Published in final edited form as:

Eur Urol Focus. 2018 July ; 4(4): 522–524. doi:10.1016/j.euf.2018.08.015.

Background and Update for S1602 “A Phase III Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming with Intradermal BCG Before Intravesical Therapy for BCG-naïve High-grade Non-muscle-invasive Bladder Cancer”

Robert S. Svatek^a, Cathy Tangen^b, Scott Delacroix^c, William Lowrance^d, and Seth P. Lerner^e

^aDepartment of Urology, University of Texas Health San Antonio, San Antonio, TX, USA;

^bSWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA, USA;

^cLouisiana State University, Department of Urology and Gulf South NCORP, New Orleans, LA, USA;

^dDepartment of Urology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA;

^eScott Department of Urology, Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA

Abstract

The S1602 Intergroup trial is a randomized phase III clinical trial that aims to test two important hypotheses: (1) priming with intradermal bacillus Calmette-Guérin (BCG) vaccine prior to standard intravesical BCG improves response to BCG in terms of recurrence-free survival and (2) Tokyo-172 BCG strain is non-inferior to TICE BCG in terms of time to high-grade recurrence. The study was approved by the Cancer Therapy Evaluation Program of the National Cancer Institute and activated in spring 2017. Here, we provide a synopsis of the study background, design, and update of the clinical trial.

Background

Prime/Boost

The concept for this study was prompted by the discovery that priming with subcutaneous BCG prior to intravesical BG instillations in pre-clinical models accelerated the entry of T cells into the bladder and improved response to BCG (1). The concept that priming could boost response to BCG was also supported by clinical observations. Patients with pre-existing BCG-specific immunity, scored by a positive purified protein derivative (PPD) test prior to intravesical BCG, was associated with an increase in recurrence-free survival. This novel work reinvigorated interest in BCG immunotherapy and examination of other methods to improve BCG-specific responses such as the placement of a purified protein derivative (PPD) prior to BCG instillation(2).

Notably, prior trials of BCG for bladder cancer tested the combined approach of “under-the-skin” injections concurrent with intravesical BCG and no significant benefit was observed in the combined approach. In these approaches, however, the BCG was given concurrent with intravesical BCG and the immunological concept of priming and then boosting was not in play. In addition, early studies of BCG scarification suggest that BCG priming can restore immune responses of some patients but *depress* immune function of others(3). Immunologic responses to vaccines are complex with a variable penetrance. Patients enrolled in S1602 are evaluated for “BCG responsiveness” through the use of standardized PPD testing before initial induction therapy and at multiple timepoints during maintenance therapy. This standardized method should allow for correlation between PPD conversion (“BCG responsiveness”) and tumor recurrence in addition to the possible accelerated benefit of intradermal vaccination in achieving this important endpoint.

BCG strains

Soon after establishing BCG’s antitumor efficacy, evidence from animal studies were published indicating that certain BCG strains may be more oncologically effective than others. To date, however, no adequately powered head-to-head trials have been conducted to examine the influence of BCG strain on clinical outcomes (4). A prospective randomized trial with 142 patients found a significantly greater 5-year recurrence-free survival in patients given Connaught compared to TICE BCG ($P=0.01$)(5). However, patients were not given maintenance BCG and the superiority of Connaught over TICE in patients treated with induction only may be mitigated with maintenance BCG(6). A randomized trial of 129 patients showing similar recurrence-free survival rates between Connaught and Tokyo-172 strains supported our decision to examine Tokyo-172 in S1602 trial.

Importantly, several different types of BCG strains are used worldwide as intravesical therapy for bladder cancer, but regulatory agencies have only approved BCG with strain-specificity. Now that Connaught strain is no longer produced, U.S. patients are dependent on one manufacturer for BCG therapy and shortages have occurred. Thus, a co-primary endpoint of S1602 is to compare BCG strains given intravesically using standard dosage regimens.

Study Design and Trial Update

S1602 is an ongoing National Clinical Trials Network (NCTN) study, allowing for participation for all cooperative groups. This is a three-arm trial and the study schema is shown in Figure 1. Eligible patients include men and women with BCG-naïve high-grade non-muscle invasive bladder cancer (CIS, Ta, and T1). In addition, patients must not report a history of tuberculosis or BCG exposure and must be PPD negative (defined as < 10mm induration following PPD test) prior to enrollment. Patients are randomized using a dynamic balancing algorithm with stratification based on age (< 75 and >75) and stage (Ta versus T1 versus CIS only versus CIS + Ta/T1).

