TOP-LINE RESULTS FROM VESIGENURTACEL-L (HS-410) IN COMBINATION WITH BCG FROM A RANDOMIZED, BLINDED PHASE 2 TRIAL IN PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC)

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Background

Non-muscle invasive bladder cancer (NMIBC) is a common malignancy managed with endoscopic surgical resection, and adjuvant intravesical treatments for T1 and high-grade Ta. Treatment goals in this minimal residual disease setting are ideal for immunotherapy: to reduce local disease recurrence following surgical resection and to prevent progression to muscle invasive bladder cancer (MIBC).

Bacillus Calmette-Guérin (BCG), is an intravesical immunotherapy which remains the mainstay of NMIBC treatment since 1976. With adequate surgical resection and BCG treatment, about 53-63% of newly-diagnosed patients will remain disease free at 1-year. The current model of BCG's mechanism of action (MOA) proposes direct cytotoxicity of the urothelium (and tumor) and an indirect effect by immune cell mediation. Given the MOA, combining T-cell activation strategies with BCG could potentiate the effect of BCG.[1,2]

Vesigenurtacel-L (HS-410) is a vaccine comprised of an allogeneic cell line, PC3, selected from a series of bladder cancer cell lines for high expression of known bladder cancer antigens. The cell line was stably transfected with a plasmid that induces the expression of a modified, secretable, heat shock protein, gp96-Ig, which is a versatile chaperone protein. The vaccine expresses a repertoire of multiple tumor antigens (including but not limited to MAGE-A3, survivin, LAGE-1, etc.) that are chaperoned by gp96-Ig. gp96 has dual antigen binding and adjuvant activity and delivers these cell-derived antigens directly to a patient's antigen presenting cells and shuttles those antigens to MHC-I. Preferential trafficking to MHC-I leads to exclusive activation of CD8+ cytotoxic T cells and enables vaccination across MHC barriers.

Here we present, for the first time, unblinded primary endpoint data (1-year Recurrence-Free Survival (RFS)) from a randomized Phase 2 trial with vesigenurtacel-L in combination with BCG in NMIBC. Trial ID: NCT02010203

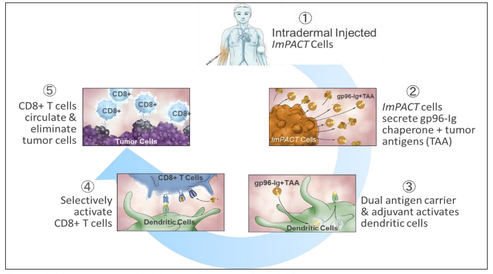


Figure 1: Vesigenurtacel-L Mechanism of Action (MOA)

Vesigenurtacel-L (*ImPACT*) cells are injected intradermally into the patient (1). Vesigenurtacel-L cells secrete TAA-gp96-Ig protein complexes (2), which act as a dual antigen carrier and adjuvant. Dendritic cells are subsequently activated (3) leading to the selective activation of CD8+ T-cells (4). CD8+ T-cells circulate within the patient's body and eliminate encountered tumor cells (5).

References

1. C. Biot, et al, Preexisting BCG-specific T cells improve intravesical immunotherapy for bladder cancer. Sci. Transl. Med. 4, 137ra72 (2012).
2. G. Redelman-Sidi, et al. The mechanism of action of BCG therapy for bladder cancer—a current perspective. Nature Reviews Urology 11, 153–162 (2014)

Trial Design

Phase II, Randomized, Blinded, Placebo-controlled trial

Primary Endpoint: 1-year recurrence free survival

Secondary Endpoints: Timepoint Recurrence/Progression; Immune Response

Exploratory Analyses: Broad immune response profiling

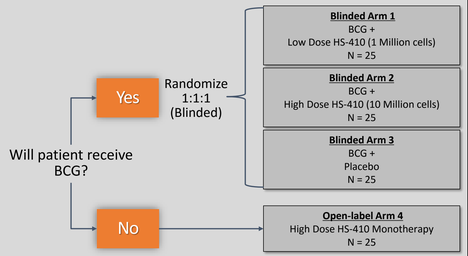


Figure 2: HS410-101 Trial Design

Patients who would receive BCG were centrally randomized into one of three blinded treatment arms. Arms were stratified at the time of randomization by baseline risk category (intermediate- or high-risk) or concomitant CIS (yes or no). Patients were assigned sequentially to the open label monotherapy arm.

