Bladder preservation strategies
New roadmaps for bladder preservation in high-risk NMIBC in 2022

Jacques Irani

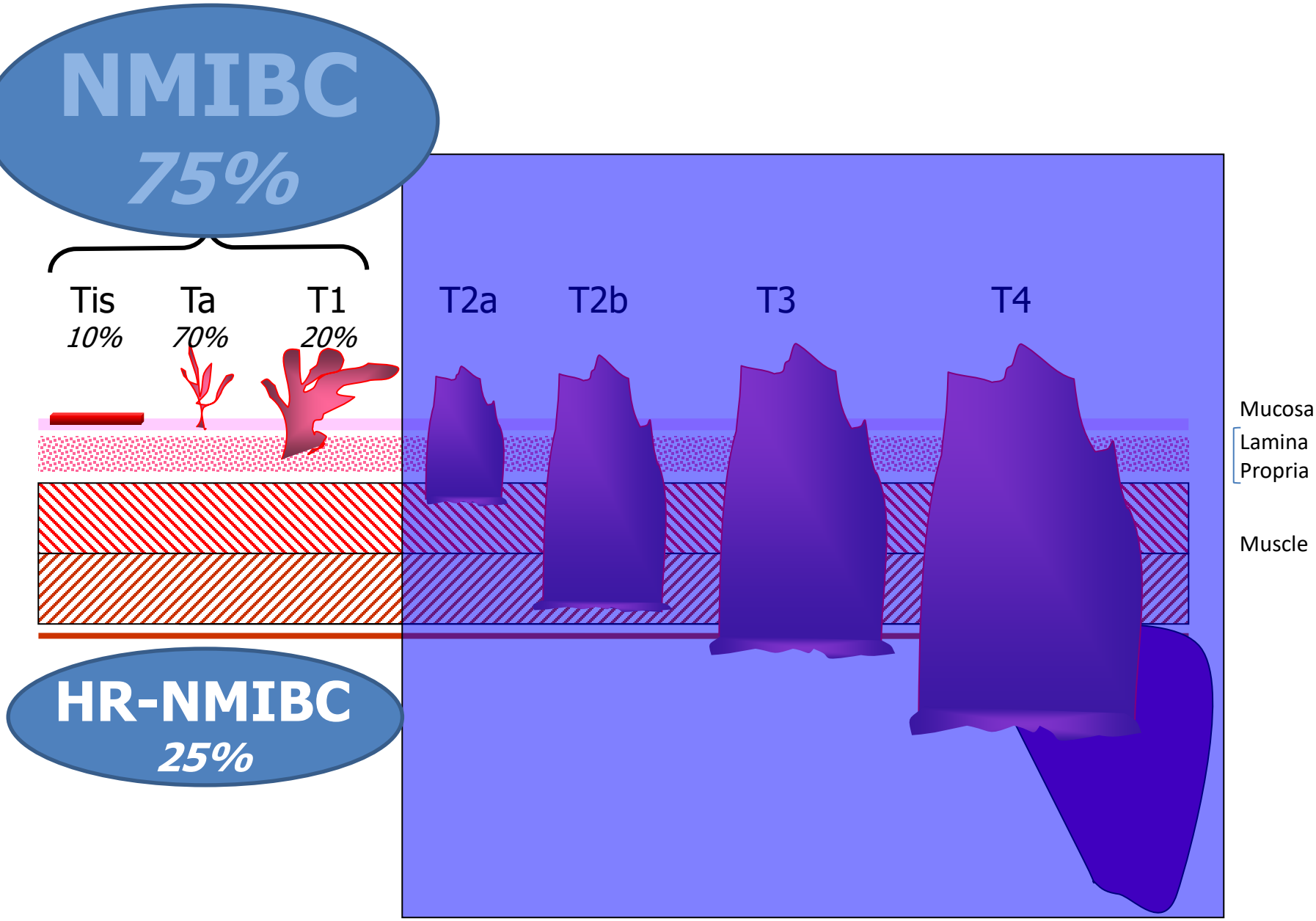
Thursday 20 October 09:15-10:05

15' presentation "New roadmaps for bladder preservation in high-risk NMIBC", including participation in the Q&A

Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	JANSSEN; GETUG;
Receipt of honoraria or consultation fees	BAYER; ASTELLAS
Stock shareholder	-
Other support (please specify):	-

High-Risk NMIBC
Still a challenging decision


NMIBC
75%
Tis
10%
Ta
70%
T1
20%
T2a
T2b
T3
T4
Mucosa
Lamina
Propria
Muscle
HR-NMIBC
25%

Treatment of NMIBC

- **Aims**:
  - Prevent recurrence
  - Prevent progression
  - Avoid the loss of the bladder
- **Management**
  - TURBT: the standard initial treatment
  - Intra-vesical instillations to reduce tumor recurrence (progression?) risk
  - Monitoring

WHEN DO WE CONSIDER PERFORMING A RADICAL CYSTECTOMY FOR NMIBC?

- 1st tumour
- single
- <3cm
- Pure T1a OR pure CIS* OR Ta HG
- T0 at re-resection
- no variant
- no LVI

BCG

Cystectomy

-patient's choice

-BCG failure

-combination of unfavourable prognostic factors

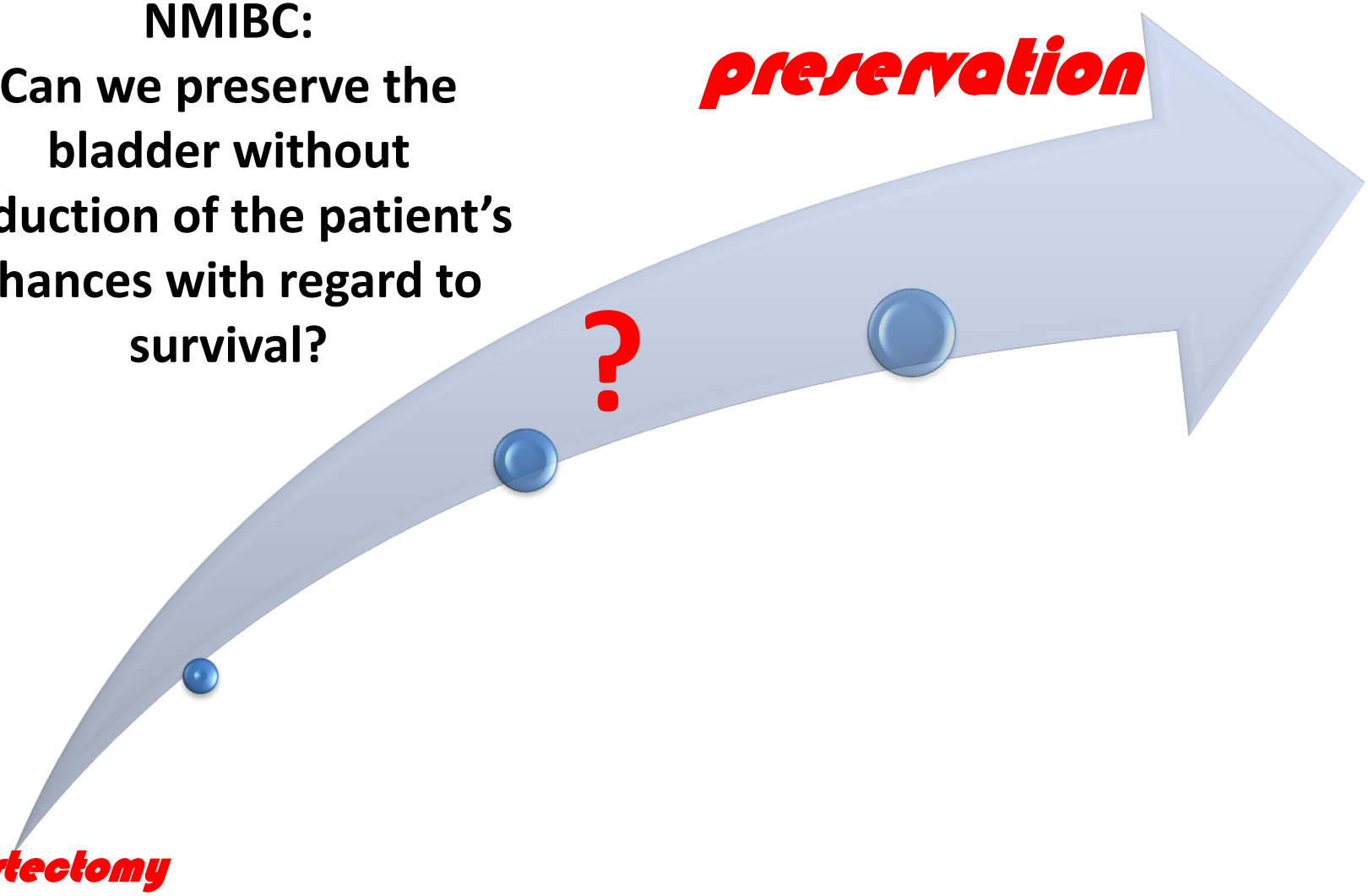
failure after intravesical BCG : what are the options?

