



Regulatory pathway for HG Ta/T1 NMIBC

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Disclosures

- Research funding and personal compensation from FKD Therapies Oy for consulting and advisory services, including serving as the Independent Chairman of steering committee for the Phase 3 Nadofaragene firadenovec (rAd-IFNa/Syn3) trial.
- Research collaboration with AIV.

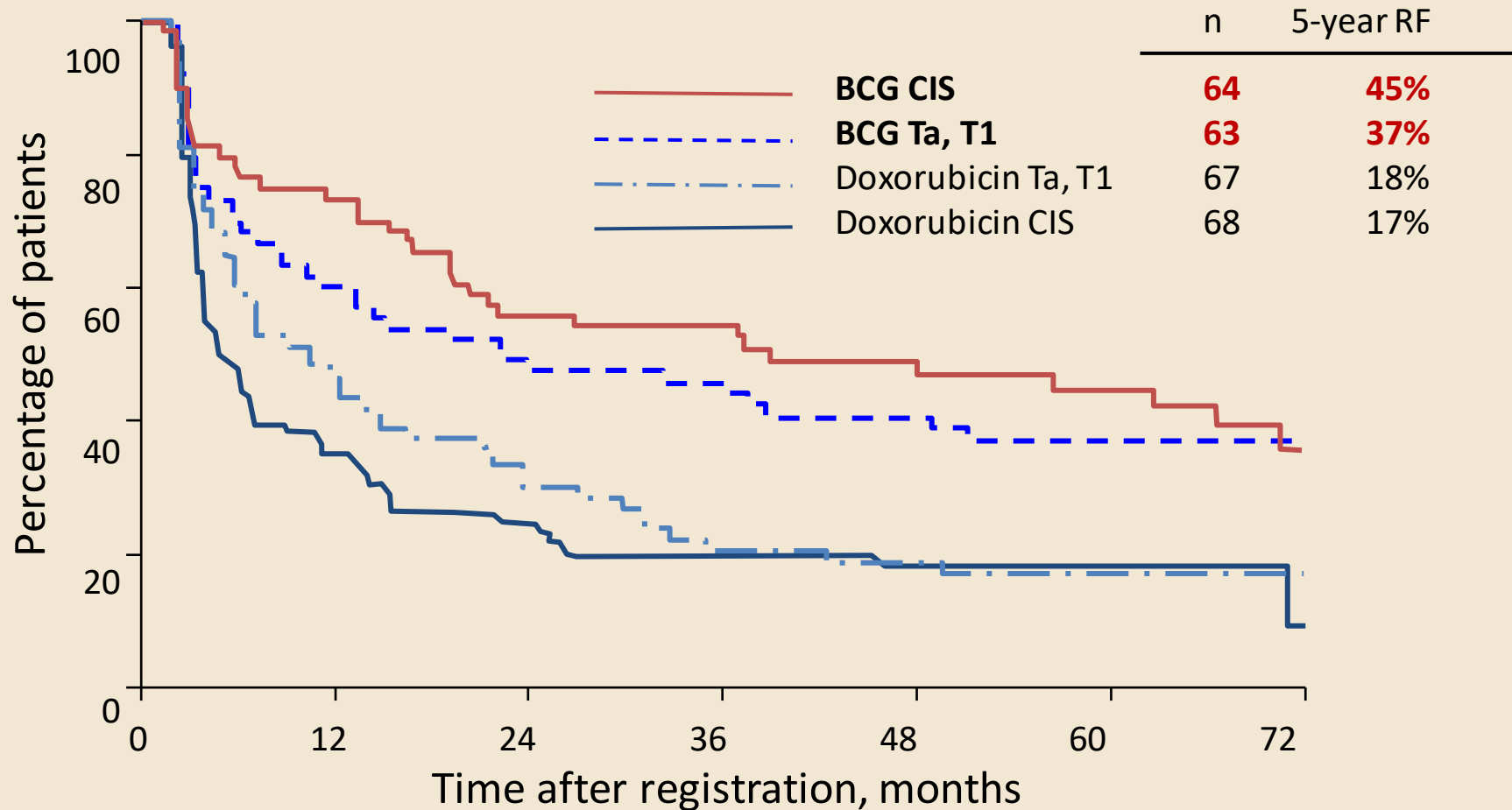
Meta-analyses: immunotherapy with BCG is recommended for high-risk NMIBC

Meta-analyses have shown that intravesical BCG reduces:

- **the risk of recurrence**
 - Shelley 2001 (TUR), 2004 (MMC)
 - Boehle 2003 (MMC)
 - Sylvester 2005 (CIS)
 - Malmstrom 2009 (MMC)
- **the risk of progression and death**
 - Boehle 2004 (MMC)
 - Sylvester 2002, 2009
 - Odens 2012

only if 1 to 3 years of maintenance BCG are given.

