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BCG Shortage: The Practice Environment

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Disclosures

- Clinical trials
  - Endo, FKD, JBL (SWOG), Genentech (SWOG), QED, UroGen, Vaxiion, Viventia
- Consultant/Advisory Board
  - Aura Bioscience, C2i Genomics, FerGene, Genentech, Merck, Pfizer/EMD Serono, Stimit, UroGen, Vaxiion, Verity
- Patent – TCGA classifier
- Honoraria – Annenberg, Clinical Care Options, Grand Rounds Urology, Ology, UroToday

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Outline

- BCG shortage update
- AUA and stakeholder guidelines
- Treatment options based on risk stratification with no or limited supply of BCG
- Survey - Impact of BCG shortage on academic and community settings

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BCG Indications

- *Any patient with high risk NMIBC*
  - TaHG, T1, Tis; multifocal and recurrent and >3cm
  - Induction + 3 years maintenance is SOC
  - TaLG – (Use intravesical chemo due to BCG shortage)
- *Recurrent*
  - BCG failure (induction only) if no indication for cystectomy or medically unfit
- *US FDA approved for CIS and high-risk Ta,T1*

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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 at time SP went off line
  - Increased production by more than 100 percent
  - In late 2016, at full capacity enabling approximately 600,000 to 870,000 vials annually

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BCG Supply

- In January, 2019 Merck began allocation distribution through their authorized vaccine distributors
  - https://www.merck.com/research-and-products/distributors
- Demand in the US decreased during pandemic but still > supply
- Demand is increasing now
- Revised US % of market not provided

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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.
- Merck to build new plant that will triple production (Jan 2021)
  - Project has begun and 4-5 years before on line (personal communication, Merck 09/23/21)

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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[1]
- Dose reduce in face of toxicity rather than abandon potentially effective therapy
  - 1/2, 1/3, 1/10, 1/30, 1/100

Intravesical BCG TICE®

SWOG S1602

Dose Levels

Full Dose	-1 Level	-2 Level	-3 Level	-4 Level
50 mg	16.67 mg (1/3 dose)	12.5 mg (1/4 dose)	5 mg (1/10 dose)	0.5 mg (1/100 dose)

Luo, et al J Immunology 162:2399, 1999

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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 may vary by state/region – should verify with carrier*

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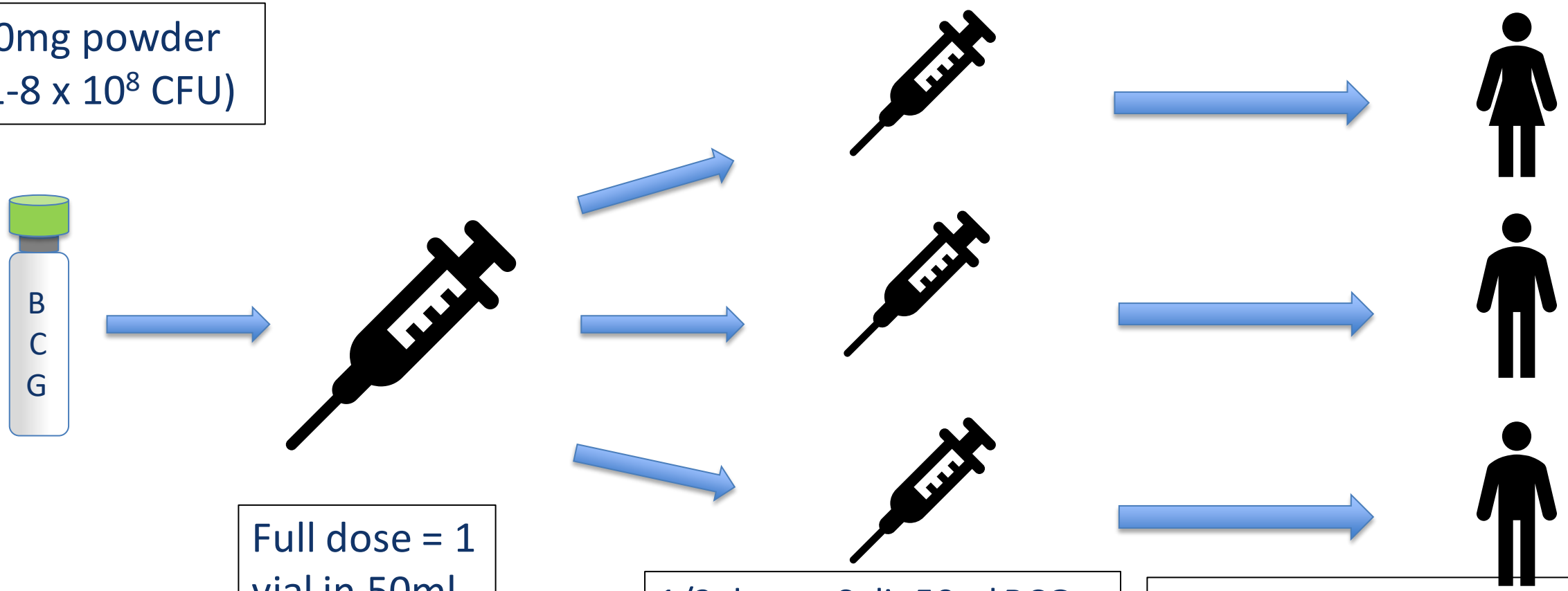
BCG Dose Reduction in Clinical Practice