EAU guidelines

7.6.4. Summary of evidence - treatment failure of intravesical therapy

Summary of evidence	LE
Treatments other than RC must be considered oncologically inferior in patients with BCG-unresponsive tumours.	3

High-risk/ very High-risk NMIBC:
Can we preserve the bladder without reduction of the patient's chances with regard to survival?



BEFORE TACKLING THE NEW ROADMAPS, ARE WE USING THE PRESENT MOST OPTIMAL TREATMENT?

High-risk NMIBC

- **Optimal TURB/ReTURB**
- **Adjuvant instillations**
  - **BCG**
  - **Full dose**
  - **Maintenance 3 yrs.**
  - **Standard protocol**

RESECT: global, multi-centre observational study

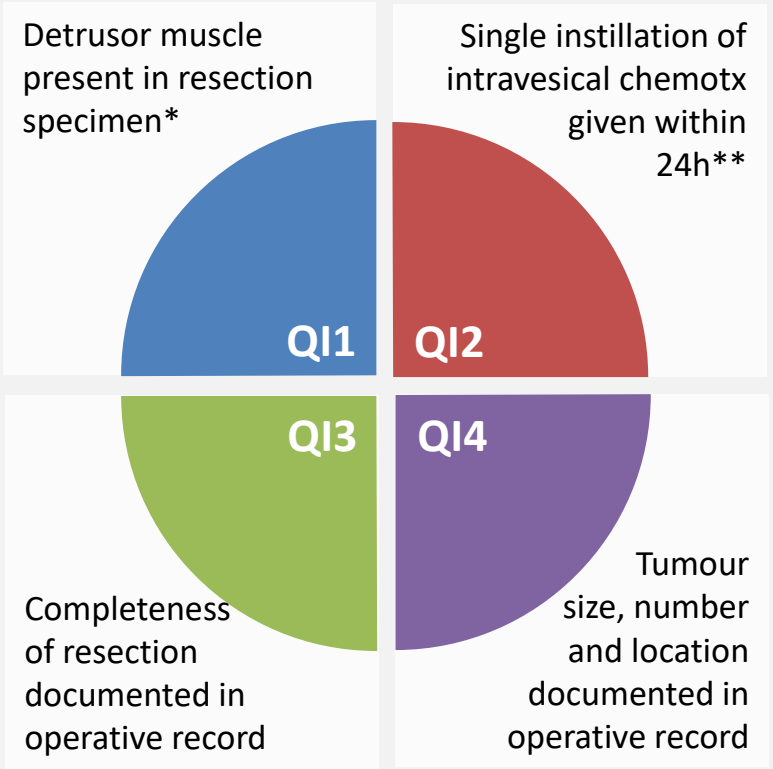
- 3,193 pts undergoing primary TURBT with curative intent
- 175 centres in 40 countries

*exclusion: tumours ≤5mm

**exclusion: intravesical chemotx not available or pt allergic to receive chemotx

Gallagher KM. EAU 2022, abs A0160

TURBT quality indicators (QI)



Courtesy of ISMAR

Is the quality of TURBT similar between centres worldwide?

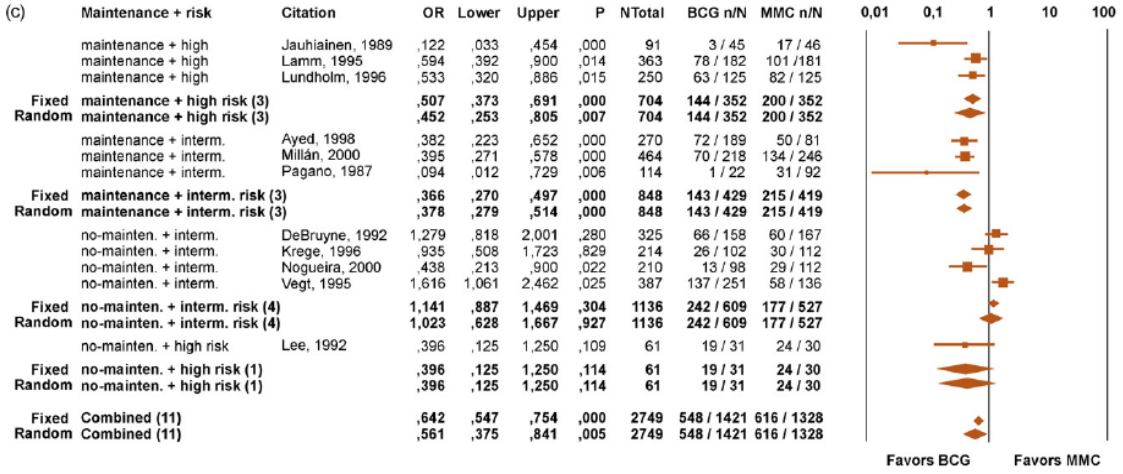
TAKE HOME MESSAGE

In this study, all 4 quality indicators varied from <10% achievement to 100% achievement, indicating a wide variation between centres.

Courtesy of ISMAR

High-risk NMIBC

- Optimal TURB/ReTURB
- **Adjuvant instillations**
  - **BCG**
  - **Full dose**
  - **Maintenance 3 yrs.**
  - **Standard protocol**



(c)	Maintenance + risk	Citation	OR	Lower	Upper	P	NTotal	BCG n/N	MMC n/N
	maintenance + high	Jauhiainen, 1989	,122	,033	,454	,000	91	3 / 45	17 / 46
	maintenance + high	Lamm, 1995	,594	,392	,900	,014	363	78 / 182	101 /181
	maintenance + high	Lundholm, 1996	,533	,320	,886	,015	250	63 / 125	82 / 125
Fixed	**maintenance + high risk (3)**		**,507**	**,373**	**,691**	**,000**	**704**	**144 / 352**	**200 / 352**
Random	**maintenance + high risk (3)**		**,452**	**,253**	**,805**	**,007**	**704**	**144 / 352**	**200 / 352**
	maintenance + interm.	Ayed, 1998	,382	,223	,652	,000	270	72 / 189	50 / 81
	maintenance + interm.	Millán, 2000	,395	,271	,578	,000	464	70 / 218	134 / 246
	maintenance + interm.	Pagano, 1987	,094	,012	,729	,006	114	1 / 22	31 / 92
Fixed	**maintenance + interm. risk (3)**		**,366**	**,270**	**,497**	**,000**	**848**	**143 / 429**	**215 / 419**
Random	**maintenance + interm. risk (3)**		**,378**	**,279**	**,514**	**,000**	**848**	**143 / 429**	**215 / 419**
	no-mainten. + interm.	DeBruyne, 1992	1,279	,818	2,001	,280	325	66 / 158	60 / 167
	no-mainten. + interm.	Krege, 1996	,935	,508	1,723	,829	214	26 / 102	30 / 112
	no-mainten. + interm.	Nogueira, 2000	,438	,213	,900	,022	210	13 / 98	29 / 112
	no-mainten. + interm.	Vegt, 1995	1,616	1,061	2,462	,025	387	137 / 251	58 / 136
Fixed	**no-mainten. + interm. risk (4)**		**1,141**	**,887**	**1,469**	**,304**	**1136**	**242 / 609**	**177 / 527**
Random	**no-mainten. + interm. risk (4)**		**1,023**	**,628**	**1,667**	**,927**	**1136**	**242 / 609**	**177 / 527**
	no-mainten. + high risk	Lee, 1992	,396	,125	1,250	,109	61	19 / 31	24 / 30
Fixed	**no-mainten. + high risk (1)**		**,396**	**,125**	**1,250**	**,114**	**61**	**19 / 31**	**24 / 30**
Random	**no-mainten. + high risk (1)**		**,396**	**,125**	**1,250**	**,114**	**61**	**19 / 31**	**24 / 30**
Fixed	**Combined (11)**		**,642**	**,547**	**,754**	**,000**	**2749**	**548 / 1421**	**616 / 1328**
Random	**Combined (11)**		**,561**	**,375**	**,841**	**,005**	**2749**	**548 / 1421**	**616 / 1328**