BCG vs. Doxorubicin in BCG naive patients



BCG naïve population

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

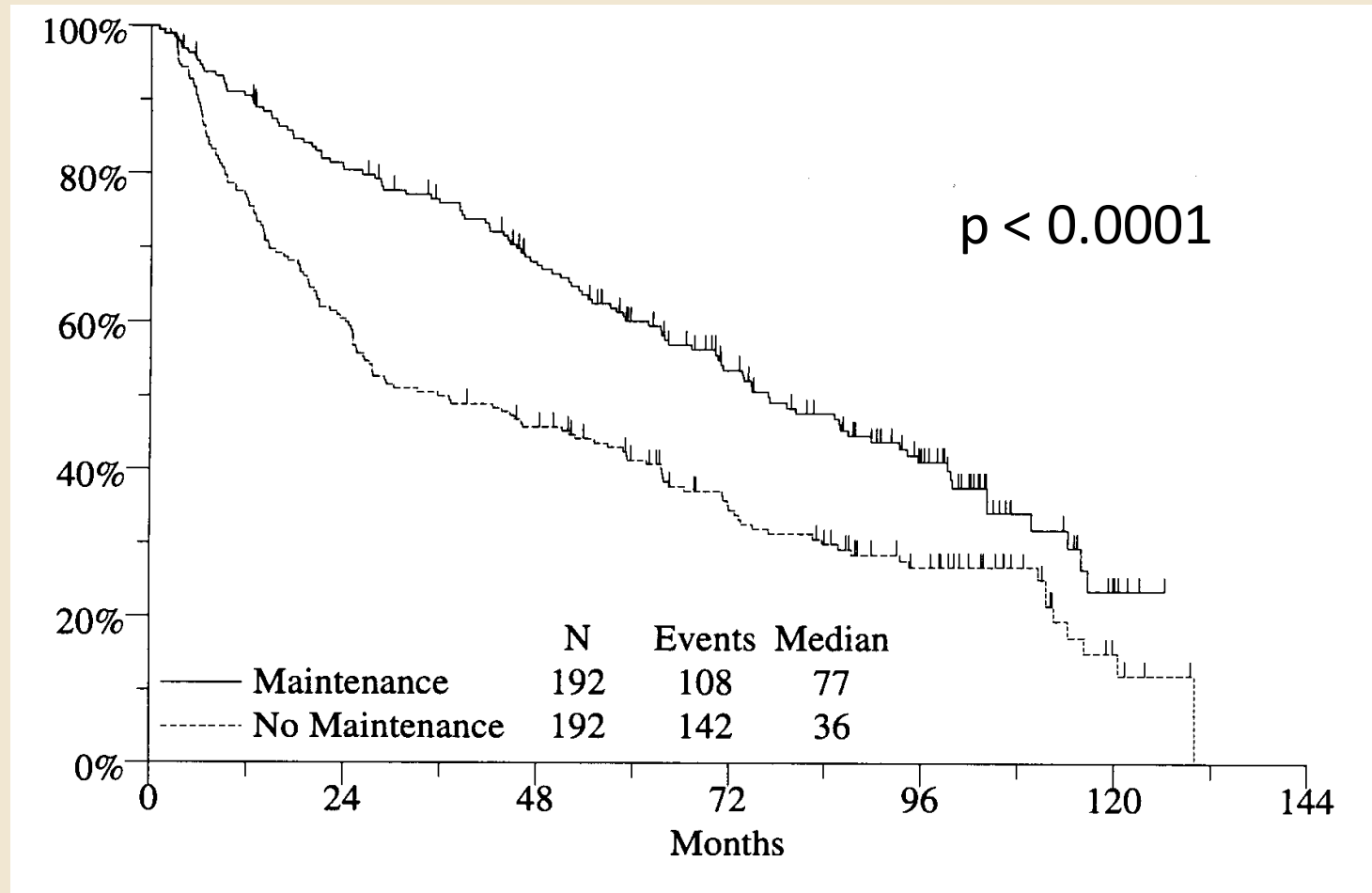
- Modest decrease in HG RFS for Ta/T1 + CIS (p= 0.02).
- PFS similar for Ta/T1, CIS, or Ta/T1 + CIS (p= 0.863).

