Evidence Acquisition:

S1.0 Response Rate Definitions:

S1.1 Complete Response Rate (CRR): defined as at least one of the following: 1) negative cystoscopy and negative (including atypical) urine cytology and 2) Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology. These criteria were recommended by the United States Food and Drug Administration's "BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment" in February, 2018. CRR should be reported as a percentage relative to a timepoint.

S1.2 Recurrence Free Survival (RFR): defined as percentage of population from randomization until disease recurrence at a specific time point.

S1.3 Disease Free Rate (DFR): defined as lack of tumor or recurrence on cystoscopic examination and a negative urine cytology.

S2.1 Systematic literature review

We performed a systematic review of prospective clinical trials utilizing different therapeutic agents in BCG-unresponsive NMIBC following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (PROSPERO CRD42019130553). The search was performed in MEDLINE (OVID), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 2000 to present day. Search terms were defined by the population, intervention, comparisons, outcomes, and study design (PICOS) approach. Terms utilized are listed below in section 2.2 by database. To saturate information, we also included unpublished literature: clinicaltrials.gov, Google scholar, conference proceedings, and reference lists. We did not set any language restrictions. Editorials, commentaries, review articles, and those not subject to peer review were excluded. In cases where multiple reports were made on the same patient cohort, the most recent comprehensive publication was used for the analysis.

S2.2 Search strategy

Medline (Ovid):
((BCG unresponsive non-muscle-invasive bladder cancer).mp or (BCG Unresponsive).mp or (BCG refractory).mp or (BCG relapsed).mp or (bacillus Calmette Guerin relapsing).mp or (bacillus Calmette Guerin refractory).mp) AND (randomized controlled trial.pt or controlled clinical trial.pt or randomized.ab or placebo.ab or randomly.ab or trial.ab or (clinical trial).mp or (randomi*ed controlled trial).mp or exp double-blind method)

Embase:
('bacillus Calmette Guerin relapsing':ti,ab or 'bacillus Calmette Guerin refractory':ti,ab or 'BCG unresponsive non muscle-invasive bladder cancer':ti,ab or 'BCG Unresponsive':ti,ab or 'BCG refractory':ti,ab or 'BCG relapsed':ti,ab) AND ('Mycobacterium Phlei Cell Wall Nucleic Acid Complex':ti,ab or MCNA:ti,ab or 'rAd IFNa Syn3':ti,ab or Pembrolizumab:ti,ab or 'PD 1 inhibitor':ti,ab or Cabazitaxel:ti,ab or Gemcitabine:ti,ab or Cisplatin:ti,ab or CGC:ti,ab or

'nadofaragene firadenovec gene therapy':ti,ab) AND ('randomized controlled trial'/exp or 'randomi*ed controlled trial':ti,ab or 'clinical trial'/exp or 'clinical trial':ti,ab or 'double blind procedure'/exp) AND [embase]/lim
('bacillus Calmette Guerin relapsing':ti,ab or 'bacillus Calmette Guerin refractory':ti,ab or 'BCG unresponsive non muscle-invasive bladder cancer':ti,ab or 'BCG Unresponsive':ti,ab or 'BCG refractory':ti,ab or 'BCG relapsed':ti,ab) AND ('randomized controlled trial'/exp or 'randomi*ed controlled trial':ti,ab or 'clinical trial'/exp or 'clinical trial':ti,ab or 'double blind procedure'/exp) AND [embase]/lim

Central (Ovid):
((BCG unresponsive non-muscle-invasive bladder cancer).mp or (BCG Unresponsive).mp or (BCG refractory).mp or (BCG relapsed).mp or (bacillus Calmette Guerin relapsing).mp or (bacillus Calmette Guerin refractory).mp) AND ((Mycobacterium Phlei Cell Wall Nucleic Acid Complex).mp or MCNA.mp or (rAd-IFNa Syn3).mp or Pembrolizumab.mp or (PD 1 inhibitor).mp or Cabazitaxel.mp or Gemcitabine.mp or Cisplatin.mp or CGC.mp or (nadofaragene firadenovec gene therapy).mp) AND (randomized controlled trial.pt or controlled clinical trial.pt or randomized.ab or placebo.ab or randomly.ab or trial.ab or (clinical trial).mp or (randomi*ed controlled trial).mp or exp double-blind method)
((BCG unresponsive non-muscle-invasive bladder cancer).mp or (BCG Unresponsive).mp or (BCG refractory).mp or (BCG relapsed).mp or (bacillus Calmette Guerin relapsing).mp or (bacillus Calmette Guerin refractory).mp) AND (randomized controlled trial.pt or controlled clinical trial.pt or randomized.ab or placebo.ab or randomly.ab or trial.ab or (clinical trial).mp or (randomi*ed controlled trial).mp or exp double-blind method)

S2.3 Study review methodology

Studies were screened (title/abstract and full text) by two investigators (KR & HG), with any conflicts being resolved by a third investigator (RL). Titles and abstracts were used to screen for initial study inclusion. Full texts of studies (or abstracts of presentations) were then reviewed. Data retrieved from the reports include publication details (year of publication and authors), methodological components, and trial characteristics (sample size, therapeutic agent, outcomes measures). The primary outcomes were complete response rate (CRR) in CIS-containing patients, recurrence-free survival (RFS) for studies limited to patients with papillary disease, and disease-free rates (DFRs) for studies with both papillary and CIS. In studies combining more than one agent, outcomes in each treatment arm were extracted separately and analyzed.

S2.4 Risk of bias assessment

We purposefully did not perform a risk of bias (RoB) assessment given the heterogeneity in the treatment agents used. Additionally, we did not feel that the existing scales would be appropriate to utilize for this systematic review. However, studies that did not report response rates per 3-6 month intervals were deemed to have a high RoB and excluded from the final analysis.

S2.5 Data Synthesis

Data synthesis was performed by reporting CRRs for studies limited to CIS-containing patients, RFS for studies limited to patients with papillary disease, and DFRs for studies with both

papillary and CIS. These were then reported as composite scores CRRs/RFRs/DFRs at different time points in each study, and grouped by the post-treatment time intervals at which they were recorded. The median and range of groups at 3, 6, 12, 18, and 24 months following treatment were reported. Heterogeneity was assessed by the I^2 statistic, and its connected chi-square test for heterogeneity. For illustrative purposes, the results were summarized using forest plots. We then performed separate subanalyses for individual agents for which at least two or more studies were performed, studies performed before and after 2015, and studies which were published vs. presented at academic meetings.