Definitions, End Points, and Clinical Trial Designs for Bladder Cancer:

Non-Muscle Invasive Bladder Cancer

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Historical Perspective (FDA 2018)

BCG-unresponsive NMIBC


FDA Public Workshop
Clinical Trial Design Issues – Development of New Therapies for Non-Muscle Invasive Bladder Cancer
May 6, 2013

Manchester Grand Hyatt - San Diego, CA
Douglas Pavilion C & D

Co-sponsored by the U.S. Food and Drug Administration (FDA) & the American Urological Association (AUA)

Co-Chairs: Jonathan Jarow, MD and Seth P. Lerner, MD, FACS

Definitions, End Points, and Clinical Trial Designs for Non–Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group

Ashish M. Kamat, Richard J. Sylvester, Andreas Böhle, Joan Palou, Donald L. Lamm, Maurizio Brausi, Mark Soloway, Raj Persad, Roger Buckley, Marc Colombel, and J. Alfred Witjes

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- **Only viable alternative: Radical Cystectomy**
  - Ethics, logistics, and feasibility of randomization to RC
  - Placebo = unethical
- In the absence of a "gold standard" ***SINGLE ARM TRIALS*** for patients with **BCG-unresponsive CIS** with/without papillary disease acceptable
    - Clinically meaningful response rates
      - CIS: 6-month CR of 40-50%
      - Durable RR of at least 30% for 18-24 months (lower bound of the 95% CI excluding 20%)

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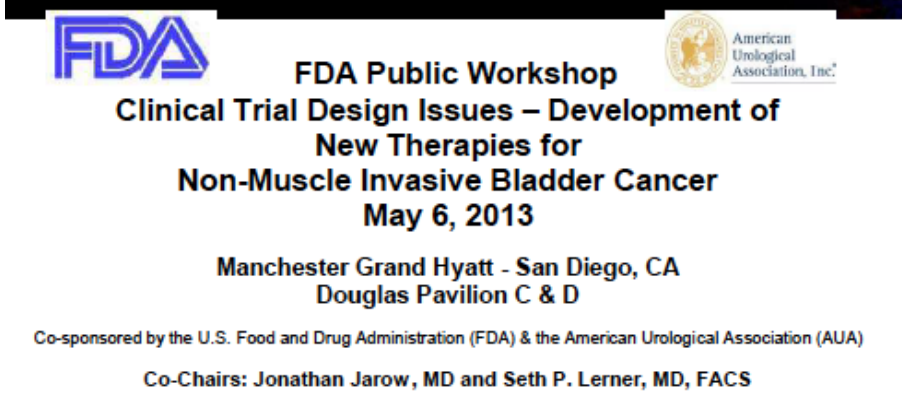
Historical Perspective (2018)

Placebo Ok if…



- Patients planning to undergo RC, an intravesical agent could be compared to placebo or active control
  - **Pathologic CR** = acceptable endpoint
- Low risk disease
- Add-on trial
  - e.g. BCG + X vs. BCG + placebo

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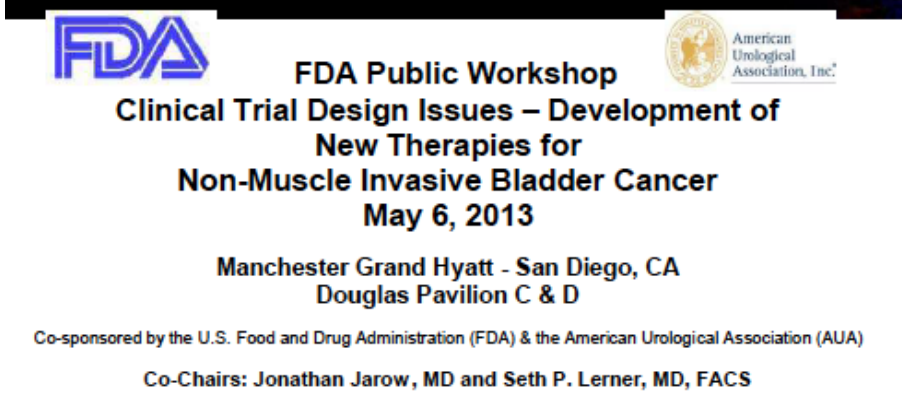
Historical Perspective (2018)
Meaningful Endpoints



- ✓High grade recurrence
- ✓Progression (stage)
- ✓Upper tract second primary in a patient treated with a systemic agent
- ✓CIS:
  - Complete response
  - Durability of response

Key Consideration: Patients with a LOW grade recurrence on trial for HIGH risk tumor: ok to stay on study treatment

