# BCG Shortage Update

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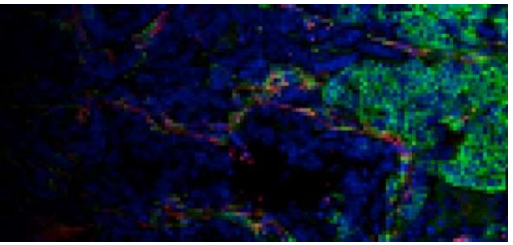
# Disclosures



- Clinical trials
  - Endo, FKD, JBL (SWOG), Roche/Genentech (SWOG), UroGen, Viventia
- Consultant
  - BioCancell, UroGen, Vaxiion, Verity
- Advisory Board
  - BioCancell, Ferring, miR Scientific, QED Therapeutics, UroGen
- Honoraria
  - MSD Korea, Dava Oncology, Nucleix

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# BCG Supply

- Connaught strain (Sanofi Pasteur) off line since 2012 then closed permanently in 2017
- Merck manufactures Tice in a single plant in US for global distribution in 70 countries
  - US market was 28 percent of the total product
  - increased production by more than 100 percent
  - In late 2016, at full capacity enables approximately 600,000 to 870,000 vials annually
  - January, 2019 begins allocation distribution

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# Joint Statement-February 19, 2019

- BCG should **not** be used for low-risk disease.
- Intravesical chemotherapy first-line option for patients with intermediate-risk NMIBC.
  - An alternative intravesical chemotherapy should be used for second line intermediate risk disease
- Patients with high-risk NMIBC prioritized for full-strength BCG. If not available, dose reduce to 1/2 to 1/3
- If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use 1/3 dose BCG and limit dose to one year.

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# Joint Statement-February 19, 2019

- BCG supply shortage: maintenance therapy should not be given and prioritize induction for BCG-naïve patients with high-risk disease.
- If BCG is not available: alternative chemotherapy options include mitomycin gemcitabine, epirubicin, docetaxel, valrubicin or sequential gemcitabine/docetaxel or gemcitabine/mitomycin
- Consider RC T1HG + CIS, LVI, P urethra, variant histology.

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# BCG Supply – Merck Update

- Producing TICE-BCG to the full extent of its manufacturing capacity remains a top priority
- Merck continues to explore alternatives that could potentially increase production capacity in the future; however, this takes time due to the complexity of the manufacturing process.
- Merck continues to work collaboratively with regulators, including the FDA and European health authorities, as well as medical societies and patient advocacy networks, including the AUA, and BCAN; and healthcare practitioners.

Personal communication 08/6/2019

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# BCG Dose Reduction

- Sometimes less is better
- An appropriate cytokine response can be achieved with as little as 1/100 of a standard dose
- Dose reduce in face of toxicity rather than abandon potentially effective therapy
  - 1/2, 1/3, 1/10, 1/30, 1/100

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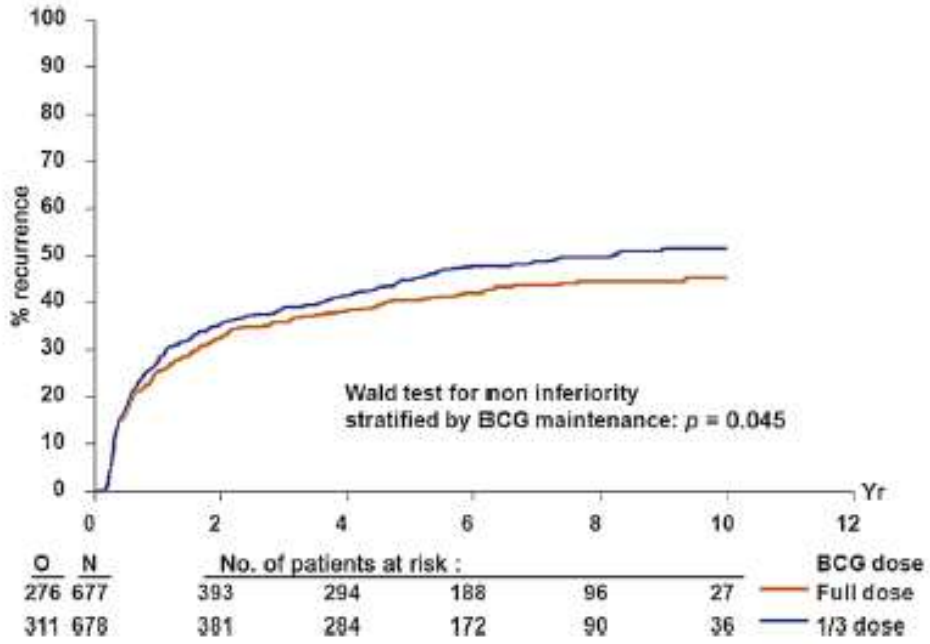
# EORTC 30962

- No significant in
  years vs. one ye
- Study did not me
  10% difference i
- There was a diff
  extremes – 1 ye




- *Full Dose-3yrs had the highest disease-free rate at 5 yrs while 1/3 Dose-1yr had the lowest*
- *But…is low dose is better than no dose?*

Oddens, et al Eur Urol 63:462, 2013

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# AUA Split Dosing Policy

- Split dosing is now supported by new HCPCS code J9030 allowing billing for 1/mg BCG and replaces J9031 (1 vial/BCG) & became effective 7/01/2019.
- *But billing for 2+ patients for split vial use is not approved by carriers as of 8/3/2019 – personal communication Neal Shore*

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# FDA

- CBER has been diligently working with Merck to enable the TICE BCG coming back on the market as soon as possible.
- CBER has posted the shortage situation on its website as well as in CBER communications to the public.
- Recommend that BCAN or other advocacy group might want to engage with any BCG manufacturer who would be interested to come to the US market.
- FDA would certainly be willing to engage and communicate with advocacy organizations in this regard.