Böhle A, et al. J Urol 2003

High-risk NMIBC

- Optimal TURB/ReTURB
- **Adjuvant instillations**
  - **BCG**
  - **Full dose**
  - **Maintenance 3 yrs.**
  - **Standard protocol**

Oddens, Eur Urol 12

Disease-free interval

1 yr of maintenance versus 3 yr of maintenance according to dose and risk group

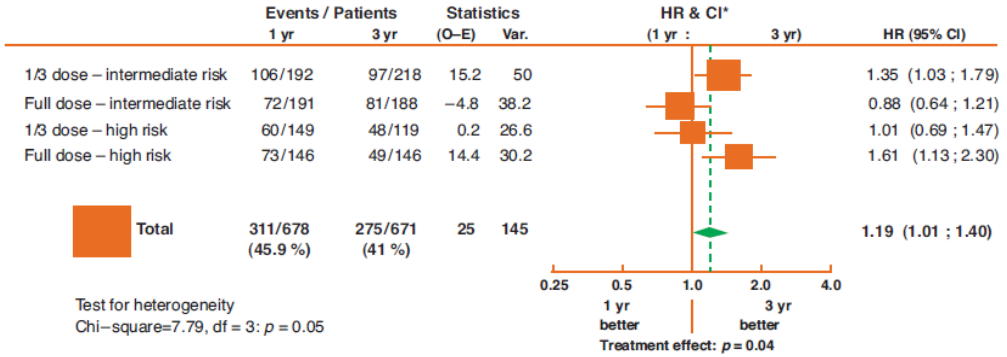
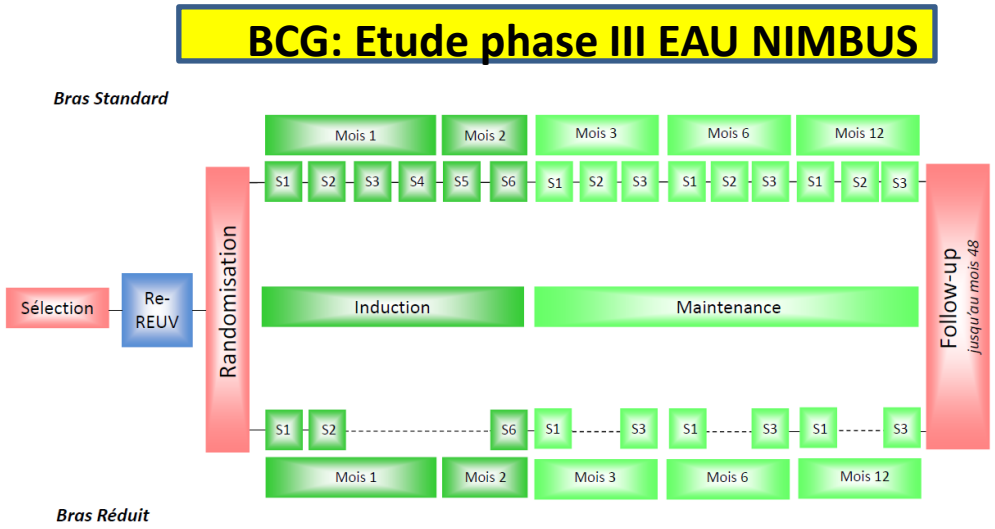


Fig. 5 – Disease-free interval: 1 yr of maintenance versus 3 yr of maintenance according to dose and risk group. HR = hazard ratio; CI = confidence interval; df = degrees of freedom.

High-risk NMIBC

- Optimal TURB/ReTURB
- **Adjuvant instillations**
  - **BCG**
  - **Full dose**
  - **Maintenance 3 yrs**
  - **Standard protocol**



Unmet needs
New roadmaps for bladder preservation

1. Selection of the right patients for BCG
2. Alternative to BCG if it is contra-indicated or unavailable
3. Alternative to BCG in the event of its failure
4. More efficient agent than BCG

New roadmaps for bladder preservation in high-risk NMIBC in 2022

INTRAVESICAL ENHANCED CHEMOTHERAPY

As a 1st adjuvant treatment or in selected cases after BCG failure

ELECTROMOTIVE DRUG ADMINISTRATION (EMDA)

Lancet Oncol. 2006 Jan;7(1):43-51.

Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial.

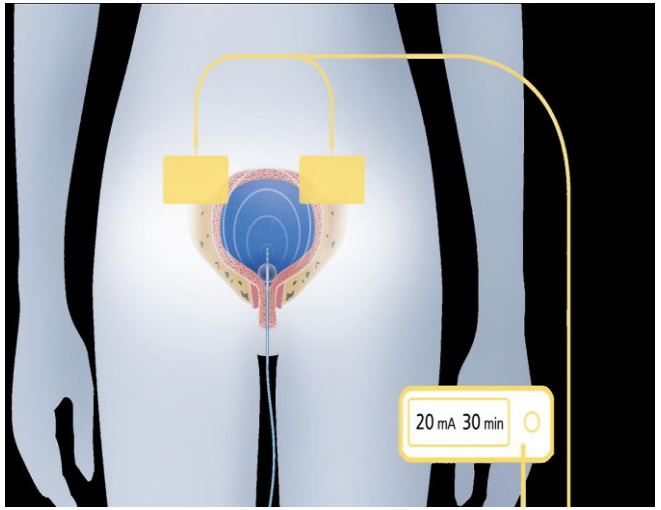
Di Stasi SM[1], Giannantoni A, Giurioli A, Valenti M, Zampa G, Storti L, Attisani F, De Carolis A, Capelli G, Vespasiani G, Stephen RL.

EAU guidelines

Electromotive drug administration

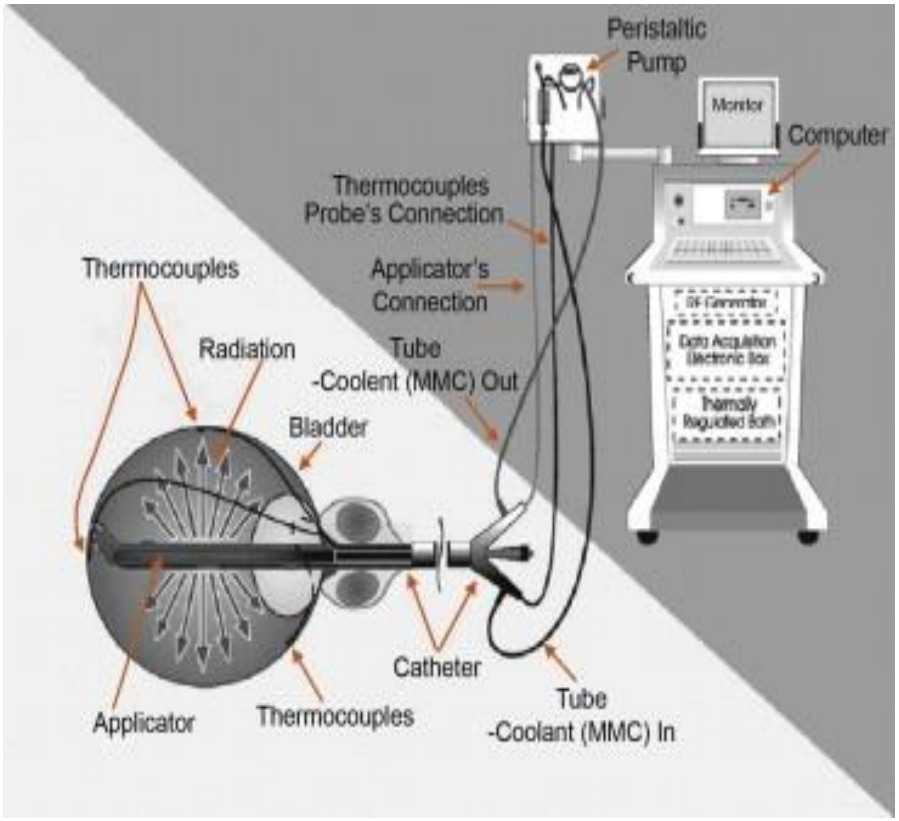
The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT.