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2024 Refinement of Risk Classification

Definitions, End Points, and Clinical Trial Designs for Bladder Cancer: Recommendations From the Society for Immunotherapy of Cancer and the International Bladder Cancer Group

Ashish M. Kamat, MD, MBBS[1]; Andrea B. Apolo, MD[2]; Marek Babjuk, MD, PhD[3]; Trinity J. Bivalacqua, MD, PhD[4]; Peter C. Black, MD, FACS, FRCSC[5]; Roger Buckley, MD, FRCSC[6]; Matthew T. Campbell, MD, MS[7]; Eva Compérat, MD, PhD[8]; Jason A. Efstathiou, MD, DPHIL[9]; Petros Grivas, MD, PhD[10]; Shilpa Gupta, MD[11]; Neil J. Kurtz, MD[12]; Donald Lamm, MD, FACS[13]; Seth P. Lerner, MD, FACS[14]; Roger Li, MD[15]; David J. McConkey, PhD[16]; Joan Palou Redorta, MD, PhD[17]; Thomas Powles, MBBS, MD, MRCP[18]; Sarah P. Psutka, MD[19]; Neal Shore, MD, FACS[20]; Gary D. Steinberg, MD[21]; Richard Sylvester, ScD[22]; J. Alfred Witjes, MD, PhD[23]; and Matthew D. Galsky, MD[24]

	Low- and Intermediate Risk	High Risk		
		BCG-Naive	BCG-Exposed	BCG-Unresponsive
Number of Tumors	Solitary	1+ →		
Primary/Recurrent	Primary	Primary	Recurrent	Recurrent
Grade	Low	High →		
Stage	pTa, pT1	CIS ± pTa/pT1 →		
Prior Treatment	none	Not BCG	BCG	BCG (5+2) ***

Different trial considerations are appropriate across these different categories

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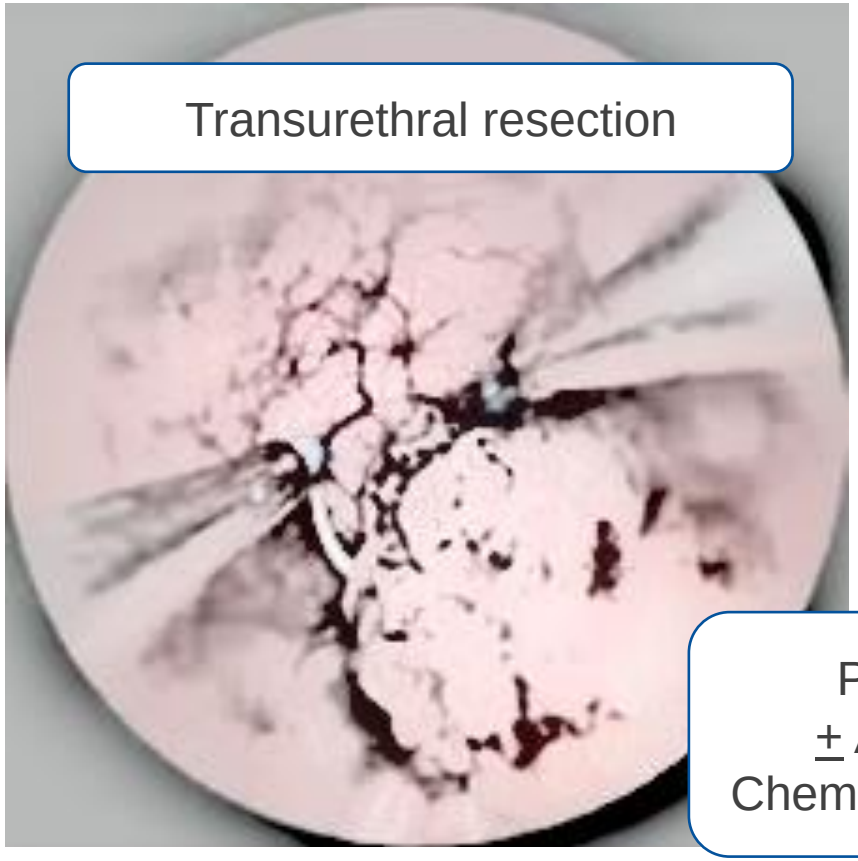
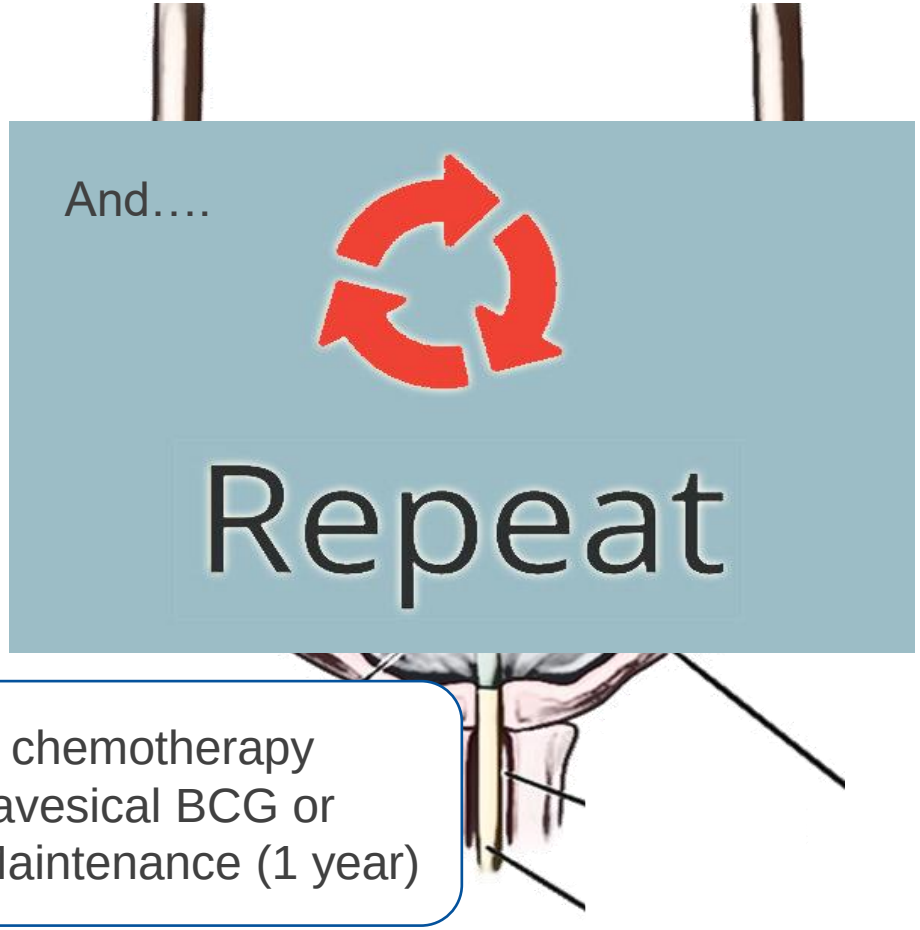
Kamat AM et al., JCO 2023; 41: 5437-5447