50mg powder
(1-8 x 10^8 CFU)



Full dose = 1 vial in 50ml NS

1/3 dose = Split 50ml BCG solution into 3 syringes and reconstitute up to 50ml

Administer to 3 patients within 2 hrs (keep refrigerated 2-8˚C)

Courtesy Chad Ritch

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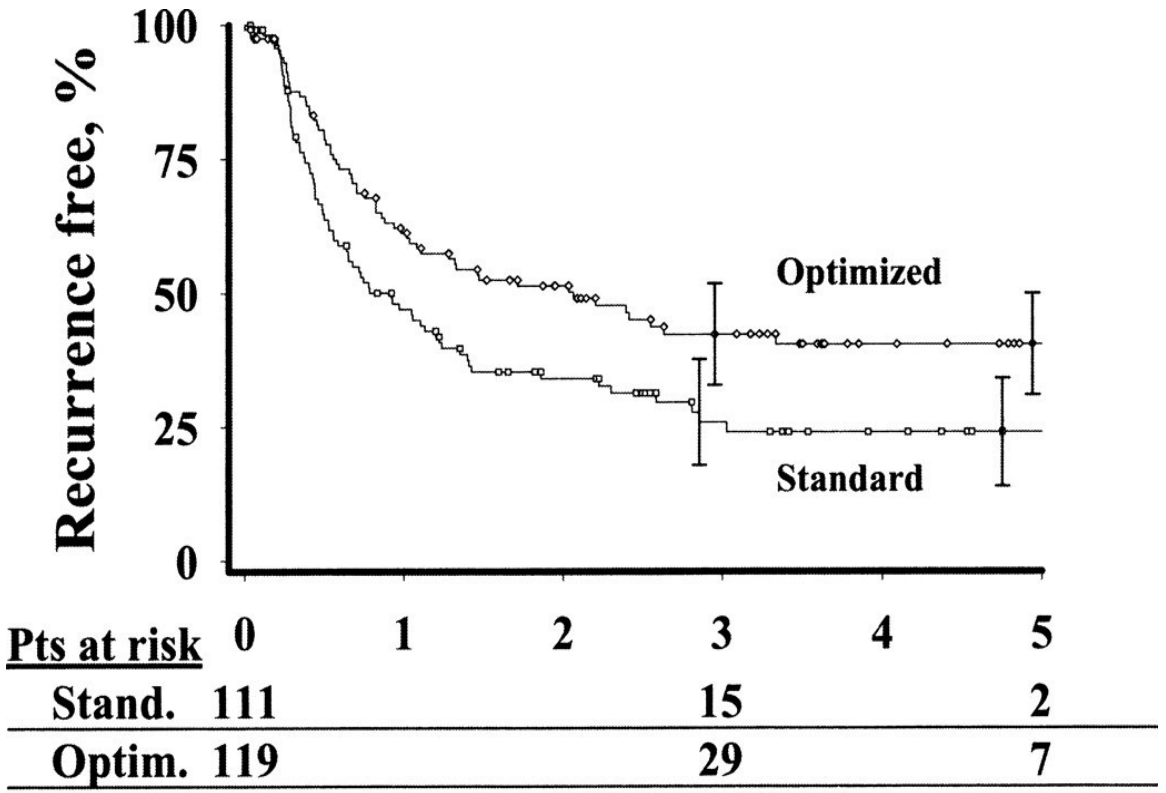
Optimized Mitomycin