Inclusion/Exclusion Criteria

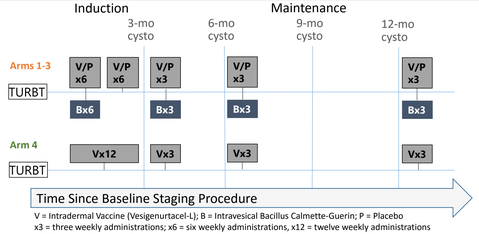
KEY INCLUSION CRITERIA:

- Intermediate- or high-risk NMIBC (Ta, T1, TIS)
- Concomitant CIS is permitted
- BCG naïve or BCG recurrent (>12 months since last BCG)
- Suitable for intravesical induction and maintenance BCG
- Adequate organ function

KEY EXCLUSION CRITERIA:

- Neo-adjuvant therapy prior to staging procedure
- Prior vaccination with BCG for tuberculosis
- Prior cancer vaccine for this indication
- Known immunodeficiency disorders (e.g. HIV); infections or illness requiring steroids or other immunosuppressive therapy
- Concomitant investigational treatment

Schedule of Events



V = Intradermal Vaccine (Vesigenurtacel-L); B = Intravesical Bacillus Calmette-Guerin; P = Placebo
x3 = three weekly administrations; x6 = six weekly administrations, x12 = twelve weekly administrations

Demographics and Patient Characteristics

	Arm 1: BCG + Low Dose Vesigenurtacel-L (N=26)	Arm 2: BCG + High Dose Vesigenurtacel-L (N=26)	Arm 3: BCG + Placebo (N=26)	Arm 4: High Dose Vesigenurtacel-L (N=16)
Age (Years)				
Median	72	69.5	70.5	73
Minimum	35	40	55	45
Maximum	93	87	88	87
Gender n(%)				
Male	23 (88.46%)	21 (80.77%)	20 (76.92%)	13 (81.25%)
Race n(%)				
White	26 (100.00%)	25 (96.15%)	23 (88.46%)	16 (100.00%)
African American	0	0	2 (7.69%)	0
Asian	0	1 (3.85%)	0	0
Other	0	0	1 (3.85%)	0
Treatment Status				
BCG Naïve	18 (69.23%)	16 (61.54%)	16 (61.54%)	7 (43.75%)
BCG Recurrent (>12 mo)	8 (30.77%)	10 (38.46%)	10 (38.46%)	9 (56.25%)
TNM Classification				
T1	12 (46.15%)	7 (26.92%)	11 (42.31%)	4 (25.00%)
TA	7 (26.92%)	11 (42.31%)	10 (38.46%)	11 (68.75%)
TIS	7 (26.92%)	8 (30.77%)	5 (19.23%)	1 (6.25%)
Carcinoma in situ				
Yes	11 (42.31%)	11 (42.31%)	9 (34.62%)	4 (25.00%)
No	15 (57.69%)	15 (57.69%)	17 (65.38%)	12 (25.00%)
WHO 2004 Grade				
High	25 (96.15%)	22 (84.62%)	24 (92.31%)	15 (93.75%)
Low	1(3.85%)	4 (15.38%)	2 (7.69%)	1 (6.25%)

Table 1: Demographics and Baseline Disease History

78 patients with NMIBC were randomized to one of three arms; concurrently, 16 patients who would not receive BCG were enrolled to an open-label monotherapy vaccine arm. Baseline demographic and disease status were well balanced across treatment arms. All patients has urothelial carcinoma except 1 patient in Arm 3 who had squamous cell carcinoma.

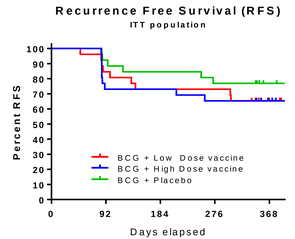
Safety

Count of Patients with: n (%)	Arm 1: BCG + Low Dose Vesigenurtacel-L (N=26)	Arm 2: BCG + High Dose Vesigenurtacel-L (N=26)	Arm 3: BCG + Placebo (N=26)	Arm 4: High Dose Vesigenurtacel-L (N=16)
Adverse Event (AE)				
Patients	21 (80.77%)	18 (69.23%)	19 (73.08%)	10 (62.50%)
Events	177 AEs	195 AEs	132 AEs	31 AEs
Vaccine-related AE				
Patients	4 (15.38%)	7 (26.92%)	4 (15.38%)	1 (6.25%)
Events	16 AEs	32 AEs	10 AEs	1 AE
Patients with Grade 3/4/5 AE	7 (26.92%)	4 (15.38%)	1 (3.85%)	1 (6.25%)
Vaccine-related Gr 3/4/5 AE	0	0	0	0
Injection Site Reaction (ISR)				
Patients	9 (34.62%)	17 (65.38%)	3 (11.54%)	8 (50.00%)
Events	27 ISRs	260 ISRs	12 ISRs	97 ISRs
Grade 3/4/5 ISR	0	0	0	0
ISR leading to treatment delay or discontinuation	0	0	0	0
Patients with any SAE	8 (30.77%)	4 (15.38%)	1 (3.85%)	3 (18.75%)
Vaccine-related SAE	0	0	0	0

Table 3: Summary of Adverse Events and Injection Site Reactions

The combination of BCG and vesigenurtacel-L was generally well tolerated. Injection site reactions appeared to increase with vesigenurtacel-L dose, though mostly mild and did not impact vaccine dosing.