Current Paradigm: Treatment of IR NMIBC



Transurethral resection



Postoperative chemotherapy
± Adjuvant intravesical BCG or
Chemotherapy ± Maintenance (1 year)

Outcomes in Intermediate Risk – Current

RFS TURBT only

- ***1 year: ~62%***
- ***5 year: ~40%***

Single dose of Adjuvant Intravesical Chemotherapy:

ARR: 27 – 31%

RFS

iBCG + 1 year mBCG:

84.6%

Recurrences of low grade NMIBC after TURBT are low grade in >90%

****Not life-threatening****

Messing E et al, JAMA 2018; Sylvester RJ et al., Eur Urol 2016; Bosschieter J et al., Eur Urol 2019; Gudjonsson S et al., Eur Urol 2009; Hinotsu et al., 2011; Herr H et al., J Urol 2007; Malmstrom PU et al., BJUI 2002; Gerace C et al., J Urol 2003; Wang EYH et al., Scand J Urol 2022

Problems with the Current Resection/ Adjuvant Therapy Paradigm

Morbidity

- 30-day complications: ***5.1%***
- Transfusion: ***1.5%***
- Readmission: ***3.7%***
  - Bleeding ***29%***
  - Infection ***21%***
- Reoperation ***1.5%***
- Mortality ***0.8%***
- ***Postoperative Delirium: 65%***
- ***Anesthesia-related long-term cognitive decline: 10%***

Cost

- Surveillance & Frequent TURBT
- Intravesical Therapy – Induction, Maintenance
- ***Resources***
- ***Financial Toxicity***
  - ***Direct and Indirect Costs***
  - ***Out of Pocket***
  - ***Patients & Caretakers***

Cumulative costs of care for IR-NMIBC 5-year period: ***$146,250***

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Mossanen M et al., World J Urol 2019; Pereira JF et al., Urology 2018

Low and Intermediate Risk Disease

Definitions, End Points, and Clinical Trial Designs for Bladder Cancer: Recommendations From the Society for Immunotherapy of Cancer and the International Bladder Cancer Group