Clinical series in the BCG exposed space: No difference in outcomes for CIS vs. HG Ta/T1 NMIBC

Author	Year	Design	Definition of previous BCG exposure	# meeting definition of BCG exposure	Treatment	RFS	PFS
Brake et	2000	Restrospective	BCG inadequate	24	2 nd induction BCG	79% and 58% at 6 and 24 mos	83% at 24 mos
Nadler et al	1994	Restrospective	BCG inadequate	66	2 nd induction BCG	58% RFS 24 mo	
Bretton et al	1990	Restrospective	BCG inadequate	28	2 nd induction BCG	36% at 30 mo	54% at 30 mo
Kavoussi et al	1988	Restrospective	BCG inadequate	87	2 nd induction BCG +/- maintenance	65% for Ta/T1 at 15.8 mo. 71% for CIS at 21.4 mo.	
Coplen et al	1990	Restrospective	BCG inadequate	53	2 nd induction BCG	50% CR after 2 nd induction 9/18 CIS CR after mean 47 mo	
Niwa et al	2018	Restrospective	BCG inadequate	92	2 nd induction BCG	59% at median follow up 91 mo	95.5% at 5 years
Steinberg et al	2016	Restrospective	BCG inadequate	198	Gem/Doce +/- maintenance	64% and 57% at 12 and 24 mo	
Steinberg et al	2016	Restrospective	BCG replapse > 12 mos	74 (60 Ta/T1, 14 CIS)	Gem/Doce +/- maintenance	Ta/T1 61% and 51% CIS 79% and 34% at 12 and 24 mo.	

Roumique et al, in press 2021

SWOG 8507: Even with maintenance therapy most patients recur



Lamm et al, 2000

BCG Unresponsive NMIBC

- While BCG is our most effective agent for treating NMIBC over time most patients eventually recur, and up to 35% may die of bladder cancer.
- Alternative therapy indicated but until recently only Valrubicin had been FDA approved for BCG refractory CIS with a CR of 10% at 12 mo.
- **Effective 2nd line therapy remains an unmet need for patients with HG Ta/T1 NMIBC facing cystectomy.**

What is the registration strategy for BCG Unresponsive Ta/T1 NMIBC?

- Randomized trials are currently recommended based on the assumption that therapy for Ta/T1 NMIBC is adjuvant since all disease is completely resected by TURBT prior to treatment.
- Is this assumption valid?
- Are CIS and HG Ta/T1 NMIBC distinct diseases that merit distinct clinical trial designs?

Should trial design be different for HG Ta/T1 and CIS?

- We know that re-resection identifies residual tumor in at least 50% of HG Ta/T1 tumors (Cumberbatch et al, Eur Urol 2018).
- Of 268 Ta/T1 pts enrolled on the pivotal UroVysion study 47 patients (16%) had tumor detected by BL only.
- There is also divergence in pathology at the time of recurrence.
- 5/11 patients (45%) treated with Nadofaragene firadenovec for HG Ta/T1 recurred with CIS.

Free urine DNA (utDNA) analysis identifies occult disease after TUR

- U-CAPP-seq, a 460 gene utDNA test, was developed to identify residual disease/recurrence after TURBT.
- Detected altered utDNA in 91% of patients who ultimately recurred.
- utDNA detection preceded clinical recurrence or progression in 92% of cases.
- Outperformed UroVysion ($p=0.02$), and cytology/cystoscopy combined ($p\leq 0.006$).
- Detected 100% of BLCA identified by cytology and 82% that were missed.

Persistence of disease in HG Ta/T1 cancers detected by UroSEEK after 'visually complete' TURBT

- UroSEEK detects mutations in 11 genes and copy number changes on 39 chromosomes in shed BLCA cells.¹
- Sensitivity of 74-96%, with average lead time to diagnosis of 6 months compared to cytology/cystoscopy.^{1,2}
- Identified residual disease in **71%** of patients (n=68) who underwent urine UROSEEK analysis following 'complete' TURBT for HG Ta/T1/CIS (8% with CIS).

