently to therapy, so now we have to figure out a way to bring that data together and assess what we actually think is happening in the patient.

But the data, even as it is now, with our current level of understanding, I think is extremely valuable and already very interpretable. Being able to compare changes to individual lesions over time, so the pre and post treatment measurement, really is the paradigm that I'm most interested in using in the near term.

One thing I don't think we really touched on and that I was very impressed with in viewing the data was the success rate of getting the imaging data. I assume I'm not the only one that's had the experience of requesting biopsies or you require biopsies, and they're taken, or you think they're taken but then you finally get a look at what you actually have at the end of the day, and if you're expecting 20 paired biopsy you only have, for example, six that are actually usable. And clearly there are a lot of problems with that, but with imaging, at least what I've seen so far, that's really not the case. You get the image data every time3 unless there's a very rare case where something went wrong but you would expect your success rate of actually getting usable data to be extremely high. This is also really, really appealing and one of the reasons why I'm really excited to have data using CD8 PET from our Clinical Trials.

[2] The CD8 Consortium is a multi-party collaboration agreement between AstraZenica, Pfizer, Takeda Pharmaceutical Company and ImaginAb, focused on furthering the clinical development of ImaginAbs' CD8 ImmunoPET technology.

Question

BriaCell have an agreement with ImaginAb so can you first of all explain why you decided to include us as part of your structure. In addition, in your keynote presentation you said you're going to use our agent in a 10-patient study design, how did you figure out 10 patients may be enough for the answer that you wanted to achieve?

Answer from Dr. William Williams:

I'll answer the second part first. The 10 patients' portion is just the safety run-in. And then we will have the opportunity to expand to get data on additional patients as well. Obviously a 10-patient study is not a powered study. When I was at GSK, there was also always a discussion with statisticians trying to distinguish between an exploratory study where you're trying to figure out what the power would be for a later study and the actual powered study.

This comes up over, and over again in clinical study design so it's an important concept, but you need to get something to power your study based on. And the 10 patients should help us do that as we go forward.

The other part of the question was how we decided to get involved with ImaginAb doing the study. We'd been looking for a way to non-invasively find out if we're inducing tumor infiltrating lymphocytes in our patients and your technology looked like a very promising method to do that.

Tumor biopsies are never fun for the patient to do. I actually have always had a dislike for subjecting late-stage cancer patients to more than they need to be subjected to. One of the main advantages of immuno-oncology is that the therapy is better tolerated than chemotherapy and that these patients who are in dire straits don't have to be subjected to terrible side effects.

While the same is true of biopsies I think that there's a lot of ethical reasons to support this kind of approach to imaging and finding out about tumor infiltration with lymphocytes. But there's also the practical aspect that the approach is certainly more acceptable for patients than to have biopsies done.

Question

What do you think the importance of measuring CD8 activational status is? Just expanding this a little, from your perspective, we know that CD8 ImmunoPET measures the total CD8, and can I ask, from your perspective, what is the relevance of this?

Answer from Professor Anna Wu:

A key point, in addressing this question, is that there's many different subsets of CD8 T cells, in different states, as well as different subsets, but I think our approach has been "if you don't have The CD8 T cell there, you really have a challenge". So having CD8 T cells there is key.

I also think, especially with our pre-treatment and on-treatment scanning protocols, that we can see significant changes in CD8, and I think when you see an increase and influx of those tumor infiltrating CD8 cells, that clearly is a hallmark of a very active immune response and that we'll be able to show that it correlates with a response.

Nevertheless, there are a variety of additional markers that one can look at more specifically on the activation state. And this can then become a complicated story in regard to which markers you look at; and if you want to look at more than one marker can be a challenge. In summary, I do think that the fact that you see an influx of CD8 T cells right there is telling you that you've got a healthy and hopefully effective immune response going on.

Answer from Dr. Laura Dillon:

I think that the choice of CD8 versus potentially something that would look at activation status comes down also on the mechanism of action of your drugs. Certainly, building on Anna's point, if you're expecting, or you know in preclinical study that you're seeing a large influx of CD8s, I think that's actually probably the better thing to measure, but if you know from your experience with your drug that you're not expecting to see significant changes in CD8 numbers then maybe this wouldn't be the technology for you and you would think of an alternate way of going at that.

Answer from Dr. William Williams:

I think that the state of CD8 activation is going to become obvious because the tumor will shrink if they're activated and it won't if they're not, so the other standard imaging that you're doing is correlated with what's going on with the CD8 ImmunoPET. My thought is that it's going to be a rare patient where there's a large influx of CD8 cells and nothing happens to the tumor, but you know that's something that remains to be seen as these studies continue.

Panel member views

...of some of the latest developments in the field of biomarkers, imaging and in immuno-oncology drug development.