The definitive conclusion, however, needs further confirmation.



THERMO-CHEMOTHERAPY

RITE (Radiofrequency Induced Thermochemotherapeutic Effect)



SYNERGO®: THE BLADDER WALL IS HEATED USING RADIOFREQUENCY

available at www.sciencedirect.com
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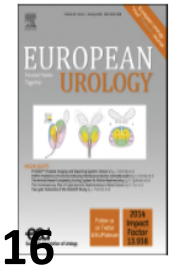
European Association of Urology



2016

Platinum Priority – Bladder Cancer

Editorial by Jorg R. Oddens and Richard J. Sylvester on pp. 1053–1054 of this issue

Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non–Muscle-invasive Bladder Cancer

Tom J.H. Arends [a], Ofer Nativ [b], Massimo Maffezzini [c], Ottavio de Cobelli [d], Giorgio Canepa [c], Fabrizio Verweij [e], Boaz Moskovitz [b], Antoine G. van der Heijden [a], J. Alfred Witjes [a,]*

[a] *Radboud University Medical Centre, Nijmegen, The Netherlands;* [b] *Bnai-Zion Hospital, Haifa, Israel;* [c] *Ente Ospedaliero Ospedali Galliera, Genova, Italy;* [d] *Istituto Europeo di Oncologia, Milan, Italy;* [e] *IRCCS Multimedica, Milan, Italy*

Conclusions: CHT is a safe and effective treatment option in patients with intermediate- and high-risk papillary NMIBC. A significantly higher 24-mo RFS in the CHT group was seen in the PP analysis. Based on the results above, CHT is an option for BCG therapy as adjuvant treatment for intermediate- and high-risk papillary NMIBC.

Synergo is an alternative to BCG
in BCG naive patients
with intermediate or high risk NMIBC

HYMN Trial : Synergo vs SOC in post-BCG recurrence

EUROPEAN UROLOGY 75 (2019) 63–71

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

2019

Platinum Priority – Bladder Cancer

Editorial by J. Alfred Witjes on pp. 72–73 of this issue

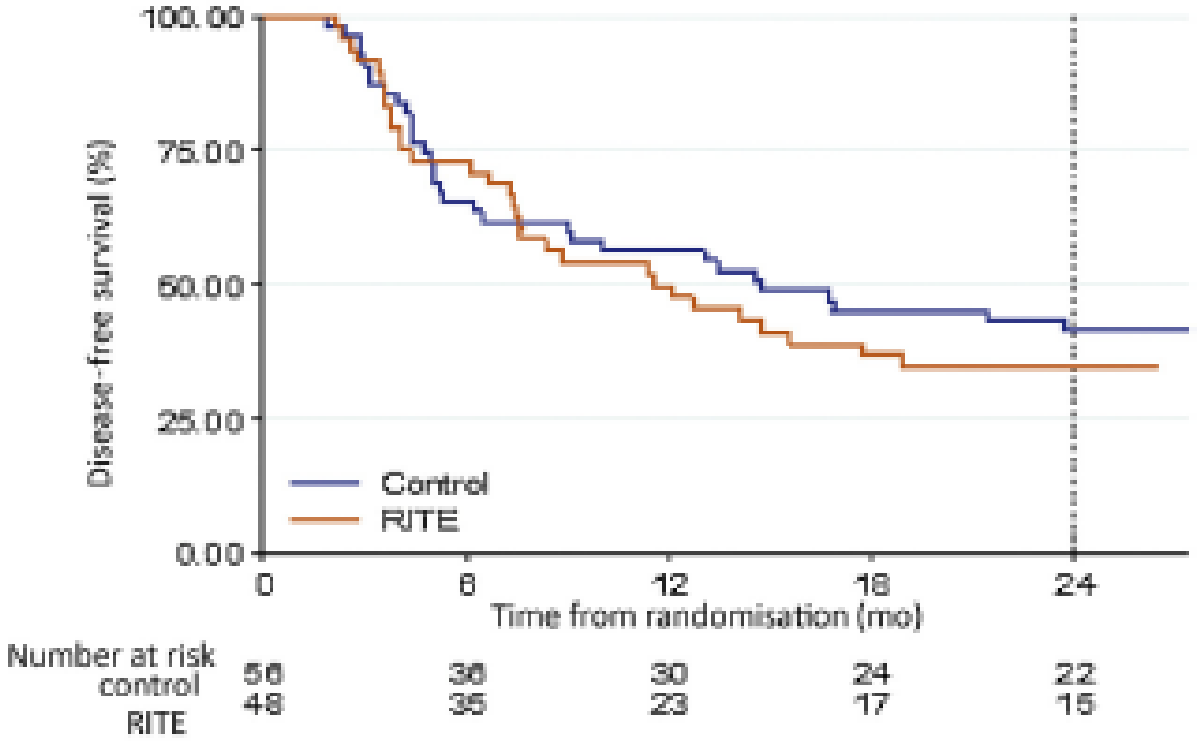
Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guérin or Institutional Standard in Patients with Recurrence of Non–muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial

Wei Shen Tan [a,b], Anesh Panchal [c], Laura Buckley [c], Adam J. Devall [c], Laurence S. Loubière [c], Ann M. Pope [c], Mark R. Feneley [b], Jo Cresswell [d], Rami Issa [e], Hugh Mostafid [f], Sanjeev Madaan [g], Rupesh Bhatt [h], John McGrath [i], Vijay Sangar [j], T.R. Leyshon Griffiths [k], Toby Page [l], Dominic Hodgson [m], Shibendra N. Datta [n], Lucinda J. Billingham [c,†], John D. Kelly [a,b,†,]*

HYMN Trial : Synergo vs SOC in post-BCG recurrence

Conclusions:

- DFS was similar between RITE and control.
- RITE patients with CIS (with/without papillary) had lower DFS than control.



HIVEC (**H**yperthermic **I**ntra-**VE**sical **C**hemotherapy)

COMBAT MEDICAL®: MMC is heated and circulates at 43°C in the bladder

- **Safety and tolerability**
- **Promising early results**

available at www.sciencedirect.com
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European Association of Urology

Platinum Priority – Bladder Cancer
Editorial by XXX on pp. x-y of this issue

Adjuvant Intravesical Chemohyperthermia Versus Passive Chemotherapy in Patients with Intermediate-risk Non–muscle-invasive Bladder Cancer (HIVEC-II): A Phase 2, Open-label, Randomised Controlled Trial

Wei Shen Tan [a,b,], Aaron Prendergast [c], Charlotte Ackerman [c], Yathushan Yogeswaran [c], Joanne Cresswell [d], Paramananthan Mariappan [e], Jaspal Phull [f], Paul Hunter-Campbell [g], Henry Lazarowicz [h], Vibhash Mishra [i], Abhay Rane [j], Melissa Davies [k], Hazel Warburton [l], Peter Cooke [m], Hugh Mostafid [n], Daniel Wilby [o], Robert Mills [p], Rami Issa [q], John D. Kelly [a,b]*

Conclusions: CHT cannot be recommended over chemotherapy alone for intermediate-risk NMIBC. Adverse events following CHT were of low grade and short-lived, although patients were less likely to complete their treatment.