Genomic alterations in CIS

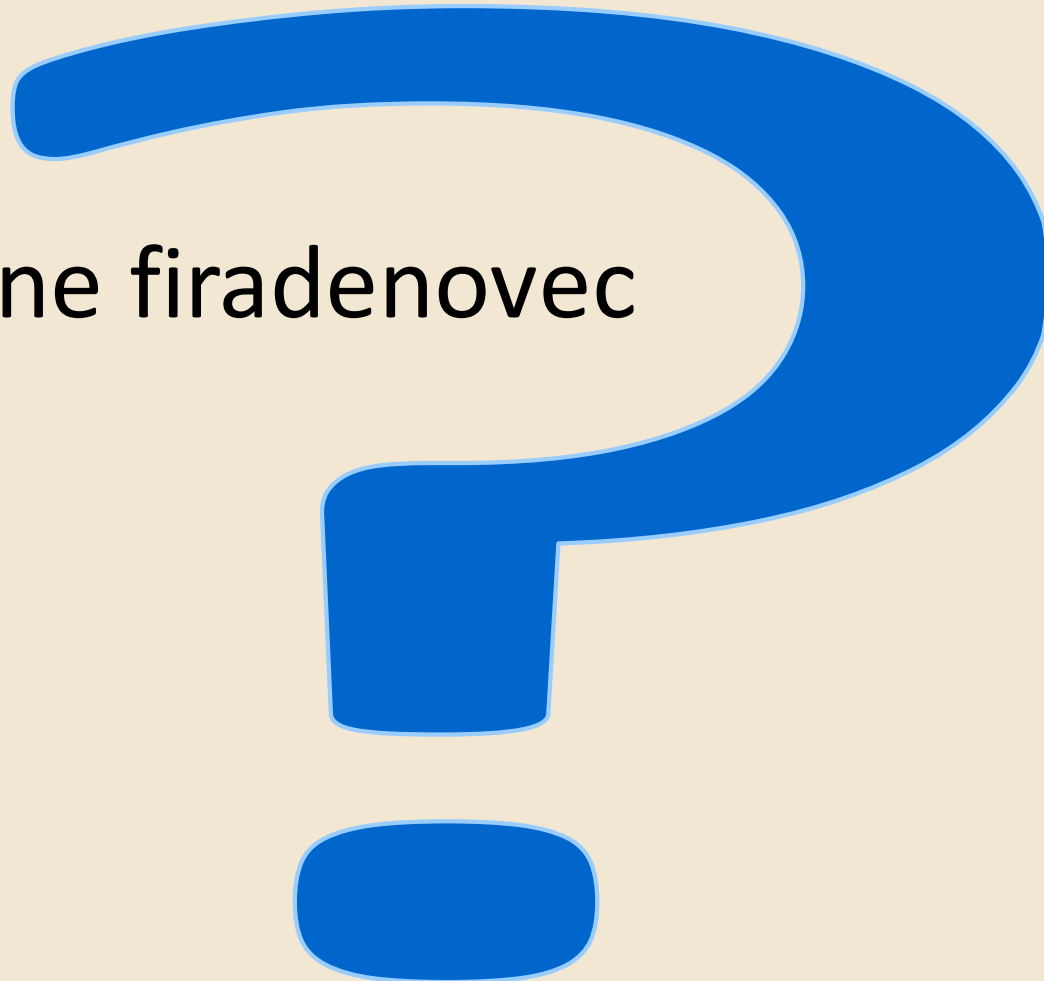
- Laser-capture microdissection of 26 FFPE cystectomy specimens for 31 gene targeted sequencing.
- TERT promoter mutations (52%) were the most common genetic alterations.
- Frequent TP53 mutations (44%), but no activating FGFR3 alterations.
- Genes encoding chromatin-modifying proteins (ARID1A, KDM6A, CREBBP, and EP300) were found to be altered in 68%.
- Aberrations in DNA damage repair associated genes (BRCA2, ATM, BRCA1, and ERCC2) in 60% of the analyzed samples.

