

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center
Making Cancer History®

RISK STRATIFICATION, DEFINITIONS OF DISEASE STATES & BCG UNRESPONSIVE DISEASE

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Co-President, International Bladder Cancer Network (IBCN)

Risk Stratification

Risk Stratification: AUA/SUO

TABLE 4: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer		
Low Risk	Intermediate Risk	High Risk
LG ^a solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP ^b	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG ^c Ta, ≤ 3cm	Any CIS ^d
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI ^e
		Any HG prostatic urethral involvement
^a LG = low grade; ^b PUNLMP = papillary urothelial neoplasm of low malignant potential; ^c HG = high grade; ^d CIS=carcinoma <i>in situ</i> ; ^e LVI = lymphovascular invasion		

Risk Stratification: EAU

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, Ta, G1* (PUNLMP, LG), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk).
High-risk tumours	Any of the following: <ul style="list-style-type: none">T1 tumourG3** (HG) tumourCISMultiple and recurrent and large (> 3 cm) Ta, G1G2 tumours (all conditions must be presented in this point)*

Risk Stratification: EAU, 2021

Risk group	
Low Risk	<ul style="list-style-type: none"> A primary, single, Ta/T1 LG/G1 tumour < 3 cm in diameter without CIS in a patient < 70 years
	<ul style="list-style-type: none"> A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (see above*)
Intermediate Risk	Patients without CIS who are not included in either the low, high or very high-risk groups
High Risk	<ul style="list-style-type: none"> All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: <ul style="list-style-type: none"> Ta LG/G2 or T1 G1, no CIS with all 3 risk factors Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors T1 G2 no CIS with at least 1 risk factor
Very High Risk	Stage, grade with additional clinical risk factors: <ul style="list-style-type: none"> Ta HG/G3 and CIS with all 3 risk factors T1 G2 and CIS with at least 2 risk factors T1 HG/G3 and CIS with at least 1 risk factor T1 HG/G3 no CIS with all 3 risk factors

Additional clinical risk factors are:

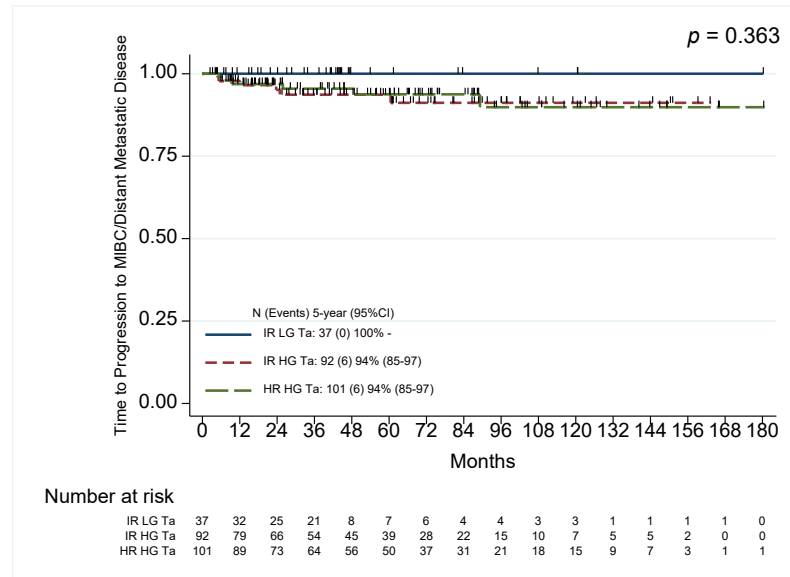
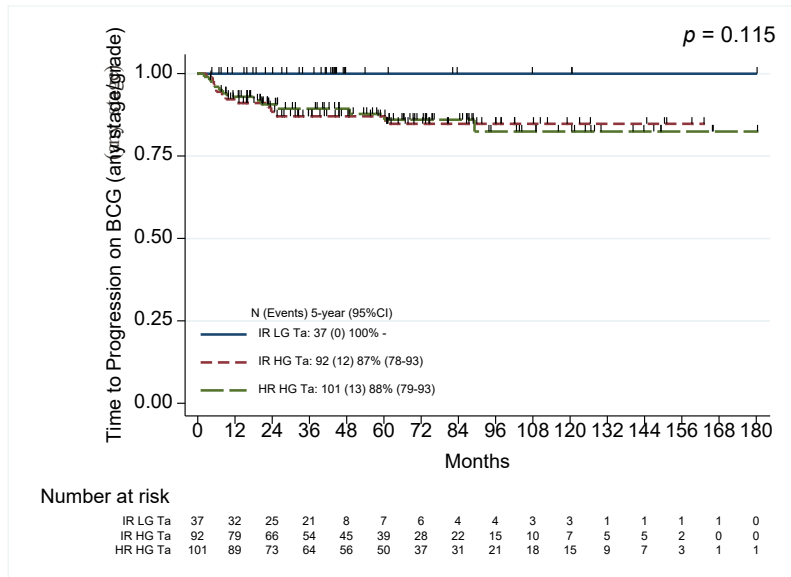
- o age > 70;
- o multiple papillary tumours;
- o tumour diameter > 3 cm.

MDACC Data:

EAU Risk Calculator Overestimates Risk in BCG Treated Patients

Updated EAU Prognostic Risk Factor	MD Anderson Cancer Center series (%) 95% CI						Sylvester 2021 predicted (%) 95% CI		
	At least induction BCG			Adequate BCG					
	n	1yr	5yr	n	1yr	5yr	n	1yr	5yr
Intermediate	136	1.5 (0.4-5.8)	4.2 (1.8-9.8)	131	1.6 (0.4-6.1)	3.4 (1.3-8.7)	845	1.0 (0.5-2.0)	4.9 (3.4-7.0)
High	313	4.3 (2.5-7.3)	7.5 (4.9-11.6)	296	2.9 (1.4-5.6)	5.8 (3.4-9.7)	752	3.5 (2.4-5.2)	9.6 (7.4-12.0)
Very high	118	9.7 (5.5-16.8)	16.7 (10.6-25.7)	104	7.0 (3.4-14.1)	14.8 (8.8-24.5)	99	16.0 (10.0-26.0)	40.0 (29.0-54.0)

MDACC Data: All TaHG disease should be considered High Risk



Simplified Definition

International Bladder Cancer Group Risk Categories^{1,2}

Risk Category	Tumor Characteristics	Outcomes
Low Risk	Ta LG: Solitary, primary, ≤ 3 cm	Low risk of recurrence/progression
Intermediate Risk	Anything that falls between low risk and high risk	Recurrence is main concern
High Risk	Any HG (Ta, T ₁ , CIS) Any T ₁	Progression is main concern