World Journal of Urology (2022) 40:999–1004
https://doi.org/10.1007/s00345-022-03928-1

2022

ORIGINAL ARTICLE

Recirculating hyperthermic intravesical chemotherapy with mitomycin C (HIVEC) versus BCG in high-risk non-muscle-invasive bladder cancer: results of the HIVEC-HR randomized clinical trial

Félix Guerrero-Ramos[1] · Daniel A. González-Padilla[1] · Alejandro González-Díaz[1] · Federico de la Rosa-Kehrmann[1] · Alfredo Rodríguez-Antolín[1] · Brant A. Inman[2] · Felipe Villacampa-Aubá[3]

Received: 7 October 2021 / Accepted: 4 January 2022 / Published online: 17 January 2022

Conclusion: HIVEC provides comparable safety and efficacy to BCG and is a reasonable alternative during BCG shortages.

7.2.1.3.2.Device-assisted intravesical chemothe

- *Hyperthermia*
- *Microwave-induced hyperthermia effect (RITE)*
  - Promising data
  - In one RCT (1 yr BCG vs 1 yr RITE in intermediate- and high-risk NMIBC, increased RFS at 24 months in the MMC group (LE: 1b).
- *Hyperthermic intravesical chemotherapy (HIVEC)*
  - data about their efficacy are still lacking.

GEMCITABINE-DOCETAXEL INTRAVESICAL CHEMOTHERAPY (BCG NAÏVE PATIENTS)

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

2022

Sequential Intravesical Gemcitabine and Docetaxel for bacillus Calmette-Guérin-Naïve High-Risk Nonmuscle-Invasive Bladder Cancer

Ian M. McElree[1], Ryan L. Steinberg,[2] Alex C. Martin,[2] Jordan Richards,[2] Sarah L. Mott,[3] Paul T. Gellhaus,[2] Kenneth G. Nepple,[2] Michael A. O'Donnell[2] and Vignesh T. Packiam[2]*

[1]Carver College of Medicine, University of Iowa, Iowa City, Iowa
[2]Department of Urology, University of Iowa, Iowa City, Iowa
[3]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, Iowa

Conclusions: Gem/Doce is an effective and well-tolerated therapy for BCG-naïve NMIBC.
Further investigation is warranted.

SUBSTITUTES IN BCG - UNRESPONSIVE NMIBC

Endovesical instillation

- **Vicinium** *targets EpCAM antigens on the surface of tumor cells*

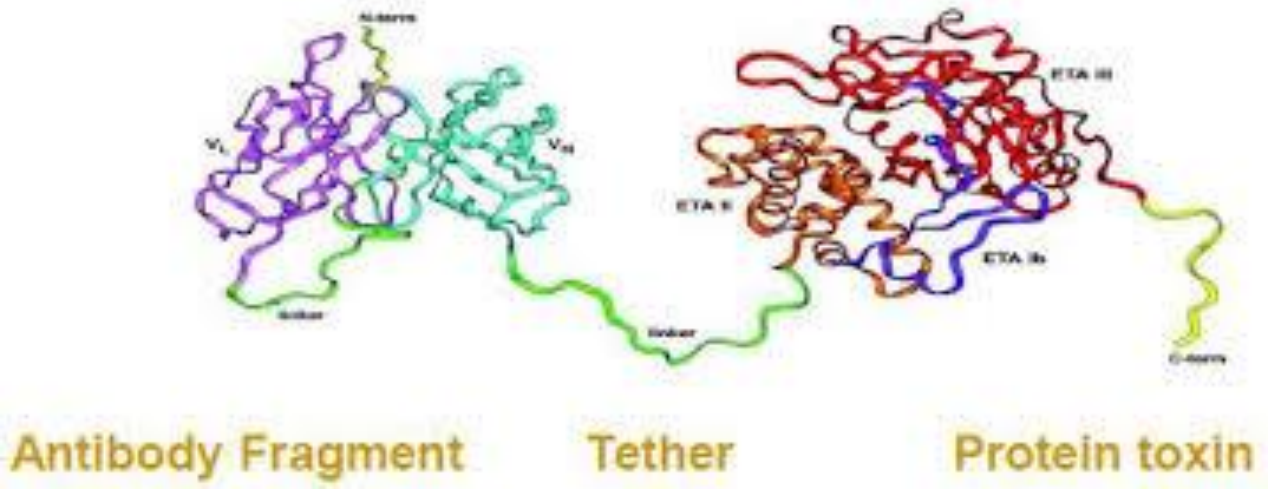
- **CG0070** *Oncolytic adenovirus that expresses GM-CSF and causes direct tumour lysis*

- **Instiladrin** *Recombinant Adenovirus Interferon alfa with Syn3 (rAd–IFNa/Syn3)*

IV treatments:

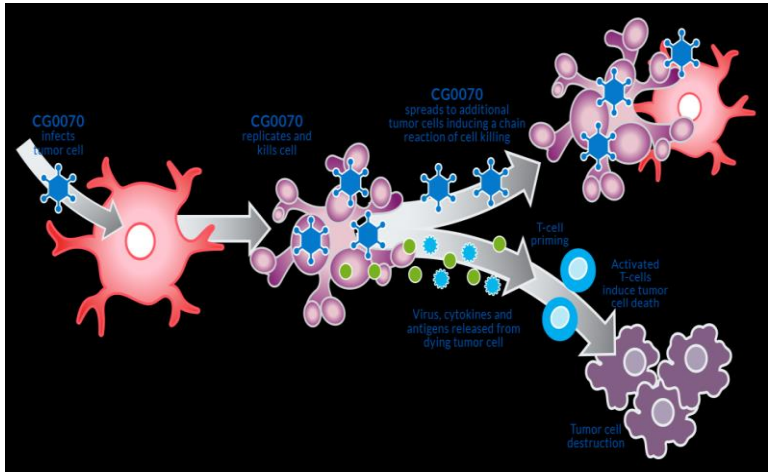
- **Immunotherapy IV:**
  - Single agent
  - In association with BCG

- **Erdafitinib**



VICINIUM
IN BCG-UNRESPONSIVE NMIBC?

- Phase II study has shown promising results with a short follow-up
- August 2021: FDA Does Not Approve Vicinium for BCG-unresponsive NMIBC
- July 2022: Sesen Bio Announces a pause in Clinical Development of Vicineum™ in the US



CG0070
IN BCG-UNRESPONSIVE NMIBC?

Phase II study has shown promising results

> 1 yr follow-up

BOND 3

A Phase 3 Study of CG0070 in Patients With NMIBC Unresponsive to BCG

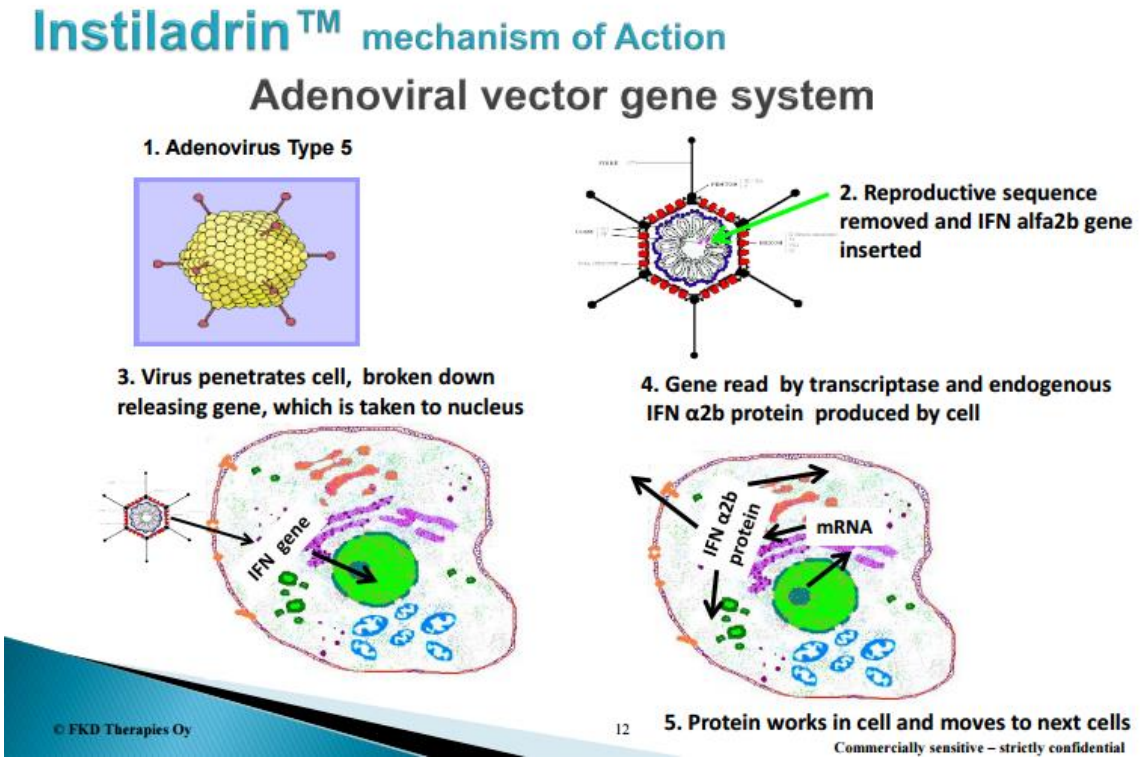
Single Arm Patients with CIS with or without concomitant high-grade Ta or T1 papillary disease.