1-year Recurrence Free Survival



	Arm 1: BCG + Low Dose Vesigen. (N=26)	Arm 2: BCG + High Dose Vesigen. (N=26)	Arm 3: BCG + Placebo (N=26)	Arm 4: High Dose Vesigen. (N=16)
1-year Recurrence Free Survival (no Recurrence/Progression/Cystectomy/ Death by 1 year +/- 28days) (%, 95% CI)	65.4% (82.8%, 44.3%)	65.4% (82.8%, 44.3%)	76.9% (91.0%, 56.4%)	6/16 * (37.5%)
Progression to MIBC	1	1	1	1
Death	0	1	0	0
Disease Free Survival (no Recurrence/ Progression/Cystectomy/Death) as of last follow-up (%)	73.1%	69.2%	69.2%	25%

Figure 2: Efficacy Data, Primary Endpoint data (1-year Recurrence Free Survival)

Vaccine-containing arms are not statistically different from the placebo-containing arm at 1-year. Patients experiencing progression to muscle-invasive disease appeared equally among the randomized arms. *Arm 4 RFS data are as of the 6-month timepoint due to enrollment and treatment schedules.

Immune Response

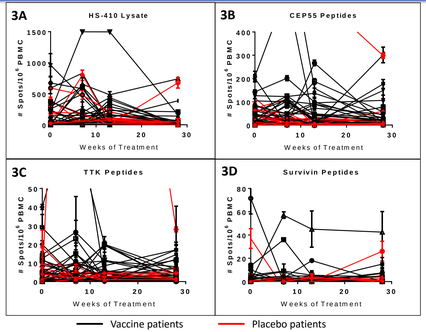


Figure 3: Vaccination induced antigen-specific cytotoxic immune responses in peripheral blood T-cells

Peripheral blood cells were re-stimulated with whole vaccine lysate (A) and overlapping peptides to tumor antigens contained within the vaccine (B-D). Increases in spots indicates activated T-cells recognizing antigen and producing cytotoxic IFN-g. Placebo treated patients (red lines) did not consistently demonstrate increases in INF-g secreting T cells. Increases in these cells was seen in vaccine patients (black lines) in an immune priming pattern.

Discussion

We conducted an efficient trial to understand the role of adding an allogeneic cell therapy vaccine to standard of care BCG. The trial enrolled well in the US, despite overcoming hurdles related to BCG supply.

Vesigenurtacel-L (HS-410) appears generally well tolerated with no SAEs or Grade 3/4/5 AEs that were thought related to vaccine. Patients in all combination arms performed better than historical data on BCG.

Vaccine-treated patients exhibited clinical signs of vaccine immune response, such as Injection Site Reactions and anecdotal reports of changes to the bladder urothelium when viewed under Blue Light. Trials with similar vaccines have defined an "immune responder" population based on ELISPOT responses which correlated with efficacy in those trials (Figure 3). These clinical signs, as well as the ELISPOT data, highlight the ability of the intradermal vaccine to generate an antigen-specific immune response, which appears to target the bladder. Furthermore, Immune Responders may have a better disease free interval when compared to Non-Immune Responders, though these are small data sets (Figure 4).

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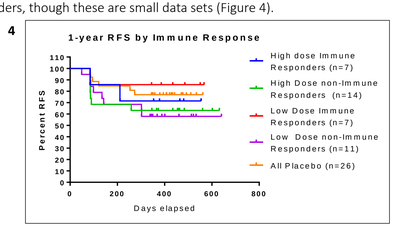

Overall, the vaccine arms did not show a statistical improvement over the placebo arm. Further understanding of the Secondary and Exploratory Endpoints will advise future development steps. The ability of the vaccine to prime T-cells suggests an opportunity to improve responses in this challenging disease. Future directions might include alternative treatment schedules, combination with other immune modulators, or as a method to reduce the BCG treatment (e.g. intravesical BCG induction followed by intradermal vaccine maintenance).

Conclusions/Next Steps

- Vesigenurtacel-L (HS-410) is generally well tolerated when combined with standard of care BCG.
- The primary endpoint (proportion of disease free patients at 1 year) did not show a statistically significant difference between the vaccine and placebo arms.
- Vaccine generated antigen-specific immune responses to multiple tumor associated peptides:
  - There was no evidence of antigen-specific immune response in the BCG+placebo arm.
- Remaining analyses are in progress to inform future development of other agents and/or combinations aimed at improving immune response durability:
  - Immune response profiles (HLA type, tumor antigen profiling, RNA sequencing, T-cell receptor sequencing, urine cytokine analysis)

Acknowledgements

The authors are grateful for the patients and their families for the commitment to this trial and advancement of the treatment of bladder cancer.

The following people helped make this trial possible: SUO-CTC, Victoria Brown, Hannah McKay, Jason Rose, Xin Xu, Alicia Williams, Sabrina Miles, David Dick, Tanya Townsend, Albert Chau, Pia Lynch, Gary Acton, Mark Schoenberg, and Mark Weinberg