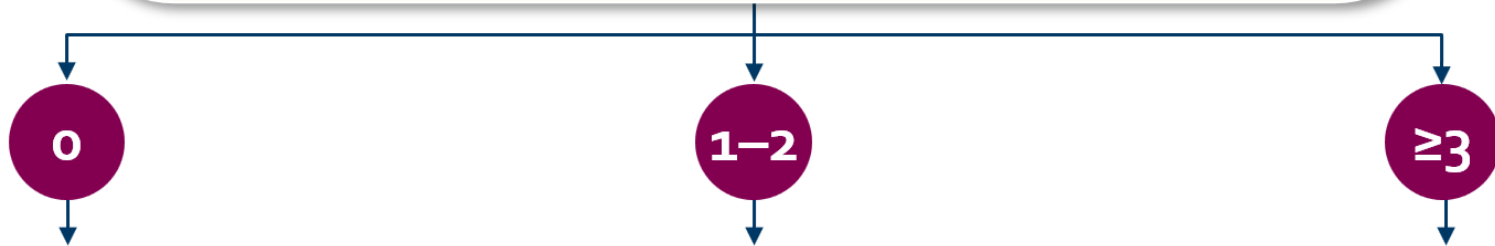
All CIS is considered high risk by AUA, EUA, NCCN



Intermediate risk tumors (low grade)

How many of the following 4 factors does the patient have?

- Multiple tumors
- Tumor size >3 cm
- Early recurrence (<1 year)
- Frequent recurrences (>1 per year)



TREAT SIMILAR TO LOW RISK:

TREAT AS INTERMEDIATE RISK:

TREAT AS HIGH RISK:

Stratification for Clinical Trials of Intermediate Risk Low Grade Tumors



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Recognizing that the AUA and now EAU classifies TaHG tumors differently, the SITC-IBCG panel recommends that

For the purpose of clinical trials, all TaHG tumors (and TaG₃ tumors if 3 stage grading is available) should be classified as high risk

Definitions of Disease States

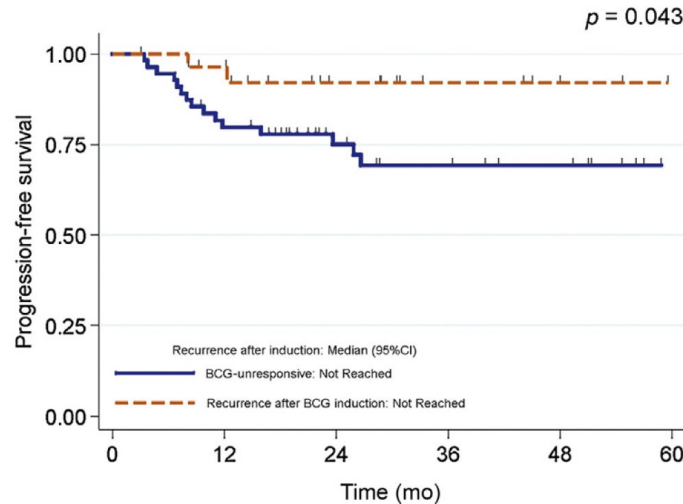
Definition of BCG Unresponsive Disease

- Persistent or new **T₁ HG** disease
 - at first evaluation (3 mos) following induction BCG
- Persistent or recurrent **CIS**
 - within 12 months of completion of adequate BCG therapy
- Recurrent **HG Ta/T₁** disease
 - within 6 months of completion of adequate BCG therapy

**Adequate BCG therapy defined as:
at least 5 of 6 doses of iBCG + at least 2 additional doses of mBCG**

Does “BCG unresponsive” define a worse prognosis HR NMIBC?

85 HG NMIBC: 55 recurred after BCG induction + first maintenance (= BCG unresponsive)
28 recurred after BCG induction only