Next-generation sequencing of NMIBC

- Included HG Ta/T1 NMIBC with/without CIS.
- Pre-treatment index tumors and matched germline DNA from 105 patients with NMIBC underwent targeted exon sequencing analysis.
- Most frequently altered genes in Ta/T1 NMIBC were the TERT promoter (73%), **FGFR3 (49%)**, KDM6A (38%), PIK3CA (26%), STAG2 (23%), ARID1A (21%), and TP53 (21%).
- **Genetic alterations for HG Ta/T1 overlap those identified for CIS.**

Single arm trials that reported outcomes for CIS and Ta/T1 BCG Unresponsive NMIBC

- Nadofaragene firadenovec
- Vicineum
- CG0070



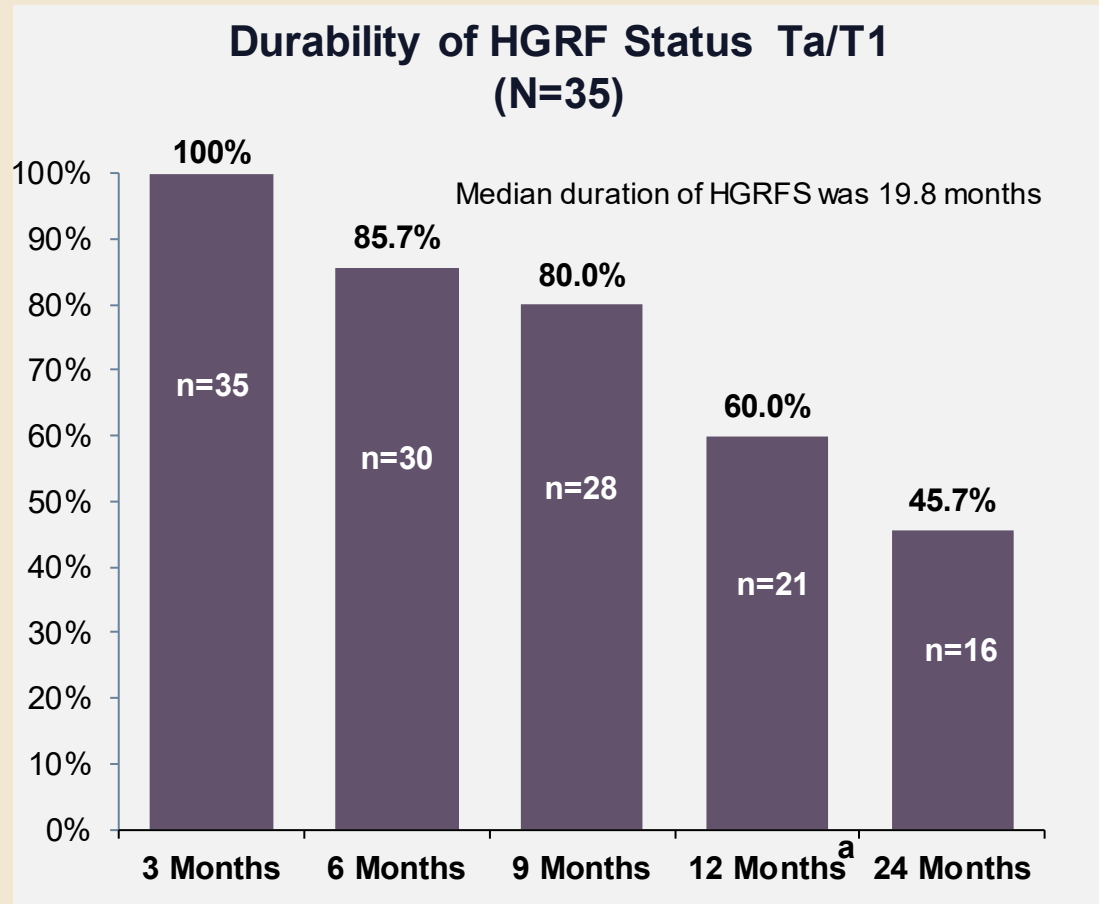
HG RFS after Nadofaragene Firadenovec, Vicinium, and CG0070

HG RFS at	Nadofaragene Firadenovec ¹		Vicinium ²		CG0070 ³	
	HG Ta/T1 (n=50)	CIS (n=107)	HG Ta/T1 (n=38)	CIS (n=89)	HG Ta/T1 (n=19)	CIS (n=45)
3 months	73%	53%	71%	40%	-	-
6 months	62%	41%	58%	26%	37%	44%
9 months	58%	35%	45%	20%	-	-
12 months	44% (48%)	24% (27%)	42%	17%	32%	29%