- 40mg/20cc
- Dehydrate patient – NPO after midnight
- Sodium bicarbonate (1.3g po night before, and in am of tx)
- Use bladder scanner to ensure bladder is empty prior to instillation (PVR<10cc)



Au et al, JNCI 93:597, 2001

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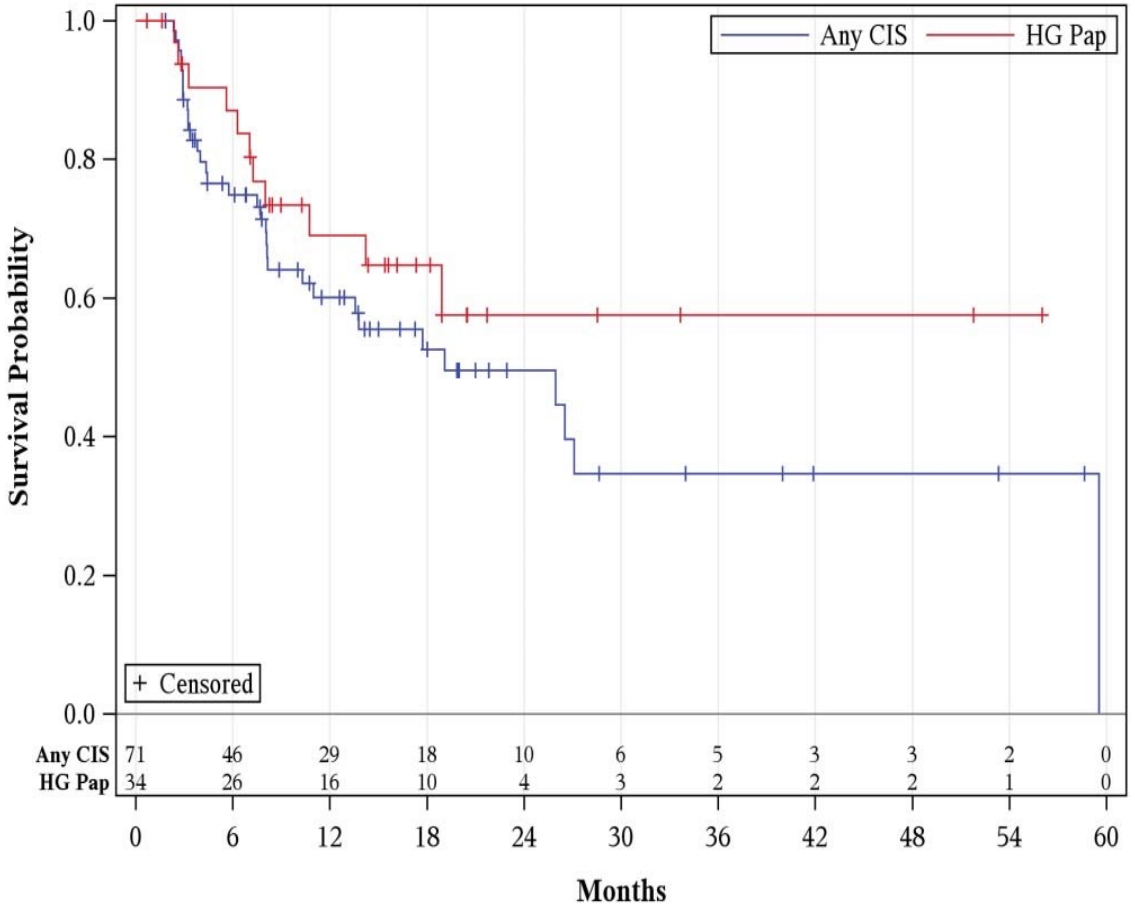
Gemcitabine/Docetaxel