Number at risk
BCG-unresponsive
Recurrence after BCG induction

55
28

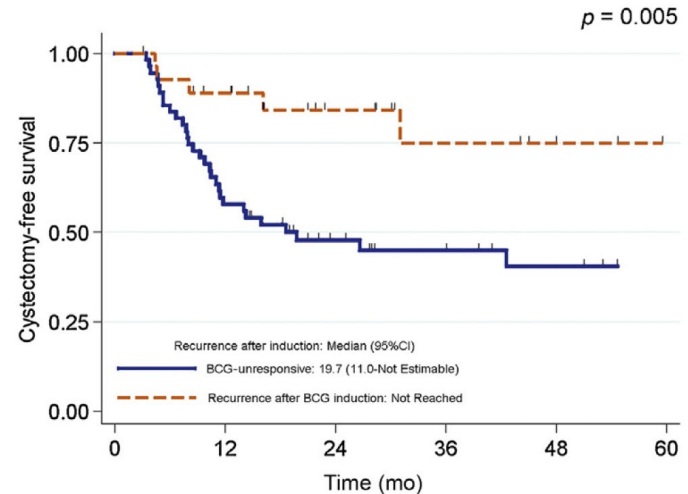
42
24

27
16

22
11

19
8

12
6



Number at risk
BCG-unresponsive
Recurrence after BCG induction

55
28

31
22

18
13

13
8

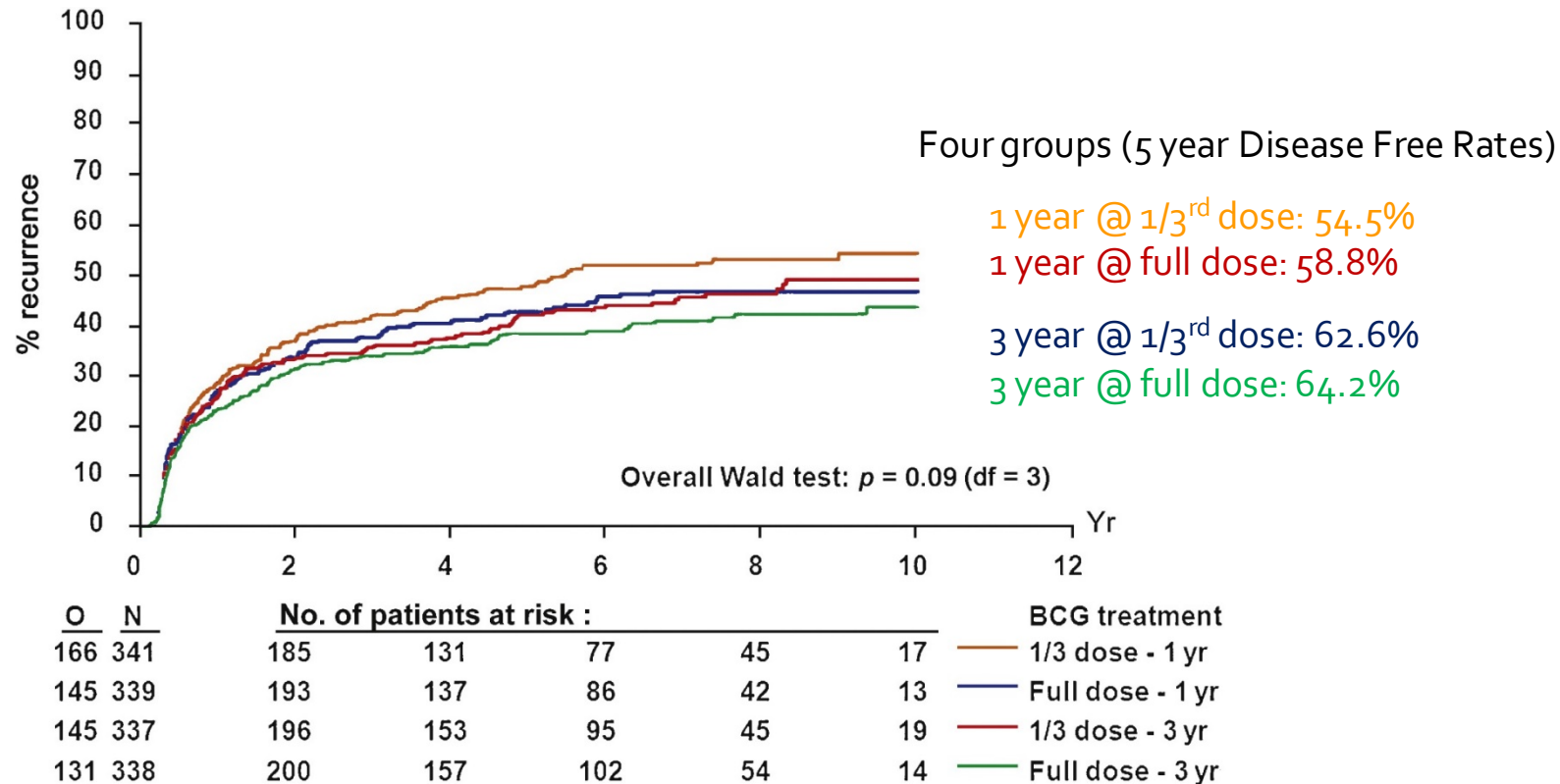
9
5

6
3

BCG unresponsive showed worse prognosis: more cystectomies, HG recurrences & progression to MIBC in truly BCG unresponsive vs induction only BCG recurrent

What about reduced dose patients?

EORTC30962 – Full Dose vs Low Dose, 1 yr vs 3 yr



BCG Shortage: Dose Reduction

TICE® BCG
BCG Live
For Intravesical Use

Package Insert

The freeze-dried BCG preparation is delivered in glass vials, each containing 1 to 8×10^8 colony forming units (CFU) of TICE BCG which is equivalent to approximately 50 mg wet weight. Determination of *in vitro* potency is achieved through colony counts derived from a serial dilution assay. A single dose consists of 1 reconstituted vial (see **DOSAGE AND ADMINISTRATION**).

BCG Shortage: Dose Reduction

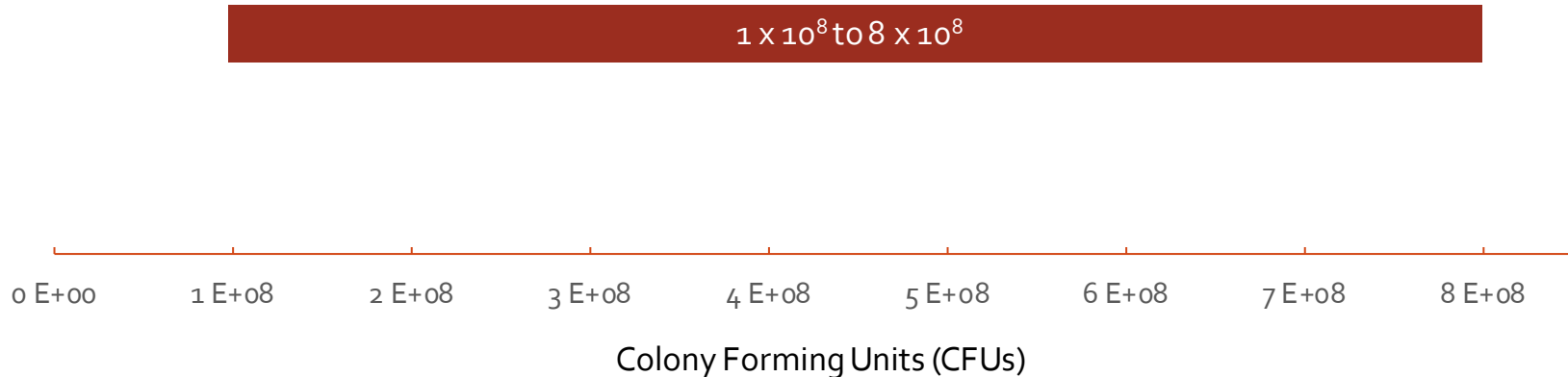
TICE® BCG
BCG Live
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Dose

Full



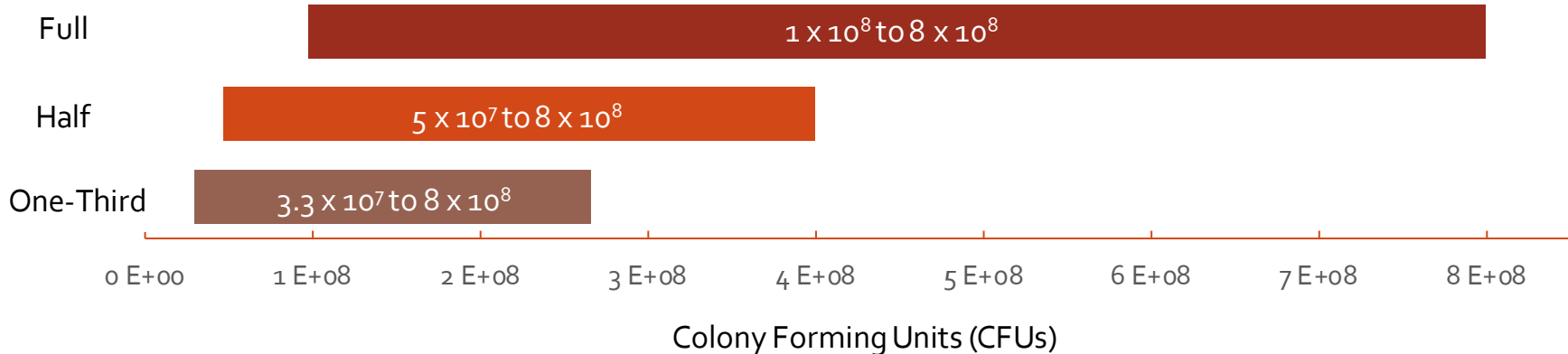
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Dose