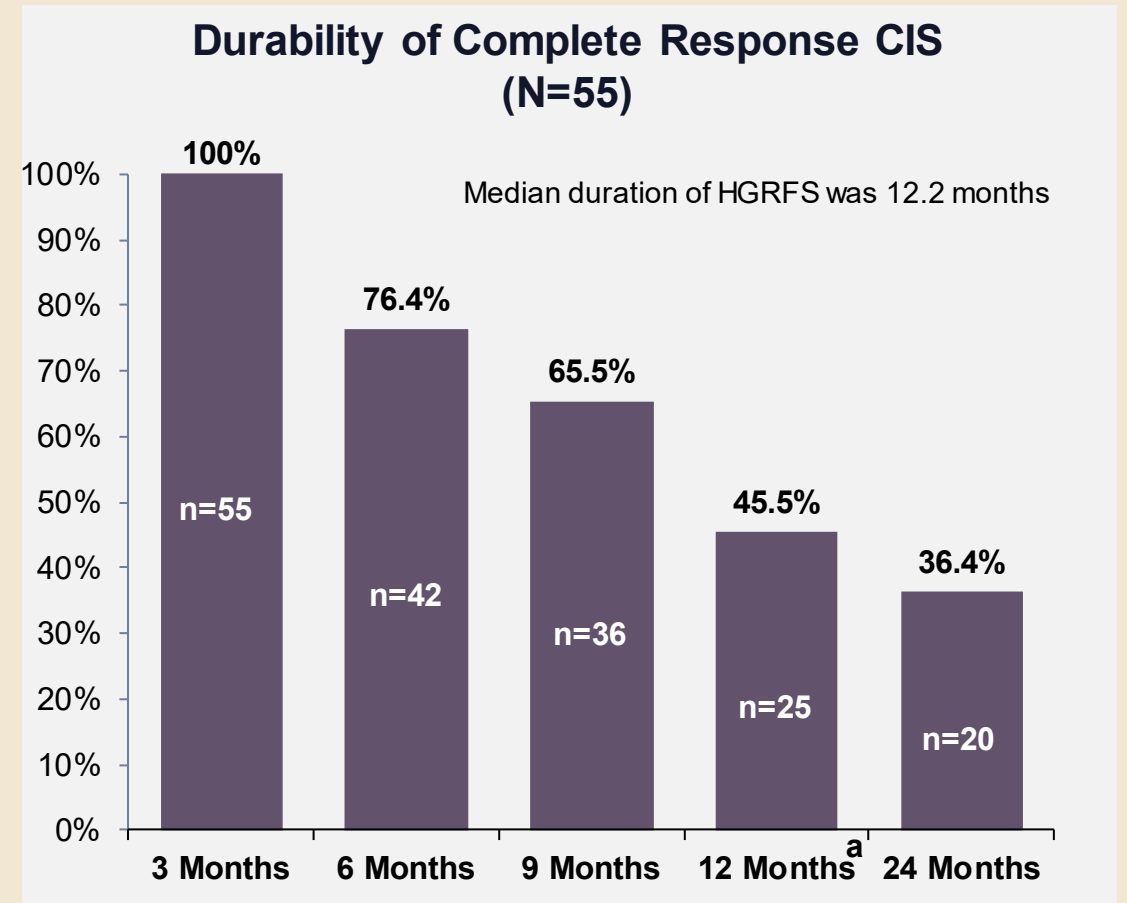
- No consistent improvement in response to novel agents for HG Ta/T1 NMIBC compared to CIS.

1. *Boorjian et al., Lancet Onc 2021*
2. *Shore et al., J Urol (suppl) 2020*
3. *Packiam et al., Urol Onc 2017*

Durability of response at 24 months after Nadofaragene



(Schuckman et al, AUA 2021)



(Lotan et al, AUA 2021)

Is a distinct trial design for Ta/T1 NMIBC warranted?

- No consistent differences in response to therapy between CIS and HG Ta/T1 NMIBC.
- Divergence in pathology reported at recurrence, patients treated for HG Ta/T1 NMIBC can recur with CIS.
- Clinical and genomic evidence indicates that residual disease persists after complete TUR in most patients with HG Ta/T1.
- Furthermore, underlying genomic alterations are similar for both HG Ta/T1 and CIS.
- Blurs the distinction between BCG Unresponsive Ta/T1 and CIS.