Patients undergo PPD testing per standard of care (recommend by product insert for TICE BCG) prior to registration. Patients are randomized to one of three treatment arms (Study Schema in Figure 1). Patients randomized to arm 3 will initiate intravesical BCG 21 days

after intradermal BCG. Intravesical BCG is given as per standard induction and maintenance resulting in an induction course of 6 weekly treatments followed by 3 week maintenance courses at 3 months, 6 months, then every 6 months for a total of 7 maintenance cycles (3 year cumulative treatment timeline). Mandatory biopsies are performed for patients with CIS at month 6.

The primary objectives are (1) to compare whether time to high-grade recurrence (TTHGR) for patients with BCG-naïve, non-muscle invasive bladder cancer (NMIBC) receiving Tokyo-172 BCG (Arm 2) is non-inferior to patients receiving BCG LIVE (TICE® BCG) (Arm 1); and (2) to test whether TTHGR for patients with BCG-naïve, NMIBC receiving intradermal Tokyo-172 BCG vaccination followed by intravesical Tokyo-172 BCG instillation (Arm 3) is superior to patients receiving intravesical Tokyo-172 BCG instillation without prior intradermal BCG vaccination (Arm 2). In addition to the primary objects, patients will be assessed for BCG-specific immune responses, BCG-specific adverse events, and changes in quality of life as differences in side effects and quality of life could be different between the BCG strains. As of June 30, 2018, 116 patients of 969 have been enrolled, including 10 (8.6%) pure CIS, 42 (36.2%) Ta, 36 (31.0%) T1, and 28 (24.1%) with Ta/T1 + CIS.

While BCG therapy has been the mainstay of treatment for NMIBC for decades, this very pragmatic trial has the potential to further improve upon this well-established treatment while also providing further insights into the mechanisms behind response/failure to therapy. Continued and further support from the urologic community are necessary in this attempt to answer important clinical questions and improve outcomes for patients with this disease.

Conflicts of interest: Statement regarding trial support:

Acknowledgments

1. Trial was developed by Southwest Oncology Group (SWOG) and is conducted through the Cancer Therapy Evaluation Program of the National Cancer Institute. Award numbers CA180888 and CA180819.
2. Japanese BCG Laboratories provides support for trial including provision of Tokyo BCG for intradermal and intravesical use, delivery and storage of drug.

References.

1. Biot C, Rentsch CA, Gsponer JR, Birkhauser FD, Jusforgues-Saklani H, Lemaitre F, et al. Preexisting BCG-specific T cells improve intravesical immunotherapy for bladder cancer. *Sci Transl Med.* 2012;4:137ra72.
2. Niwa N, Kikuchi E, Matsumoto K, Kosaka T, Mizuno R, Oya M. Purified Protein Derivative Skin test prior to bacillus Calmette-Guerin Therapy May have Therapeutic Impact in Patients with Nonmuscle Invasive Bladder Cancer. *J Urol.* 2018;199:1446–51. [PubMed: 29307686]
3. Schwarzenberg MC, Simmler MC, Pico JL. Human toxicology of BCG applied in cancer immunotherapy. *Cancer Immunol Immunother.* 1976;1:69–76.
4. Boehm BE, Cornell JE, Wang H, Mukherjee N, Oppenheimer JS, Svatek RS. Efficacy of Bacillus Calmette-Guerin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis. *J Urol.* 2017.

5. Rentsch CA, Birkhauser FD, Biot C, Gsponer JR, Bisiaux A, Wetterauer C, et al. Bacillus Calmette-Guerin Strain Differences Have an Impact on Clinical Outcome in Bladder Cancer Immunotherapy. *Eur Urol*. 2014.
6. Witjes JA, Dalbagni G, Karnes RJ, Shariat S, Joniau S, Palou J, et al. The efficacy of BCG TICE and BCG Connaught in a cohort of 2,099 patients with T1G3 non-muscle-invasive bladder cancer. *Urol Oncol*. 2016;34:484 e19–e25.

Figure 1. S1602 Study Schema