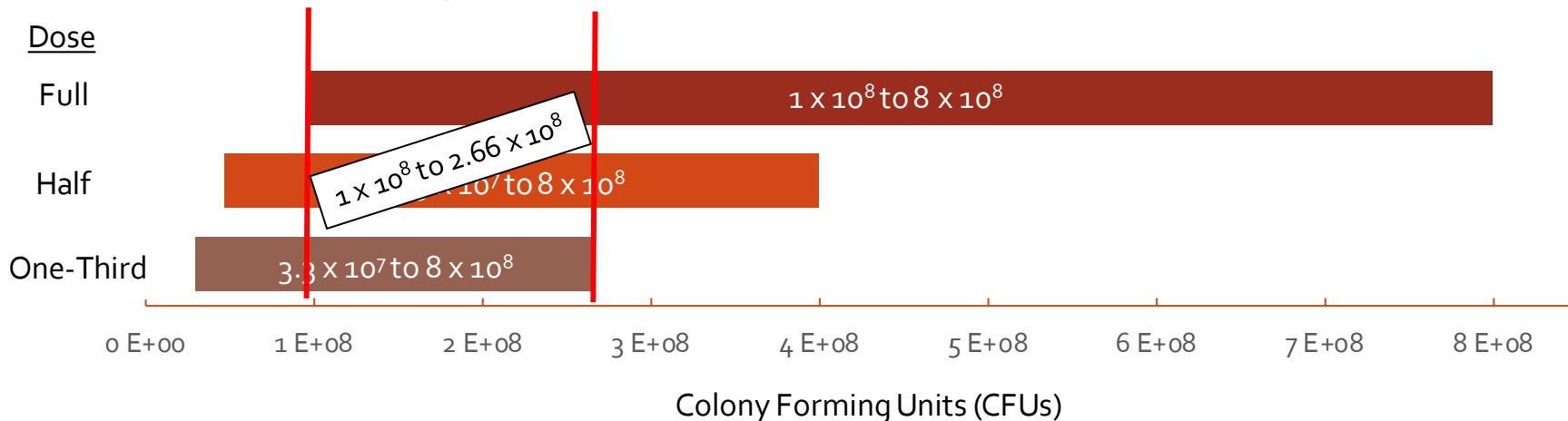


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TICE® BCG
BCG Live
For Intravesical Use





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Patients who have received reduced dose BCG should be included in trials for BCG Unresponsive Disease