Professor Anna Wu:

It's a very exciting time to have tools to image the immune system in action. CD8 is one part of it and I think that we need to work in concert with teams who are working on biomarkers to understand what other markers would be useful to image, whether they are lineage markers of different cell types or whether they are activation markers.

To me, the holy grail would be some universal market that tells us the overall immune state of a tissue. Is it immunosuppressed? Is it inflamed? However, immunology's complicated, so I don't know if there's an easy answer to that, but to reemphasize, I think the importance of being able to look at the immune system in action, and not just in immuno-oncology, because immune responses have potential relevance for so many other conditions.

We're just beginning to tap into what we can do with this kind of very specific molecularly targeted imaging agent. And again, I'll put a plug in for antibodies, because they do offer this incredible specificity to start to look at these questions in vivo.

Dr. Laura Dillon:

In the imaging and biomarker development space there's definitely a move towards modalities that are less invasive, especially as companies are increasingly competing with one another for patients to enroll in their clinical trials.

I don't think anytime soon we're going to be moving completely away from biopsies. We certainly are continuing to try to collect them at least in some settings. I'm very interested in biomarkers based on multiplex immunofluorescence and looking at multiple immune cell types in addition to targets of interest. And then certainly there's a lot of activity in the H&E biomarker space using artificial intelligence methods.

Going more towards the less invasive, there's also this big increase in people trying to look at blood-based biomarkers, although I think the downside of that is that it isn't really providing a direct measurement of the tumor microenvironment and it certainly doesn't allow us to assess any signal that is coming from different tumors if tumors are behaving differently. So, PET imaging really is attractive because it's both non-invasive and it provides data on specific tumors. It can be done over time and I'm already seeing multiple applications for how can be used to look at target distribution and to monitor cells in the tumor microenvironment.

One of the more interesting uses I've seen recently is serial utilization of multiple PET probes against different targets. This can be done when the first probe in the sequences uses a shorter-lived radio isotope, so that a second one, like CD8 could then be done afterwards in fairly short order. So, I expect we'll continue to see some of these more kind of creative designs and uses of PET.

I'm excited to also see developments coming in PET/CT Image Analysis. It's clear to me that there's value gained in assessing all lesions for a patient rather than just to get a very limited number of the target lesions. However, right now looking at all the legions and finding all of them is very time consuming and therefore, it is very expensive and needs novel solutions to help reduce this bottleneck. There is an opportunity here for AI for tumor segmentation, that will also be increasingly possible to develop as more data become available.

But then, as I mentioned before, comes the complexity of how you interpret all this data from multiple lesions. This is another area that's being worked on, and I expect we'll see some progress on that the near term.

In summary, there's a lot of value to be gained from implementing CD8 PET in early I-O trials and I expect this value will only increase as additional analysis method comes on. I and my colleagues at Parthenon are very much looking forward to using PET in our own trials.

Dr. Jeff Evelhoch:

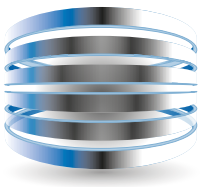
I will try to keep it short and reemphasize the blood-based biomarkers Laura mentioned because I think that it has to be one of the ways to go, there's no question about it.

But blood-based biomarkers only provide an integrated measure of what's in the body. If you can detect meaningful information, then the presence of various different biomarkers that can give you both a status of the patient overall and an indication of what would be the best drug to treat with would be a wonderful thing for patients.

The other thing that I'm curious to see is, as Laura mentioned, artificial intelligence methods for analysis of imaging. One of the things that's being looked at a lot is the CT images which you generally think of as being uninformative. But it turns out there are a lot of different things that are in there that the eye can't see that have useful Information. And it appears that even at base line there's good information. And certainly, when you look from baselines to the change after the first study after treatment, it's amazing to see how well it predicts whether the patient's going to respond or not. So, there's information in those images and I'm interested to see how that plays out as well.

Dr. William Williams:

I think that this is a tremendous opportunity to gain important information on how our drugs are working in our patients in the future. I'm hoping that you'll also produce CD4 ImmunoPET maybe CD14. There's a lot of things that we would love to see! The other part that this may allow us to do is to image the tumor. We've noticed in our study, where we've been looking at circulating cancer cells and cancer associated cells, in over 90% of our patients express PDL-1 and it goes up with therapy in some patients so that would be a fantastic thing to be able to look at. I think this type of technology has a tremendous potential and I'm looking forward to seeing it develop over the coming years.



ImaginAb

Challenge • Create • Transform

ImaginAb Inc
Head Office
423 Hindry Ave.
Suite D
Inglewood
CA 90301
Tel: +1.310.645.1211

ImaginAb Ltd
European Office
Lily Hill House, Room 11
Bracknell, Berks
RG12 2SG
England
Tel: +44 (0) 1344 390 536