Ashish M. Kamat, MD, MBBS[1]; Andrea B. Apolo, MD[2]; Marek Babjuk, MD, PhD[3]; Trinity J. Bivalacqua, MD, PhD[4]; Peter C. Black, MD, FACS, FRCSC[5]; Roger Buckley, MD, FRCSC[6]; Matthew T. Campbell, MD, MS[7]; Eva Compérat, MD, PhD[8]; Jason A. Efstathiou, MD, DPHIL[9]; Petros Grivas, MD, PhD[10]; Shilpa Gupta, MD[11]; Neil J. Kurtz, MD[12]; Donald Lamm, MD, FACS[13]; Seth P. Lerner, MD, FACS[14]; Roger Li, MD[15]; David J. McConkey, PhD[16]; Joan Palou Redorta, MD, PhD[17]; Thomas Powles, MBBS, MD, MRCP[18]; Sarah P. Psutka, MD[19]; Neal Shore, MD, FACS[20]; Gary D. Steinberg, MD[21]; Richard Sylvester, ScD[22]; J. Alfred Witjes, MD, PhD[23]; and Matthew D. Galsky, MD[24]

- ***Critical Objectives (hypotheses)***: To determine an agent's efficacy with respect to reducing:
  - ✓risk of **recurrence** within the bladder
  - ✓risk of **progression**
  - ✓**treatment and surveillance burden**
    - Treatment toxicity and time
    - Financial toxicity
    - Impact on quality of life

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Stage	pTa, pT1	CIS ± pTa/pT1 →		
Prior Treatment	none	Not BCG	BCG	BCG (5+2) ***

Strategy 1: Ablative Trials

~ Neoadjuvant

Strategy 2: Adjuvant Trials

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Low and Intermediate Risk Disease

- **Baseline Evaluation**
  - Detailed History
    - Date of Dx
    - Grade, Stage, Multiplicity, Size
    - Prior Recurrences
    - Prior Treatment
    - Cystoscopic findings
  - *If Advanced Cystoscopic evaluation used → use consistently*
  - Cytology: Rule out HG disease
  - Contrast-enhanced cross-sectional imaging

- **Follow-ups:**
  - **Ablation:** Evaluate index tumor or scar
    - Cystoscopy
    - Cytology
    - Biopsy of scar = optional
  - If residual tumor is present → SOC (Resect)
  - Consider **maintenance therapy** for complete response and adjuvant trials for residual disease (after resection)
  - Surveillance
    - Years 1/2: q3-4 months
    - Years 3/4: q6 months

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Note: Intermediate Risk Disease can be further risk-stratified

Intermediate-risk Non–muscle-invasive Bladder Cancer: Updated Consensus Definition and Management Recommendations from the International Bladder Cancer Group

Wei Shen Tan[a,b], Gary Steinberg[c], J. Alfred Witjes[d], Roger Li[e], Shahrokh F. Shariat[f,g], Morgan Roupret[h], Marko Babjuk[i], Trinity J. Bivalacqua[j], Sarah P. Psutka[k], Stephen B. Williams[l], Michael S. Cookson[m], Juan Palou[n], Ashish M. Kamat[o,]*

Low-risk NMIBC
Primary, solitary G1/LG Ta

Intermediate-risk NMIBC [*]:
pTa LG/G1: recurrent
pTa LG/G1: new diagnosis and (multifocal or ≥3 cm)
pTa G2: new diagnosis or recurrent
pT1 LG/G1–2: new diagnosis or recurrent

High-risk NMIBC
Any HG
Any CIS
Variant histology

How many of the following risk factors:
Multiple tumors
Early recurrence (<1 yr)
Frequent recurrence (>1/yr)
Tumor size (>3 cm)
Failure of previous intravesical treatment

0 risk factor
- TURBT + single-instillation postoperative chemotherapy
- Consider office fulguration and observation where appropriate

1–2 risk factors
- TURBT + single-instillation postoperative chemotherapy
- Recommend intravesical induction chemotherapy
- Recommend BCG with maintenance (up to 1 yr) if recurrence following prior chemotherapy

≥3 risk factors
- TURBT
- Recommend intravesical induction BCG with maintenance up to 1 yr or intravesical induction chemotherapy with maintenance
- Consider alternative intravesical treatments such as combination chemotherapy or chemohyperthermia in patients who develop recurrence following BCG or chemotherapy if BCG unavailable