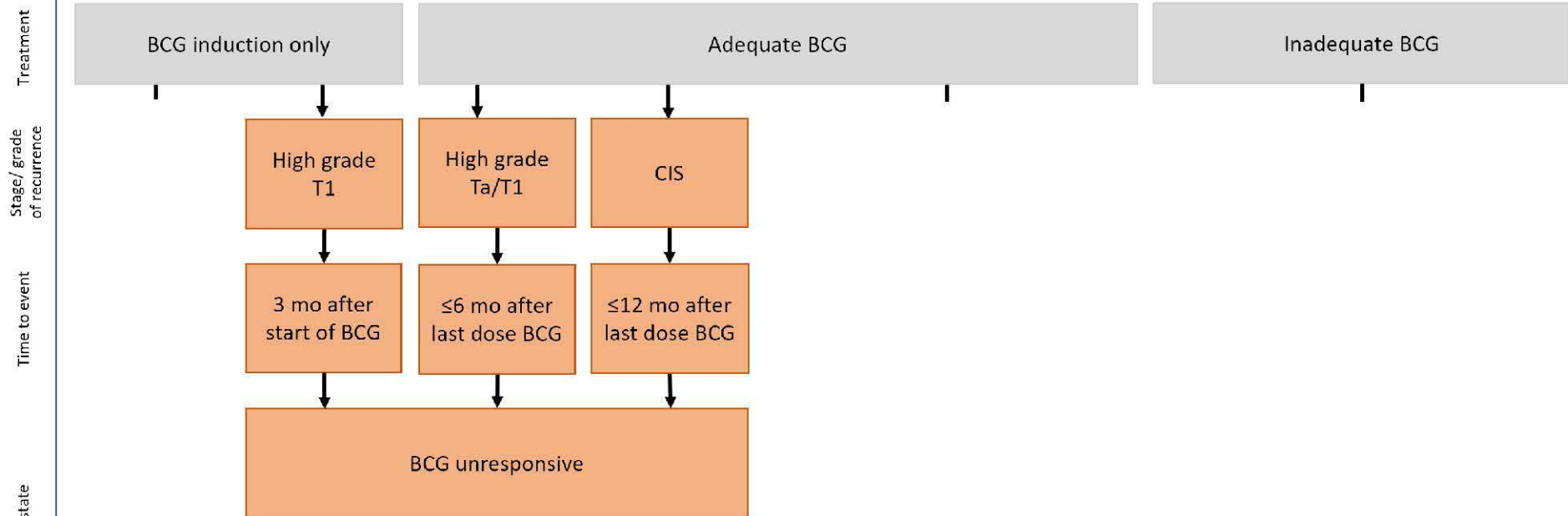
BCG Exposed Disease State

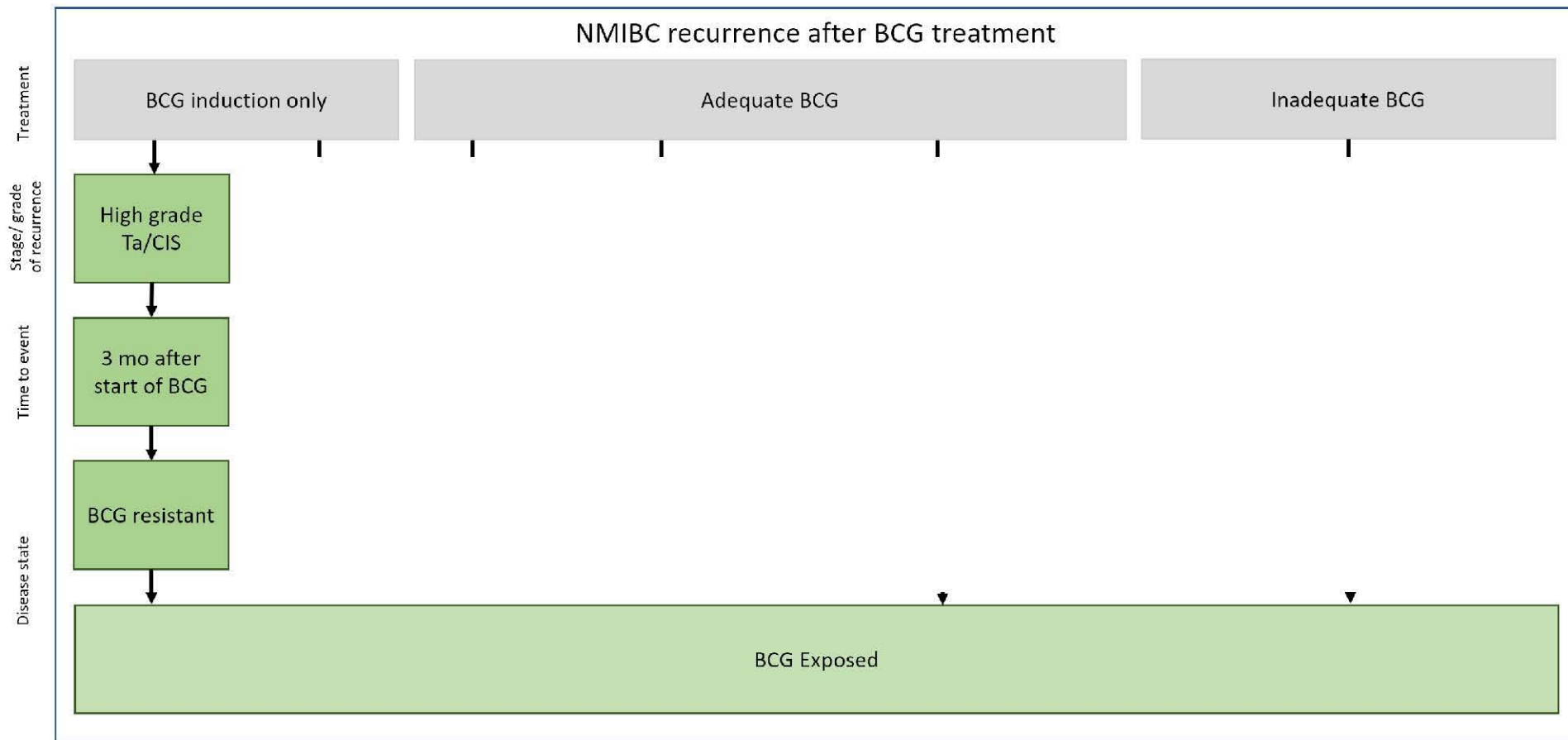


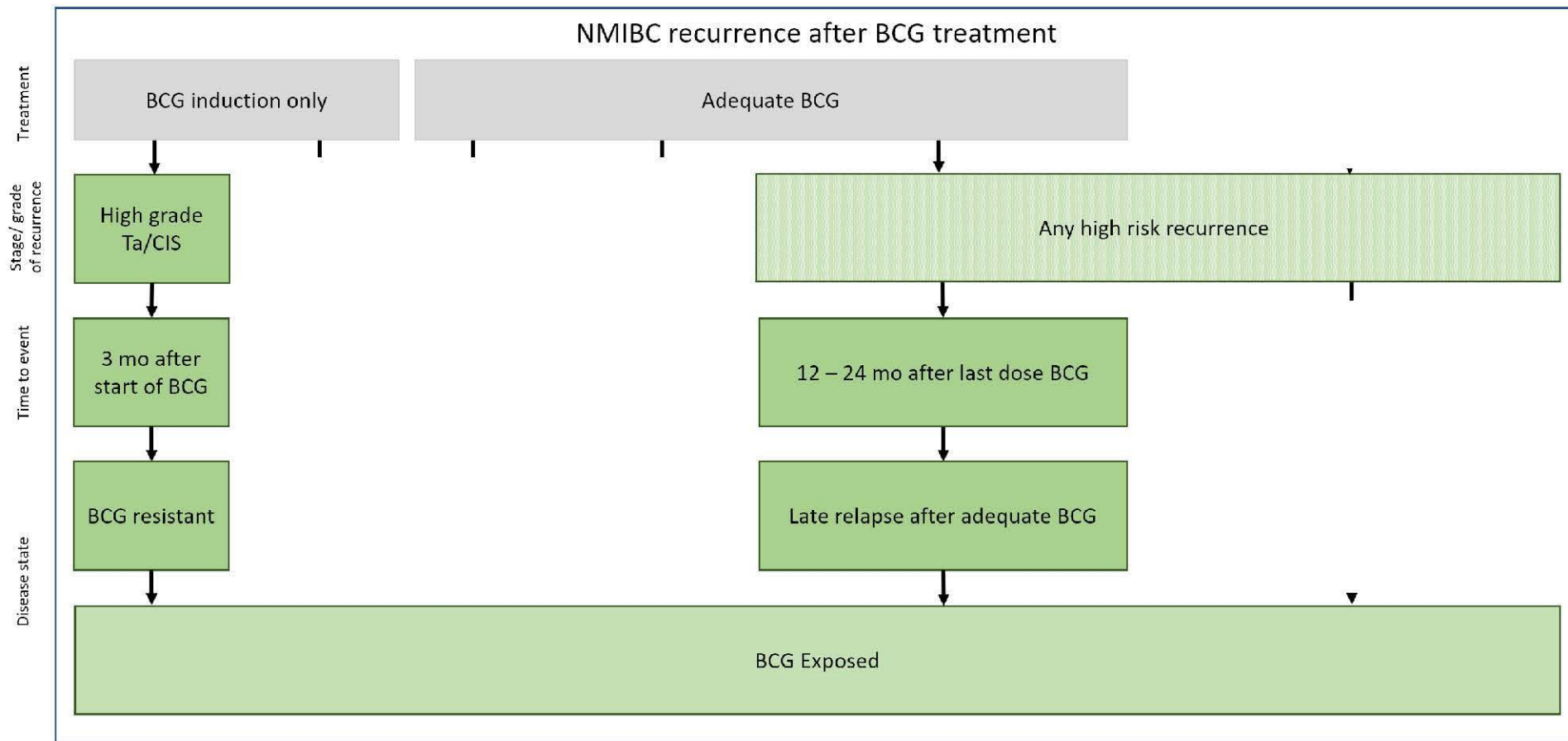
International Bladder Cancer Group (IBCG) Consensus Statement on Clinical Trial Design for Patients with **BCG-Exposed** High Risk NMIBC