Opportunities for BCG naïve and exposed HG Ta/T1 NMIBC

- Study drug and BCG vs. BCG
- Study drug vs. BCG
- Study drug vs. investigators choice (BCG shortage)
- Primary endpoint: durable event-free survival

Trial designs for BCG Unresponsive Ta/T1 NMIBC

- Randomize study drug vs. investigators choice.
- Burden of proof does not support the distinction between HG Ta/T1 and CIS.
- Supports a single-arm trial design of study drug for Ta/T1 similar to that approved for CIS.
- Primary endpoint: Durable event-free survival

Standardizing registration trials for Ta/T1 HG NMIBC

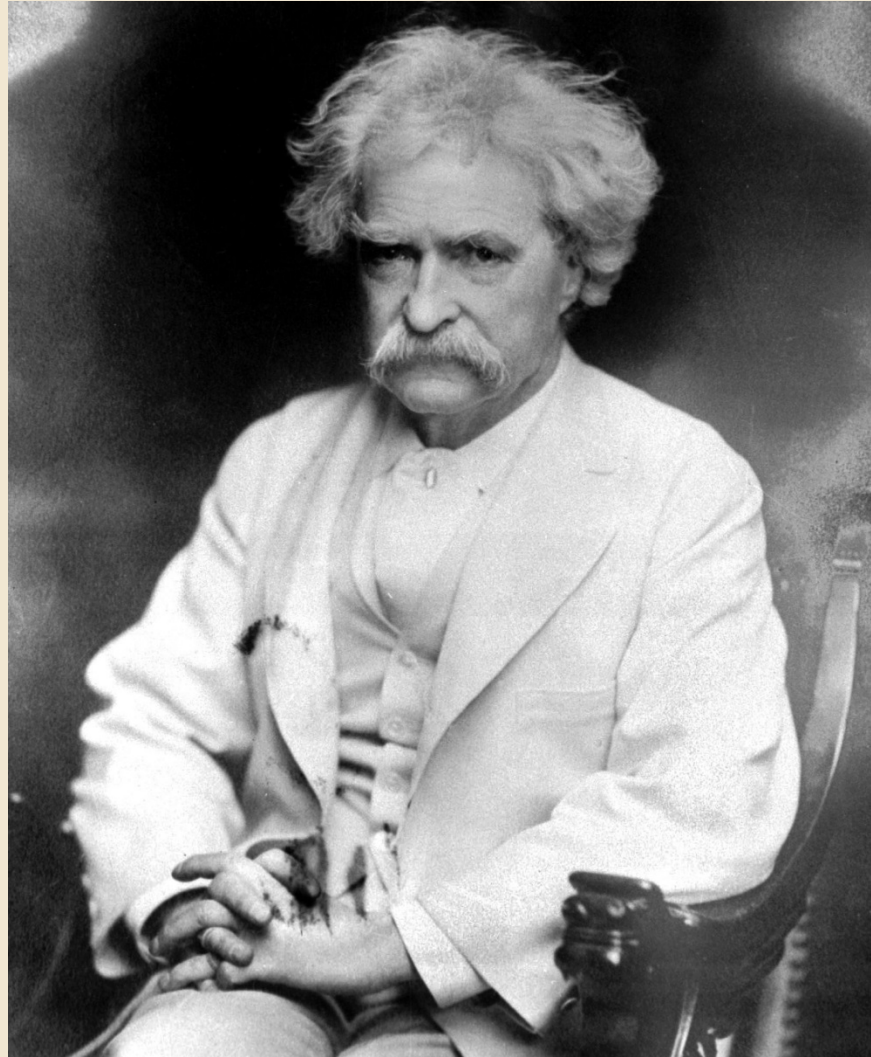
- How do we ensure the quality of the TUR for Ta/T1?
- How do we detect the presence of occult disease after TUR?
- Should blue light or enhanced cystoscopy be required?
- How do we deal with suspected CIS detected with blue light.
- What about mandated re-resection or random biopsies at screening for all patients with HG Ta/T1 disease?
- Timing of a recurrence with a previous positive cytology.

Specific considerations for single arm trials

- The timing of the determination of a CR or HG RFS after the first dose of a study drug will influence the response rate.
- CR rate improved as much as 25% using a 6 mo. endpoint that allows for retreatment of persistent disease at 3 mo.
- What about direct comparisons between trials that employ combination therapy (often with BCG) vs. monotherapy?
- Even in patients with BCG unresponsive disease at least 20% will achieve a CR secondary to BCG.
- Consider an end of study biopsy as it identifies occult disease that minimizes investigator bias.

It ain't what you
don't know that
gets you into
trouble. It's
what you know
for sure that
just ain't so.

Mark Twain



Samuel Langhorne Clemens