- **CG0070 administered intravesically** weekly x 6 followed by maintenance
- **Primary Outcome Measures** : Percentage of patients with a complete response as defined by FDA guidance document dated February 2018 for NMIBC.
  [Time Frame: 24 months]
- **110 participants**
- **Estimated Study Completion Date : December 2024**

CORE1

Phase 2, single-arm study of CG0070 combined with pembrolizumab in patients with NMIBC unresponsive to BCG

- Single Arm Patients with CIS with or without concomitant high-grade Ta or T1 papillary disease.
  - **CG0070 administered intravesically** weekly x 6 followed by maintenance
  - **Pembrolizumab** will be given IV concurrently every 3 weeks for up to 2 years.
  - **Primary Outcome Measures** : Percentage of patients with a complete response (FDA guidance)
  - **Estimated Study Completion Date : June 2023**



Recombinant Adenovirus Interferon alfa with Syn3 (rAd–IFNa/Syn3)

INSTILADRIN

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Intravesical rAd–IFNα/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin–Refractory or Relapsed Non–Muscle-Invasive Bladder Cancer: A Phase II Randomized Study

Neal D. Shore, Stephen A. Boorjian, Daniel J. Canter, Kenneth Ogan, Lawrence I. Karsh, Tracy M. Downs, Leonard G. Gomella, Ashish M. Kamat, Yair Lotan, Robert S. Svatek, Trinity J. Bivalacqua, Robert L. Grubb III, Tracey L. Krupski, Seth P. Lerner, Michael E. Woods, Brant A. Inman, Matthew I. Milowsky, Alan Boyd, F. Peter Treasure, Gillian Gregory, David G. Sawutz, Seppo Yla-Herttuala, Nigel R. Parker, and Colin P.N. Dinney

Conclusion

rAd-–IFNa/Syn3 was well tolerated. It demonstrated promising efficacy for patients with HG NMIBC after BCG therapy who were unable or unwilling to undergo radical cystectomy.

J Clin Oncol 35.

Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial

Stephen A Boorjian, Mehrdad Alemozaffar, Badrinath R Konety, Neal D Shore, Leonard G Gomella, Ashish M Kamat, Trinity J Bivalacqua, Jeffrey S Montgomery, Seth P Lerner, Joseph E Busby, Michael Poch, Paul L Crispen, Gary D Steinberg, Anne K Schuckman, Tracy M Downs, Robert S Svatek, Joseph Mashni Jr, Brian R Lane, Thomas J Guzzo, Gennady Bratslavsky, Lawrence I Karsh, Michael E Woods, Gordon Brown, Daniel Canter, Adam Luchey, Yair Lotan, Tracey Krupski, Brant A Inman, Michael B Williams, Michael S Cookson, Kirk A Keegan, Gerald L Andriole Jr, Alexander I Sankin, Alan Boyd, Michael A O'Donnell, David Sawutz, Richard Philipson, Ruth Coll, Vikram M Narayan, F Peter Treasure, Seppo Yla-Herttuala, Nigel R Parker, Colin P N Dinney

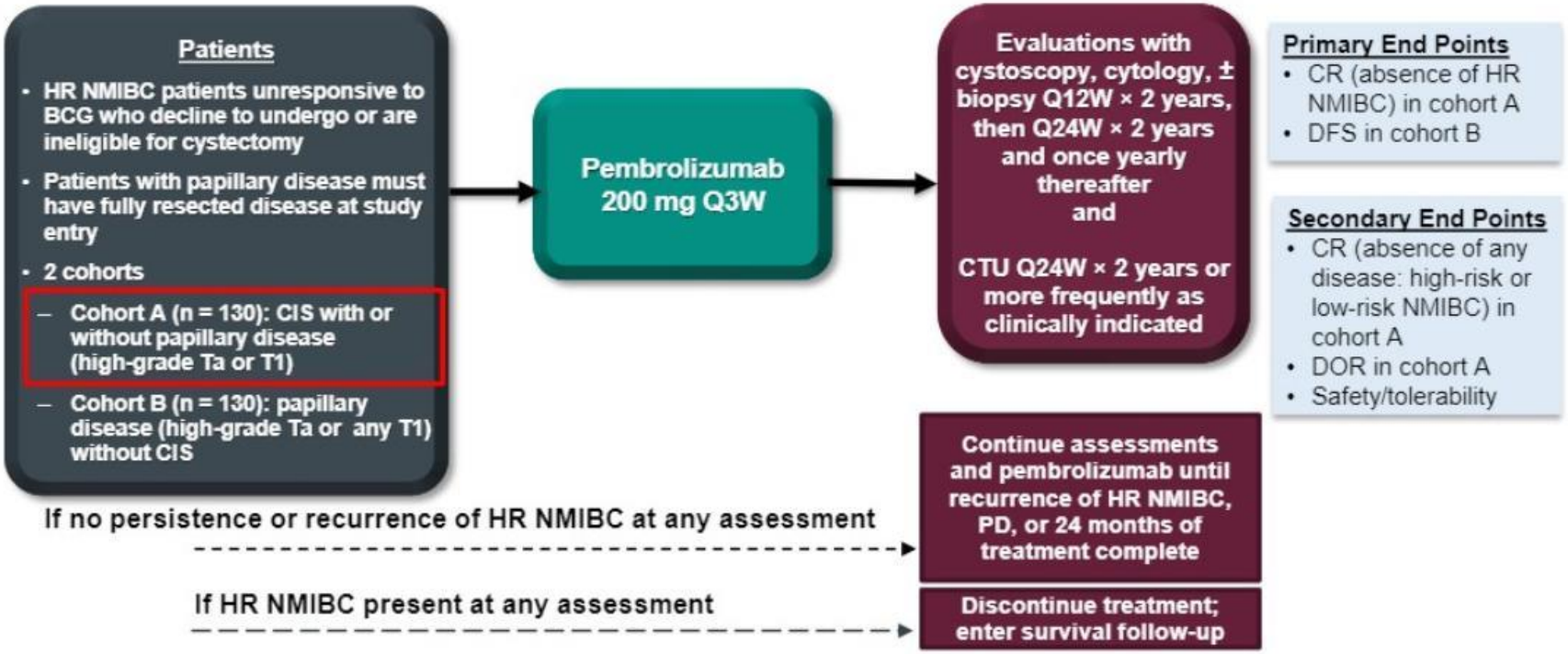
Lancet Oncol 2021; 22: 107–17

Interpretation Intravesical nadofaragene firadenovec was efficacious, with a favourable benefit:risk ratio, in patients with BCG-unresponsive non-muscle-invasive bladder cancer. This represents a novel treatment option in a therapeutically challenging disease state.

favourable benefit:risk ratio, ***in patients with BCG-unresponsive NMIBC***

IMMUNOTHERAPY AND NMIBC

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Lancet Oncol, 2021

Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

Interpretation Pembrolizumab monotherapy was tolerable and showed promising antitumour activity in patients with BCG-unresponsive non-muscle-invasive bladder cancer who declined or were ineligible for radical cystectomy and should be considered a a clinically active non-surgical treatment option in this difficult-to-treat population.