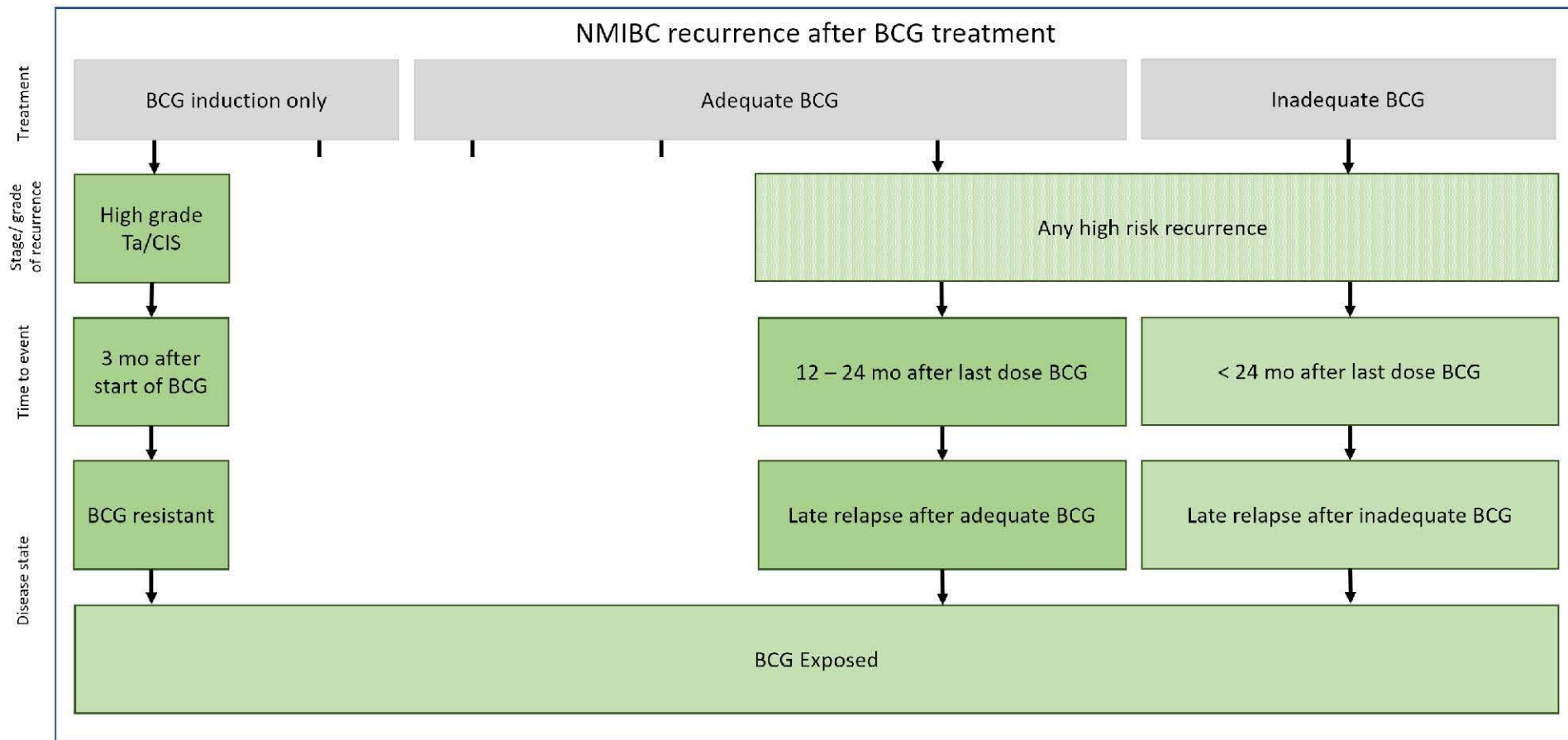
M. Roumiguié^{1,b}, A.M. Kamat³, T.J. Bivalacqua⁴, S. Lerner⁵, W. Kassouf⁶, A. Böhle⁷, M. Brausi⁸, R. Buckley⁹, R. Persad¹⁰, M. Colombel¹¹, D. Lamm¹², J. Palou-Redorta¹³, M. Soloway¹⁴, Brothers K¹⁵, G. Steinberg¹⁶, Y. Lotan¹⁷, R. Sylvester¹⁸, A.J. Witjes¹⁹, P.C. Black¹,

NMIBC recurrence after BCG treatment



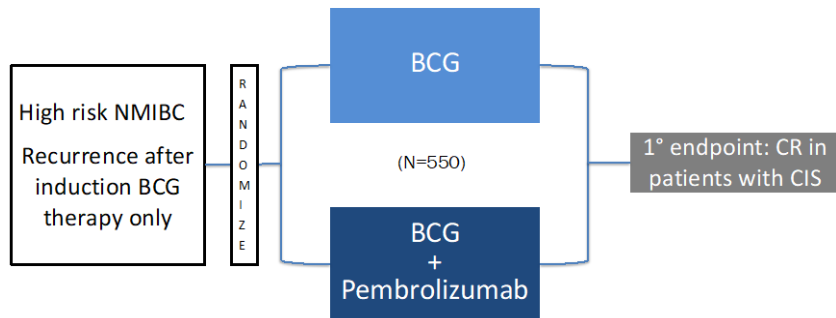






What's next: Trials Earlier in NMIBC

BCG "Exposed"



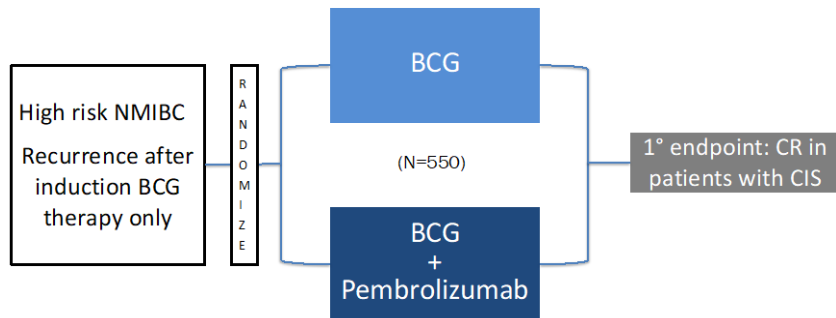
Keynote 676

Similar Trials:

- Checkmate 7G8 with nivolumab
- ADAPT-Bladder durvalumab + RT

What's next: Trials Earlier in NMIBC

BCG "Exposed"