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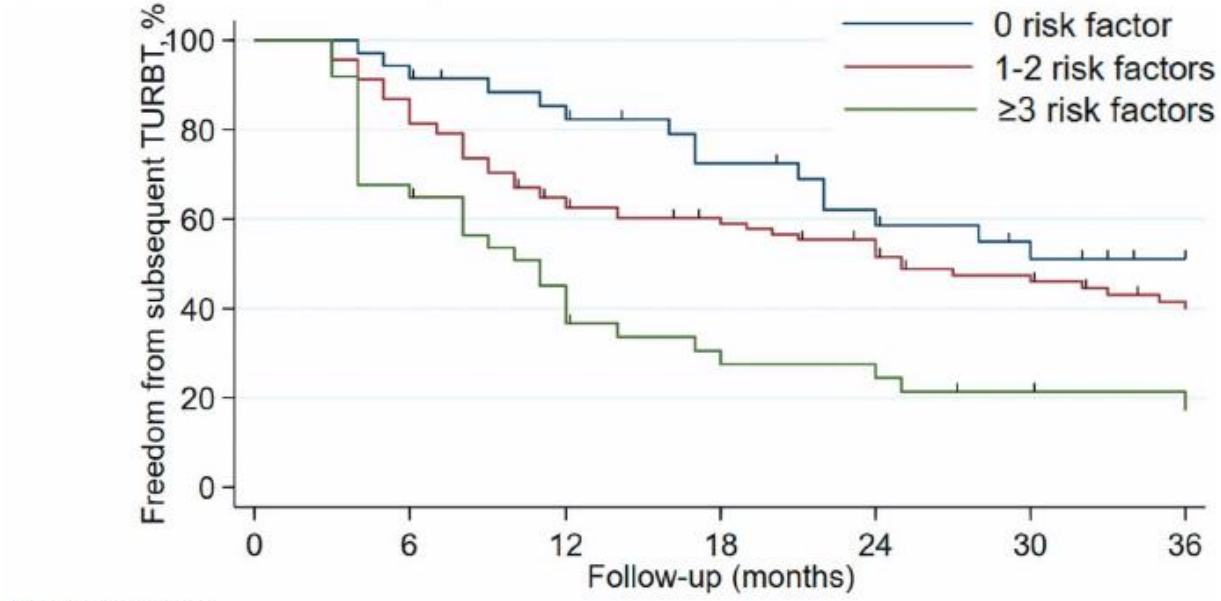
IBCG IR NMIBC Risk Group Independent Validation

International Bladder Cancer Group Intermediate-risk Nonmuscle-invasive Bladder Cancer Scoring System Predicts Outcomes of Patients on Active Surveillance

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

Wei Shen Tan,[1]* Roberto Contieri,[1,2,3]* Nicolò Maria Buffi,[2,3] Giovanni Lughezzani,[2,3] Valentina Grajales,[1] Mark Soloway,[4] Paolo Casale,[3] Rodolfo Hurle,[3†] and Ashish M. Kamat[1†‡]



MV Cox Proportions Hazards Analysis adjusted for age, T-stage, and sex → IBCG risk classifications associated with risk of subsequent TURBT vs. remaining on AS