- One and 2-year RFS rates 60% and 46%
- 3.6% progression and cystectomy free survival 84%
- No patient, disease, or prior treatment factors predict relapse
- Maintenance matters



R Steinberg J Urol May 2020

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BCG Naïve Clinical Trials

Trial	SPONSOR	AGENT	PHASE	NUMBER PTS	START DATE
	ImmunityBio	Alt 803 + BCG vs. BCG	IIb	596	Jul-14
POTOMAC	Astra Zeneca	Durvalumab + BCG vs. BCG	III	1019	May-18
	Hamlet	Alpha 1 H (α-lactalumbin+oleic acid)	I/II	57	May-18
Alban	Unicancer (FR)	Atezo +BCG vs. BCG	III	516	Jan-19
	NanOlogy	NanoDoce	I/II	75	Apr-19

Source: www.clinicaltrials.gov September 2021

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BCG Naïve Clinical Trials

Trial	SPONSOR	AGENT	PHASE	NUMBER PTS	START DATE
BladderGate	Fundacion Oncosur(SP)	Atezo +BCG	1b	40	Feb-20
	Hopkins	Gem/Doce	II	26	Jul-20
Keynote-676	Merck	Pembro + BCG vs. BCG (Cohort B)	III	1525	18-Dec
CREST	Pfizer	Sasanlimab (PF-06801591) + BCG vs. BCG	III	999	19-Dec
EVER	Verity	Verity (Russian strain) BCG vs Tice BCG	III	540	Not started

Source: www.clinicaltrials.gov September 2021

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Summary – BCG Shortage

- BCG shortage continues to plague access to standard of care and creates challenges in clinical trial enrollment
- Driving innovation and alternative risk adapted therapies
- S1602 – CR and durability results in CIS patients will be reviewed
- Optimized intravesical MMC and doublet chemotherapy regimens are active in both intermediate and high-risk disease
- Robust clinical trials portfolio for high-risk BCG naïve

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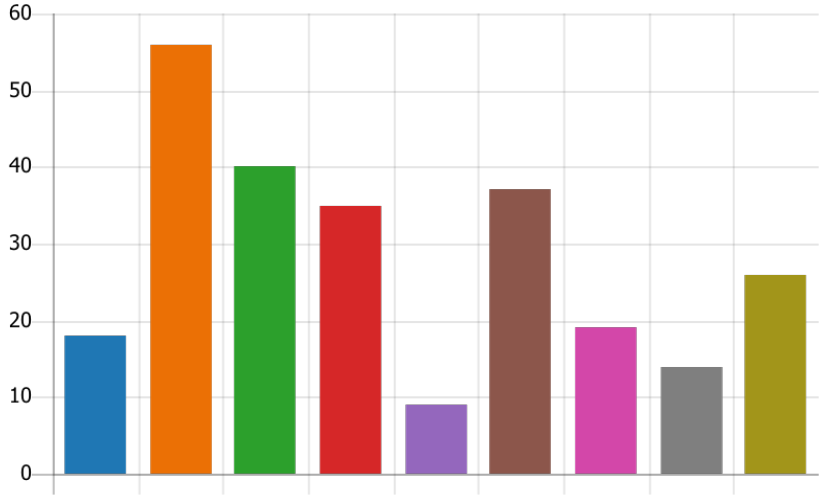
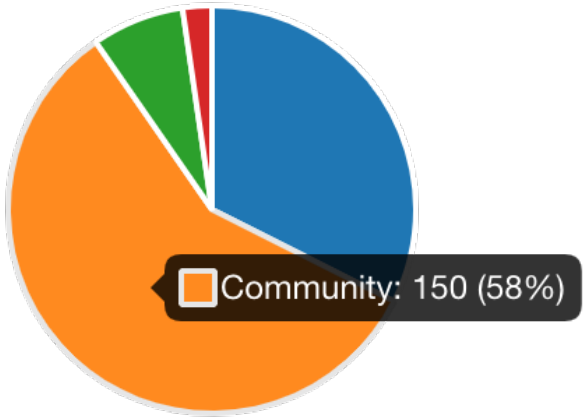
BCG Shortage Survey