Pembrolizumab monotherapy was tolerable
and showed promising antitumour activity in patients with BCG-unresponsive NMIBC

ASSOCIATION OF BCG AND IMMUNOTHERAPY : ONGOING STUDIES

BCG NAÏVE

ALBAN
Study design

PURPOSE

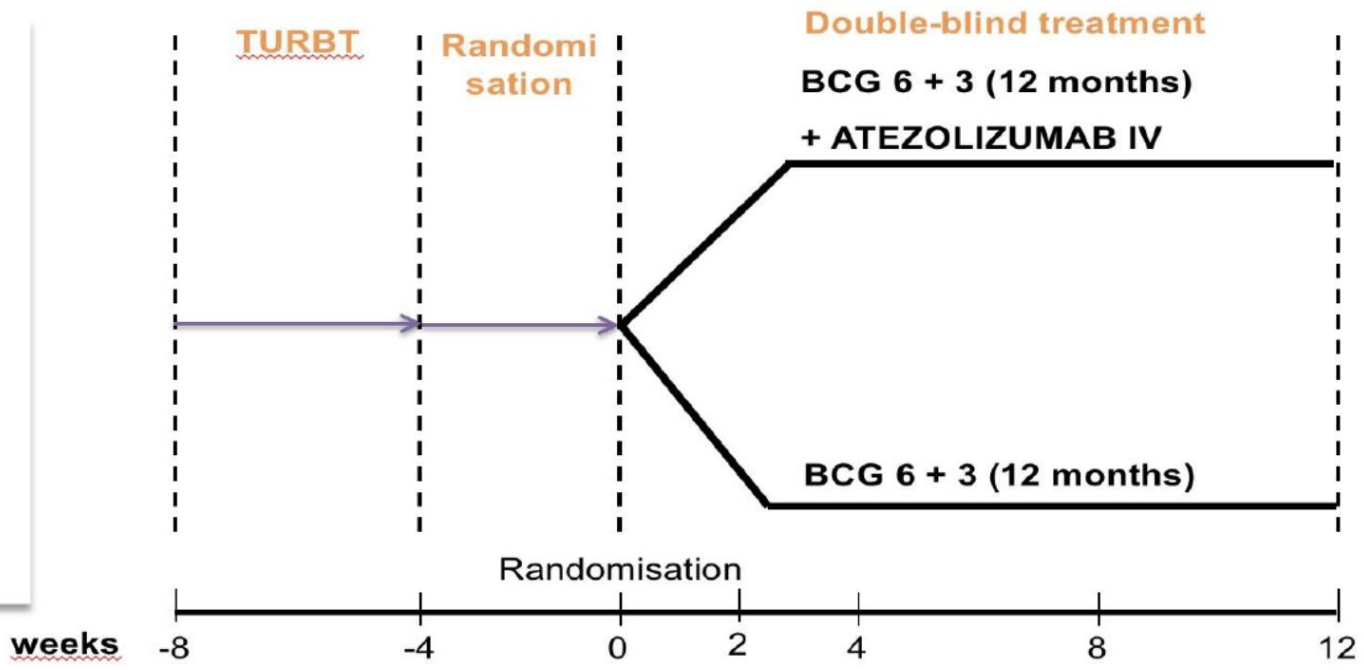
To compare oncologic outcomes after BCG instillations vs. BCG + ATEZOLIZUMAB in High Risk NMIBC

N men radomised:
500
10 - 15 centres in France

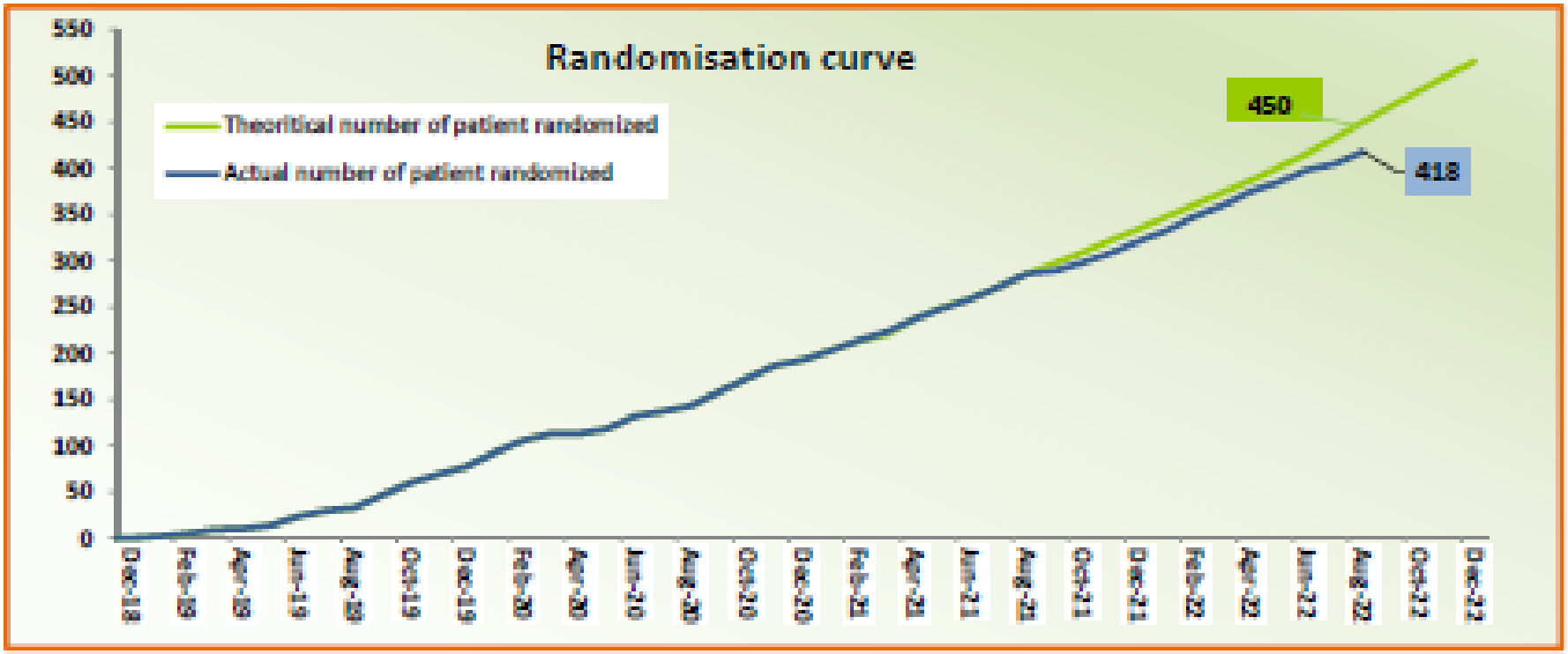
Inclusion criteria:
High risk NMIBC

Primary endopint:
Recurrence free survival

Secondary endpoints
Progression free survival- time to cystectomy
Overall survival
Cancer specific survival



ALBAN
Randomisation curve



Estimated Primary Completion April, 2024

POTOMAC

A phase III, randomized, open-label, multicenter, global study of durvalumab and BCG versus BCG alone in high-risk, BCG-naïve NMIBC patients (POTOMAC).