0 Risk Factors: N=25

1-2 Risk Factors: N = 91; HR 1.66, 95%CI 0.96-2.9, p=0.07

≥3 Risk Factors: N = 37; HR 3.21, 95% CI 1.7-6.1, p<0.001

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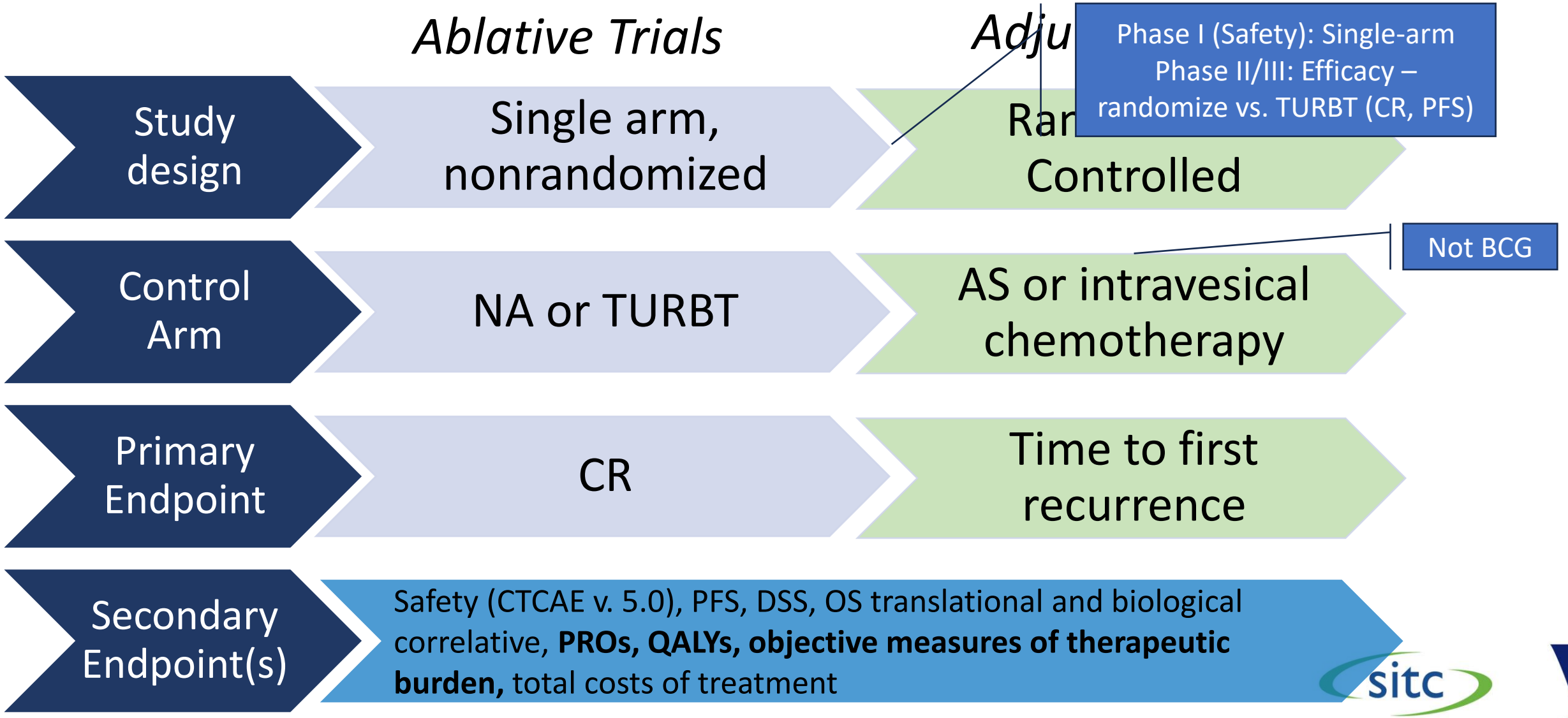
Wei ST et al., J Urol 2023

Low and Intermediate Risk Disease Trial Considerations



Kamat AM et al., JCO 2023; 41: 5437-5447

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Low and Intermediate Risk Disease
Endpoints to Consider

- ***Primary Endpoint Assessment (Ablative Trials-Phase II)***
  - Cystoscopy with photographic documentation
  - Negative Urine Cytology
    - Option: biopsy prior resection site/scar

3-month

- ***Critical Value for Effect Size/Response Rate***
  - Ablative trials: CR > 60%
  - Adjuvant trials: 10% increase in RFS

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Evolution 2016 > 2024: *Characterizing "BCG Failure"*