Personal communication Chana Weinstock July 2019

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# FDA – Clinical trials

- No change in eligibility for BCG unresponsive disease defined as patients who have received doses as specified in the FDA guidance with approved BCG strains.
- Patients treated with lower doses of BCG and experiencing recurrent NMIBC would not be considered as having received “adequate BCG treatment” and would not meet the definition of BCG unresponsive disease.
- Despite these patients not meeting criteria for BCG unresponsive disease, evaluation of these patients and their responses on study may still have clinical merit and whether these patients are included in trial is at the sponsor’s discretion.

Personal communication Chana Weinstock July 2019

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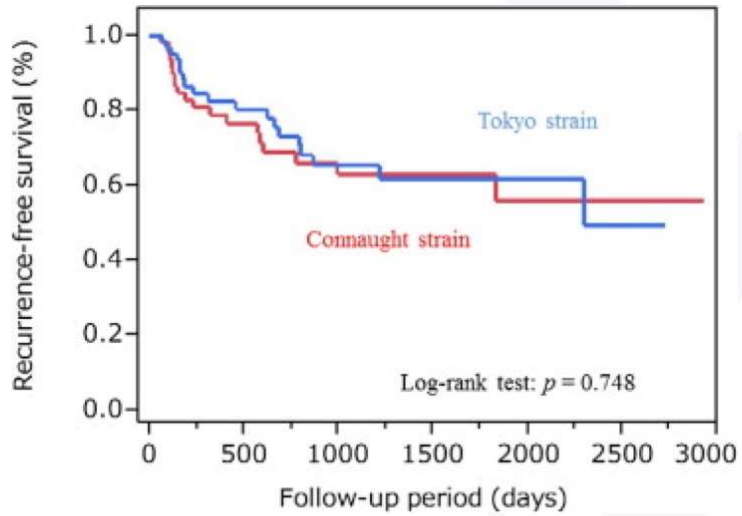
# BCG Phylogeny and Rationale for Strain Differences

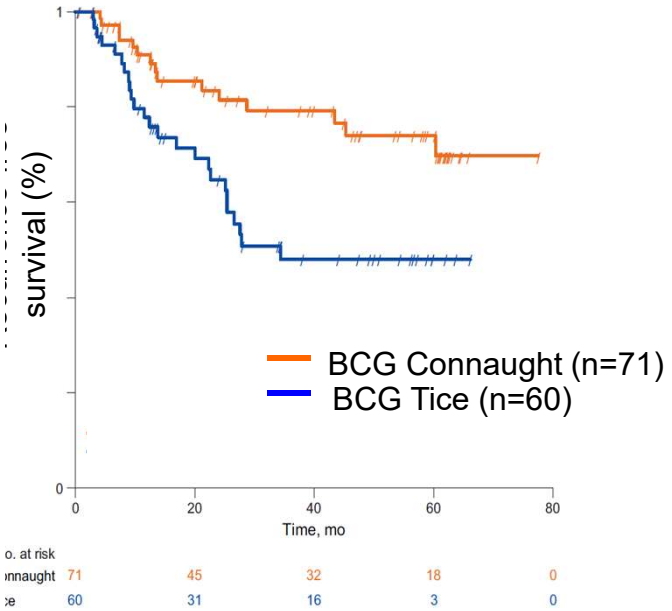
**A Prospective Comparative Study of Intravesical Bacillus Calmette-Guérin Therapy with the Tokyo or Connaught Strain for Nonmuscle Invasive Bladder Cancer**

Atsushi Sengiku, Masaaki Ito, Yu Miyazaki, Harutake Sawazaki, Takeshi Takahashi, Keiji Ogura




SWOG Leading cancer research. Together.

**Rationale for Strain evaluation**: Differences in genotype/phenotype between BCG substrains could influence antitumor efficacy.




*Rentsch, et al. European Urology 2015*

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# Health Canada

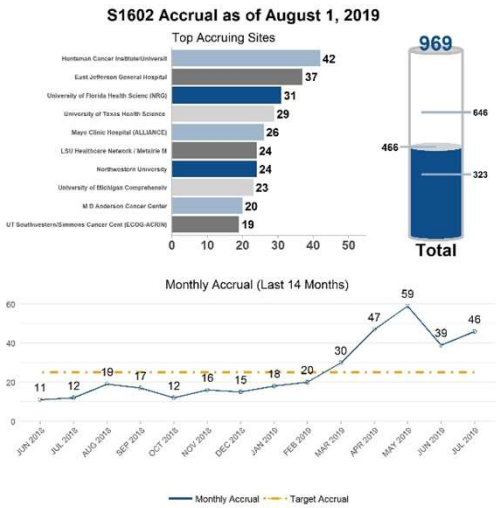
- Verity
- Russian strain produced by Serum Institute of India
- File to supply BCG in Canada has been reviewed and company optimistic about approval - expect answer within 30-60 days
- Verity has made initial contact with FDA and plans to set a date to review the Canadian file

# S1602 (Prime) Trial Schema

CIS, TA high grade, or T1 high grade urothelial bladder cancer

→ Randomize

- Intravesical BCG TICE (50 mg/dose)
- Intravesical BCG (Tokyo strain 80 mg/dose)
- **Prime**: intradermal BCG (Tokyo strain 100 µl at 0.5 mg /ml) + Intravesical BCG (Tokyo strain 80 mg/dose)




Treatment includes induction weekly for 6 weeks then maintenance with 3 weekly instillations at months 3, 6 and every 6 months to 3 years

Merck agrees to supply Tice