- BCAN (94), SUO(1010), LUGPA(2200)
- Completed surveys n = 255
- Preliminary data



New England
Mid Atlantic (22%)
South Atlantic
East North Central
West North Central
East South Central
West South Central
Mountain
Pacific



Academic 84 (32%)
Community 150 (58%)
Hybrid 19
Other 6

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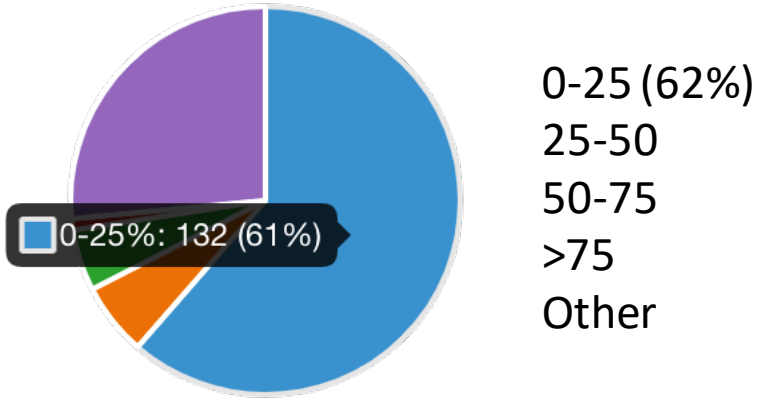
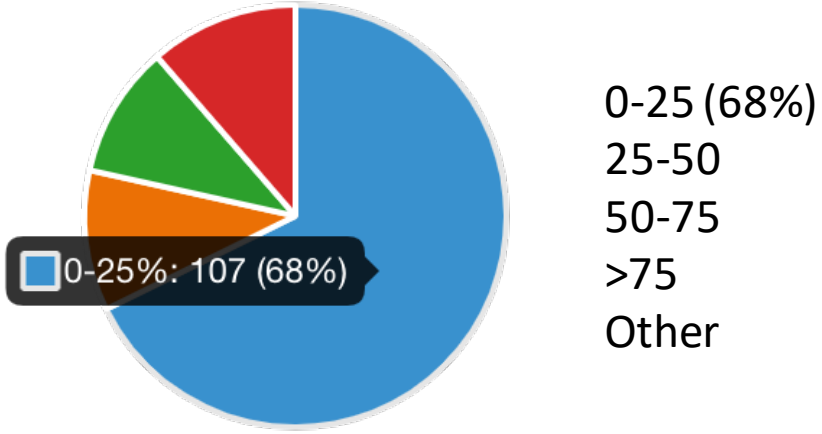
BCG Shortage Survey

Shorter induction (%)



Dose reduction during induction (%)



- For what proportion of high-risk NMIBC treated in the last 12 months did you avoid giving any maintenance BCG due to the BCG shortage
  - 0-25% (58%)
- For what proportion of high-risk NMIBC did you treat with maintenance for less that 3 years due to the BCG shortage?
  - 50-100% (58%)

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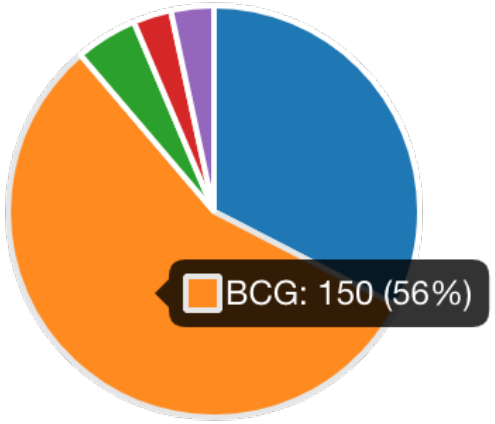
BCG Shortage Survey