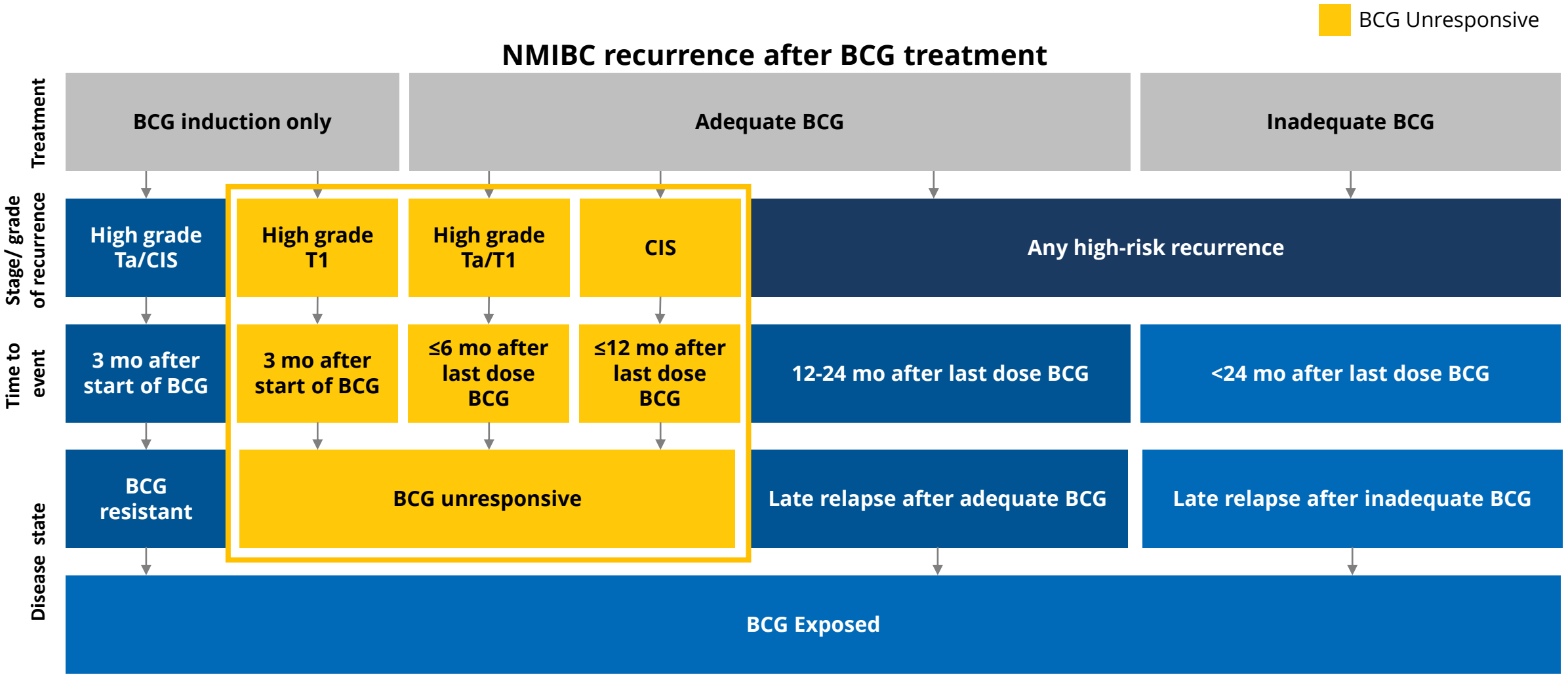

Fig.1 – Summary of disease states related to prior bacillus Calmette-Guerin (BCG) treatment. See the text for additional definitions. Patients with high-risk recurrence >24 mo after last dose of BCG are not covered by these definitions, as these patients are generally treated in the same way as for BCG-naïve patients. NMIBC = non-muscle-invasive bladder cancer; CIS = carcinoma in situ.

Roumigue M et al. Eur Urol 2022

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High Risk Disease

- ***Critical Objectives (hypotheses)***: To determine an agent's efficacy with respect to:
  - ✓**Complete response** within the bladder (CIS)
  - ✓**Improving DFS**
  - ✓Reducing risk of **progression**
  - ✓**Treatment burden**
    - **Cystectomy-free survival**
    - Treatment toxicity
    - Financial toxicity
    - Impact on quality of life

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Research Hypothesis: High risk NMIBC

- Augmentation of antitumor immune response

Investigational agent + BCG
Alternative to BCG

- **Investigational agents** = agent + BCG, new strain of BCG, alternative to BCG →

? *BCG-naïve/exposed: better than BCG?*
BCG-unresponsive: better than historic controls?

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Key Entry Criteria: High Risk NMIBC
Adjuvant Therapy Studies

Evaluation of CIS ± papillary disease vs. papillary disease only	Papillary disease is expected to be completely resected prior to study entry, CIS is not Treatment = **ADJUVANT** → Goal: prevent Recurrence
Untreated high risk NMIBC: high risk of progression	Placebo = unethical
Other Stratification Parameters:	Prostatic-urethral involvement Variant histology > 50%