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	1018 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Actual Study Start Date	May 14, 2018
Estimated Primary Completion Date :	**October 31, 2024**
Estimated Study Completion Date :	September 30, 2025

Erdafitinib

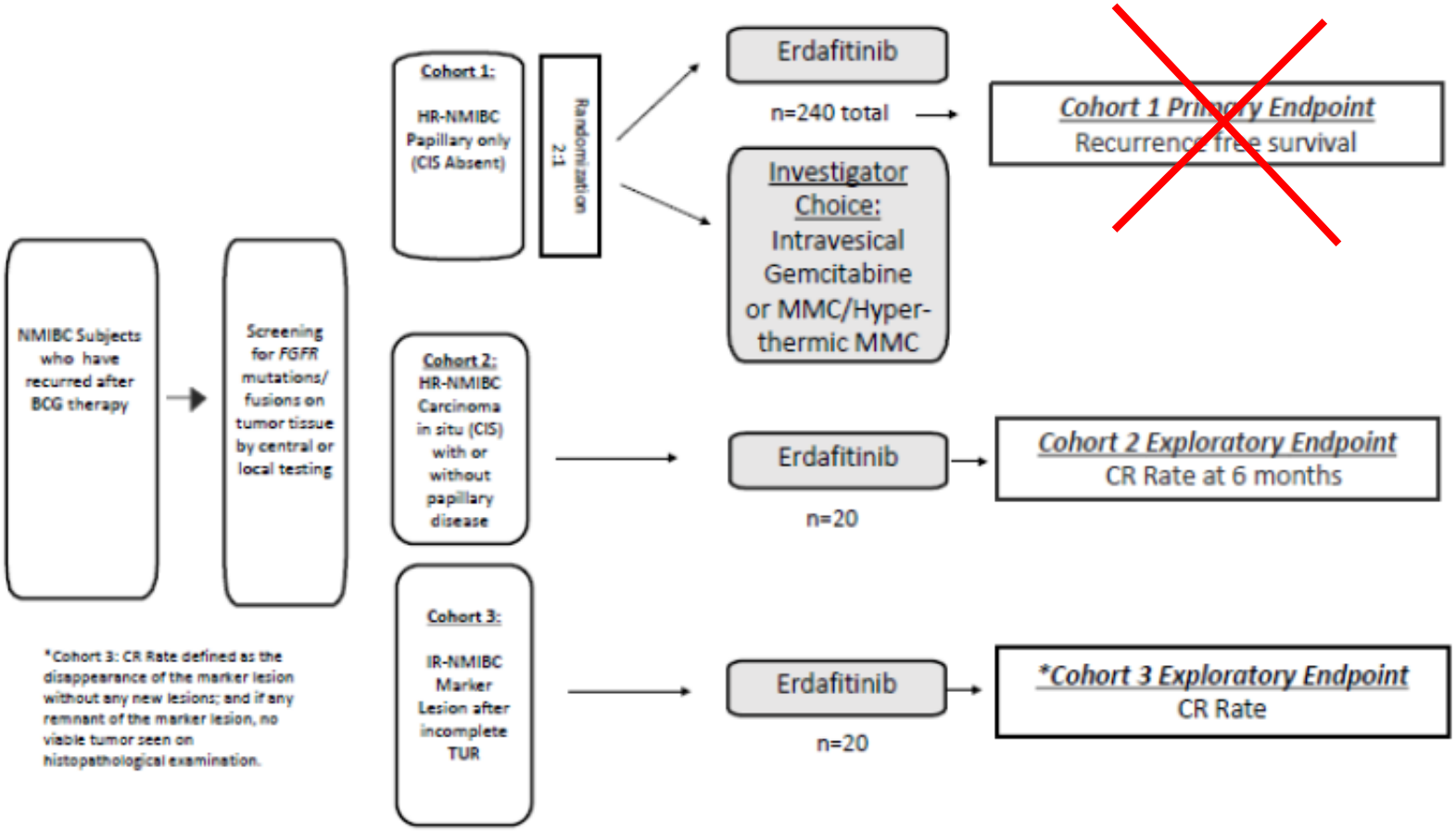
TKI inhibitor of FGFR

FOLLOWING BCG FAILURE

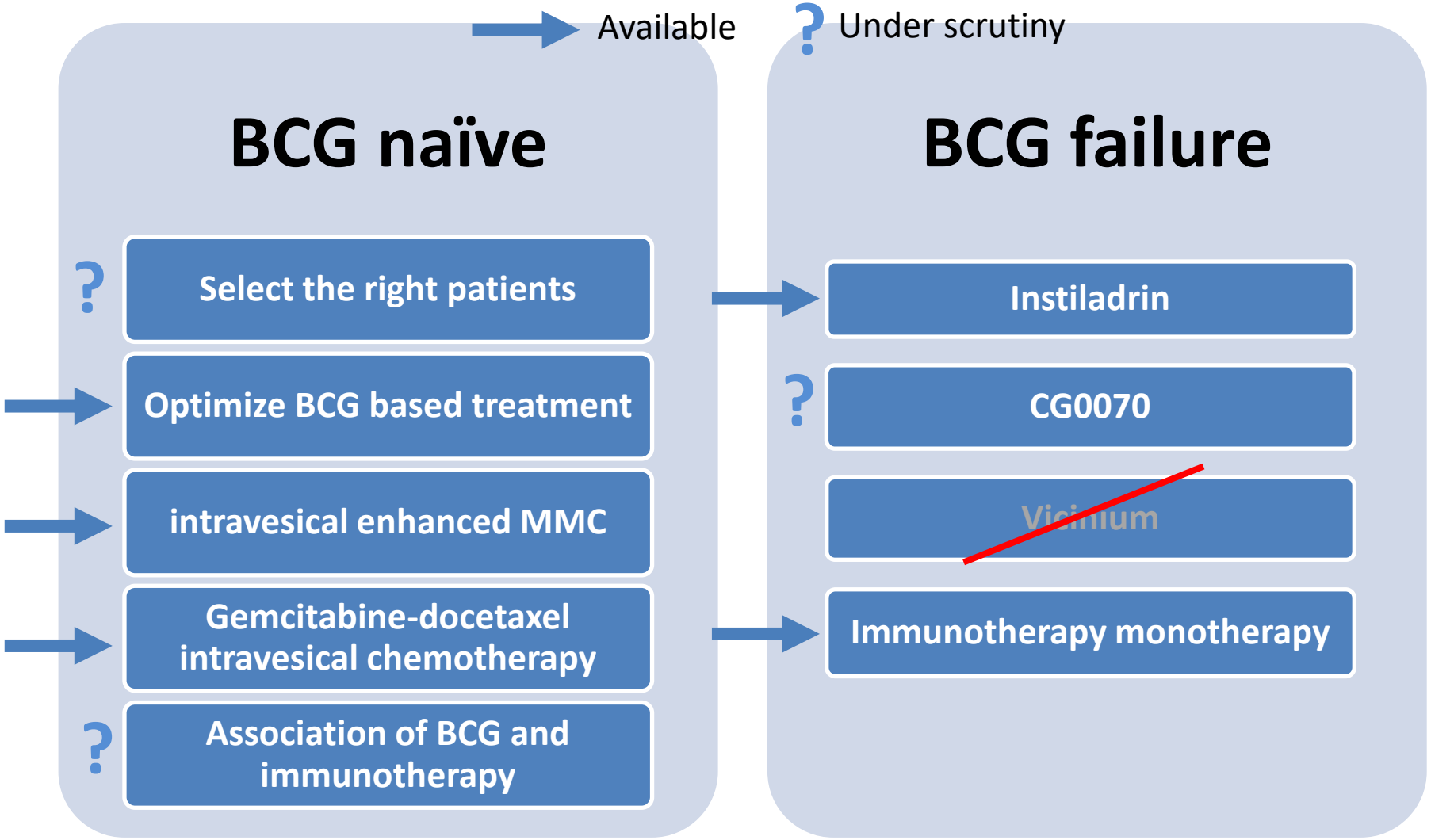
ERDAFITINIB VS INTRAVESICAL CHEMOTHERAPY IN PATIENTS WITH FGFR MUTATIONS OR FUSIONS

A Randomized Phase 2 Study of Erdafitinib vs Investigator Choice of Intravesical Chemotherapy

in Subjects Who Received BCG and Recurred with HR-NMIBC and FGFR Mutations or Fusions



New roadmaps for bladder preservation in high-risk NMIBC in 2022



Bladder preservation strategies
New roadmaps for bladder preservation in high-risk NMIBC in 2022

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