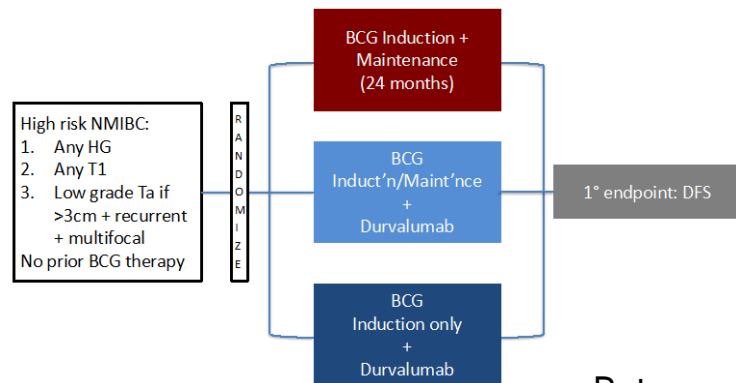


Keynote 676

Similar Trials:

- Checkmate 7G8 with nivolumab
- ADAPT-Bladder durvalumab + RT

BCG Naïve



Potomac

Similar Trials:

- ALBAN with atezolizumab
- CREST with sasanlimab (subq)

Contemporary Outcomes of Patients with Nonmuscle-Invasive Bladder Cancer Treated with bacillus Calmette-Guérin: Implications for Clinical Trial Design



Justin T. Matulay ^{ID}, Roger Li, Patrick J. Hensley ^{ID},* Nathan A. Brooks, Vikram M. Narayan ^{ID}, H. Barton Grossman, Neema Navai ^{ID}, Colin P. N. Dinney ^{ID}† and Ashish M. Kamat ^{ID}§,‡

Table 2. Survival analysis based on Kaplan-Meier estimates at 1, 3 and 5-year time points

	RFS-HG			PFS			CFS			OS			Median Mos Followup
	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	
% Overall	81	76	74	97	93	92	95	89	86	99	93	86	47.8
% EAU risk group:													
Intermediate	95	92	86	100	100	100	98	96	90	98	94	79	43.1
High	80	74	72	96	92	91	95	88	86	99	93	87	49.4
% AUA NMIBC risk group:													
Intermediate	89	85	82	98	98	98	93	91	88	99	96	86	46.9
High	79	73	71	96	94	93	96	89	86	99	92	86	48.2
% Presence of CIS:													
LG Ta/T1 only	94	90	85	100	100	100	98	96	92	98	94	82	43.0
HG Ta/T1 only	81	77	75	97	93	92	96	91	89	99	94	88	44.8
CIS only	77	70	66	91	91	91	81	74	74	97	90	80	42.3
Ta/T1+CIS	77	68	67	96	92	89	94	85	81	99	91	86	65.3

Once BCG-Unresponsive, Always BCG-Unresponsive

Bladder Cancer 3 (2017) 145–146
DOI 10.3233/BLC-170118
IOS Press

145

Letter

Once BCG Unresponsive, Always BCG Unresponsive: An Open Letter to the FDA to Enhance Recruitment into Clinical Trials in Bladder Cancer

Ashish M. Kamat^{a,*}, Seth Lerner^b, Peter Black^c, Joaquim Bellmunt^d, Colin Dinney^a, Noah M. Hahn^e, Michael O'Donnell^f and Diane Z. Quale^g

Some Considerations for Clinical Trial Design



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Bladder biopsies should be mandatory for high risk NMIBC trials

Mandatory biopsies of the bladder should be at 6 months



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**For patients with BCG unresponsive CIS, who have
recurrence at 3 months**

**one additional course of treatment (until the 6 month
evaluation) should be allowed**



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For patients enrolled in trials for high risk NMIBC—including BCG-unresponsive disease—prostatic urethral involvement is excluded in most trials.

The SITC-IBCG panel recommends patients be included, but stratified for randomization



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Patients with NMIBC undergoing cystoscopy may have this with white light or blue light depending on referral patterns.

There is no need to mandate blue light cystoscopy prior to study entry



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For patient with BCG-unresponsive disease, the FDA guidance document recommends single-arm studies. Despite recent developments, and currently available data, the SITC-IBCG panel (n=23) was split

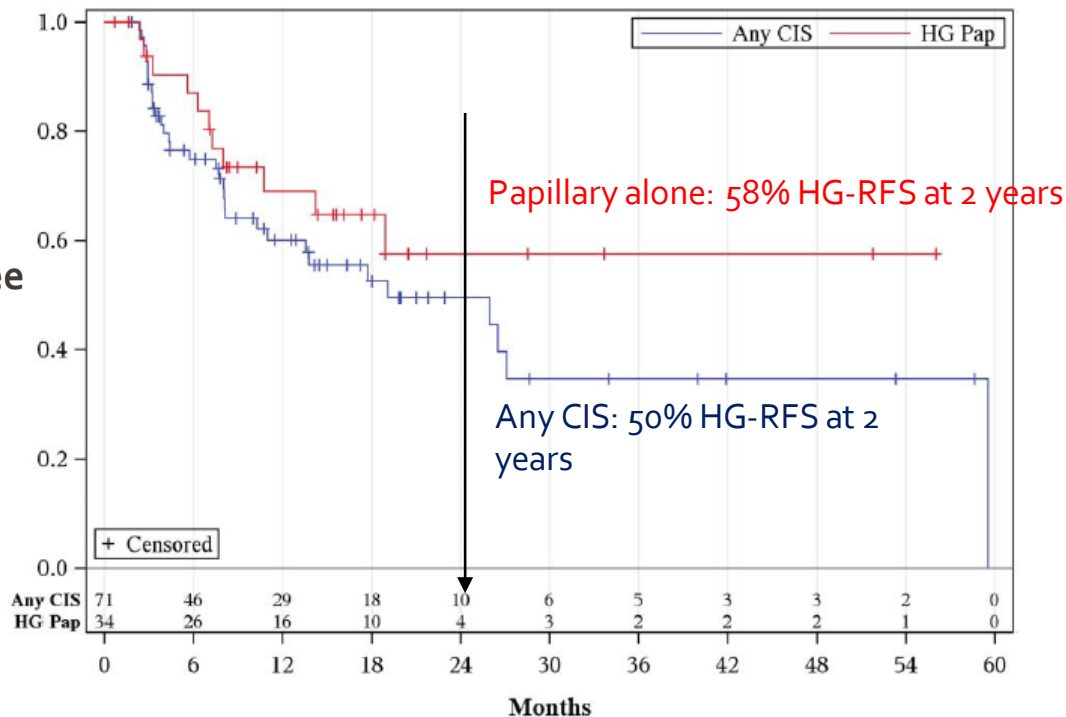
51%: recommend best practice as control arm (eg Gem/Doce, Pembro, other ...)