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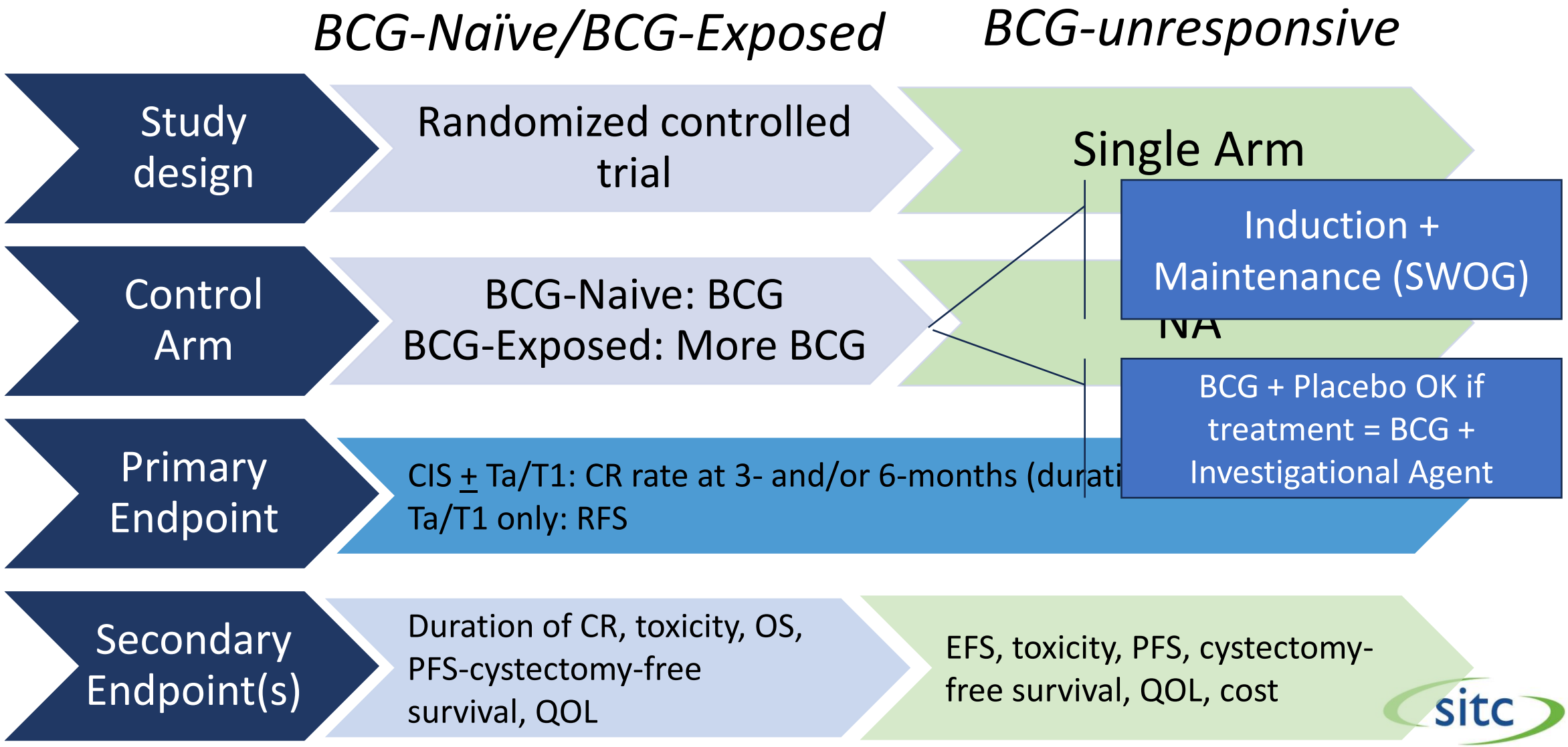
High Risk NMIBC Trial considerations



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High-Risk NMIBC Disease Trial Considerations

- ***Primary Endpoint Assessment***
  - Cystoscopy and Cytology @ 3-month intervals
  - CT/MRI Urography at 6-12 month intervals
- ***Critical Value for Effect Size/Response Rate***

CIS	3/6-month CR rate	Ta/T1	RFS
BCG-naïve	70%	BCG-naïve	10% increase in 2-year RFS rate
BCG-exposed	60%	BCG-exposed	
BCG-unresponsive	50%	BCG-unresponsive	1-year RFS rate: 30%

Recurrence of CIS at 3-months? → one additional course of treatment allowed
Historically: 60% persistent CIS will convert with additional treatment

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Follow-up Consideration Recommendations

Random biopsies

Not mandated by FDA 2018 guidance

Recommended at (6-) 12 months as an option

Study duration: minimum 2 years

Majority of recurrence or progression events will occur within the first 2 years from start of treatment

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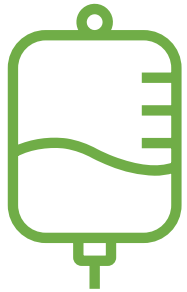
Final considerations - NMIBC



Prior to study entry

Importance of **visually complete TURBT**

- Caveat: Ablation trial

Single-course post-operative adjuvant chemotherapy allowed (not mandatory)

Multicenter studies

Adjust for receipt of postoperative single-dose adjuvant chemotherapy

Stratify by center

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Conclusions/Final Take-aways: NMIBC Study Design

- Appropriate Risk Stratification
- Stratification for prior treatment receipt
- Appropriate study design, endpoints for risk strata/disease state
- Secondary Endpoints: Patient-focused