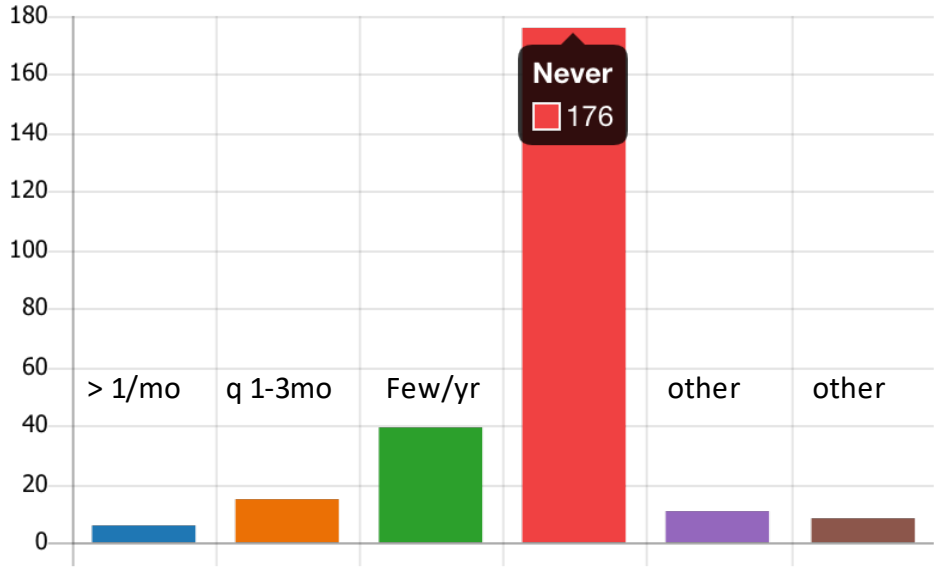
Preference for BCG vs Ctx for intermediate risk (%)



Ctx (33%)
BCG (56%)
No tx (5%)
Other

BCG
Academic 33%
Non-academic 66%

Have you had to borrow BCG



Other: never, no one to borrow from, not allowed

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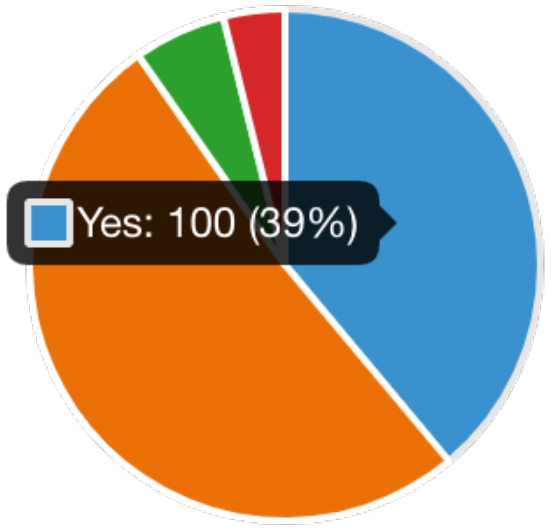
BCG Shortage Survey

Adverse Outcome due to Shortage



- Do you consider the development of non-BCG based alternative therapies as a high priority for BCG-naïve high-risk patients?
  - Yes (92%)
- Is the BCG shortage affecting your ability to enroll patients in clinical trials in the BCG-naïve, refractory or unresponsive?
  - Yes (24%)

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BCG Shortage Survey Summary

- One-third respondents academic sites
- Majority have been able to maintain full dose induction
- Majority have been able to give maintenance but majority have also given < 3 years maintenance
- One-third of academic sites and 2/3 community sites continue to use BCG for patients with intermediate risk disease
- 39% report adverse outcomes related to BCG shortage
- Overwhelming majority favor developing alternatives to BCG for patients with BCG naïve high risk disease
- One-quarter report negative impact on clinical trial accrual