48%: continue to recommend single arm studies

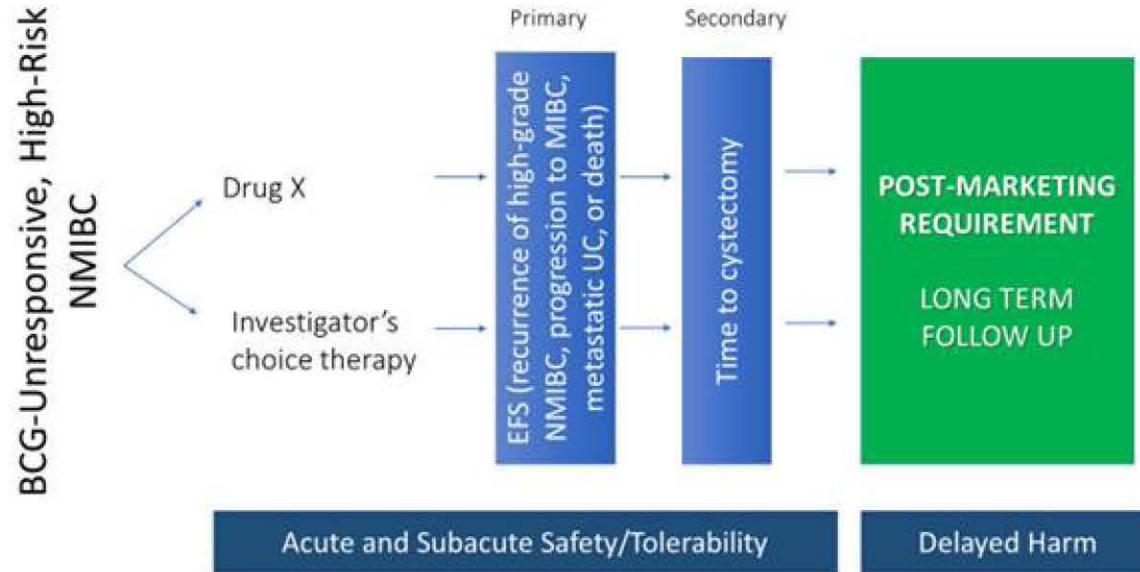
Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer



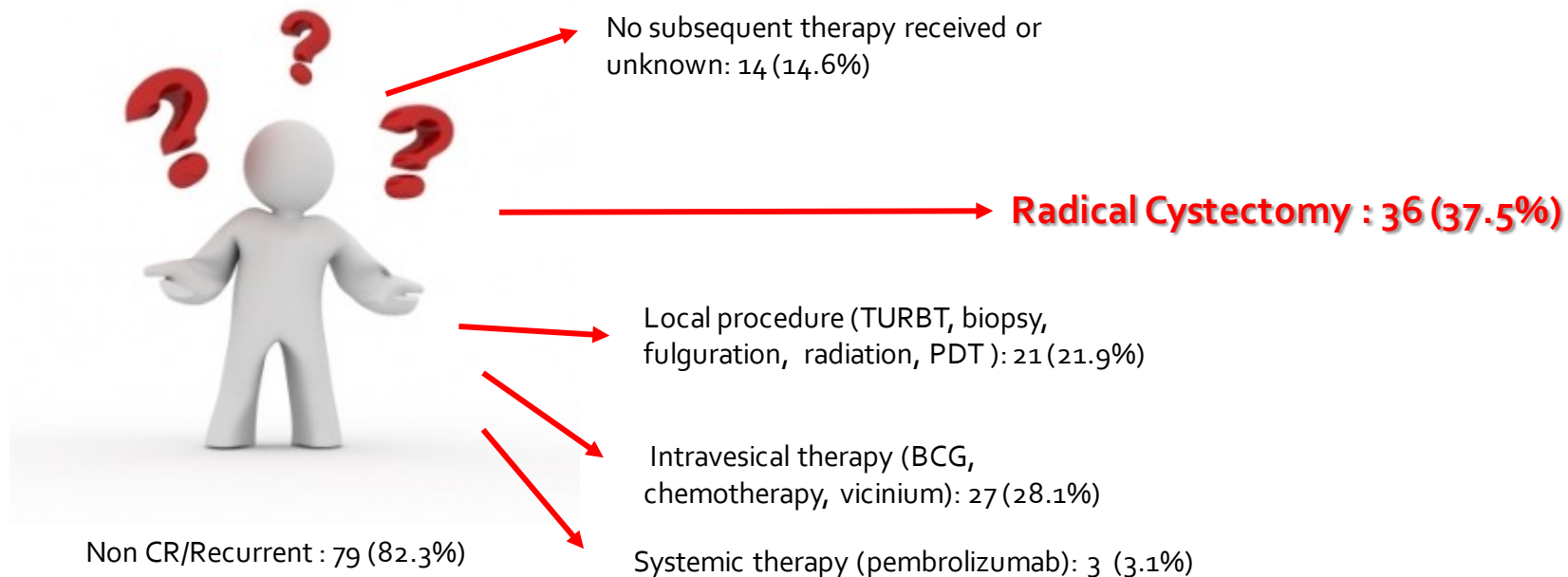
High grade
bladder
recurrence-free
survival for
BCG
unresponsive
cases



Cystectomy as an Endpoint?



KN57: Cystectomy Free Survival: 62.5% at 2 years



Total N=96

From ODAC Presentation, FDA Dec 2019

Nadofaragene: Cystectomy Free Survival: 65% at 2 years



No subsequent therapy received or unknown: ???

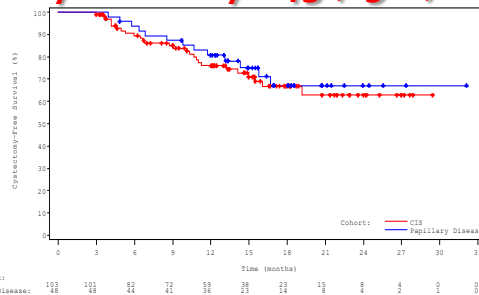
Radical Cystectomy : 43 (29%)

Local procedure (TURBT, biopsy, fulguration, radiation, PDT): ???

Intravesical therapy (BCG, chemotherapy, vicinium): ???

Systemic therapy (pembrolizumab, other): ???

Non CR/Recurrent : 78 (75.7%)



Total N=103

Data courtesy: Colin Dinney, 2021

Cystectomy Free Survival: Valid End Point?

- Important to patients – retain bladder (90+% of enrolled patients)
- Nebulous – hard to control
 - Indication for cystectomy (recurrence? Or progression?)
 - Timing of cystectomy (before or after progression?)
 - Patient/clinician preferences
 - Access to care
- Recommendation:
 - Important to collect and report the data
 - Not formally include it as a secondary endpoint

