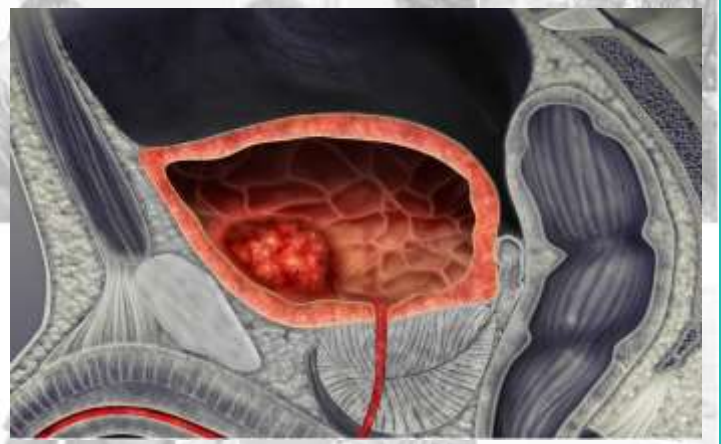
SUM
Sociedad Urológica Madrileña

Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud



CVNMI tras fracaso a BCG

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Servicio de Urología

HU Fundación Jiménez Díaz

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Introducción

- **9º o 10º** tipo de cáncer > frecuente
  - DI **9.5**/100.000 pers/año *Hombres*
  - DI **2.4**/100.000 pers/año *Mujeres*

- **80%** de los tumores diagnosticados → CVNMI (<T2)

- **BCG** *gold standard* tto. adyuvante tras RTUv en AR

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Introducción

RESPUESTA A BCG:

- **70%** en tumores papilares
- **80%** en *cis* inicialmente

↓ Recurrencia **Y** Progresión*

Aprox. ***1.5 millones*** *de dosis ANUALES a nivel global*

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Fracaso a BCG

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Fracaso a BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1 HG/G3 tumour is present at 3 months [236, 384, 387] (LE: 3). 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [360] (LE: 4).

6 months after either
, an additional BCG

l response [388] (LE: 3).

p T1/Ta HG recurrence
months of completion

330].

BCG failure.
ction course plus at least
erapy.

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Fracaso a BCG

- Progresión
- Recidiva AG

Fracaso a BCG

Progresión

Recidiva AG

- *Anteriormente* → FRACASO a 1-2 tandas de BCG
- *Posteriormente* → FRACASO = tiempo en el que se produce
- Necesidad de consenso en cuanto a la definición (EAU 2018)

"Adequate BCG" = Dosis adecuada BCG

≥ 5/6 Inducción Y **≥2/6** Reinducción O **2/3** dosis mantenimiento

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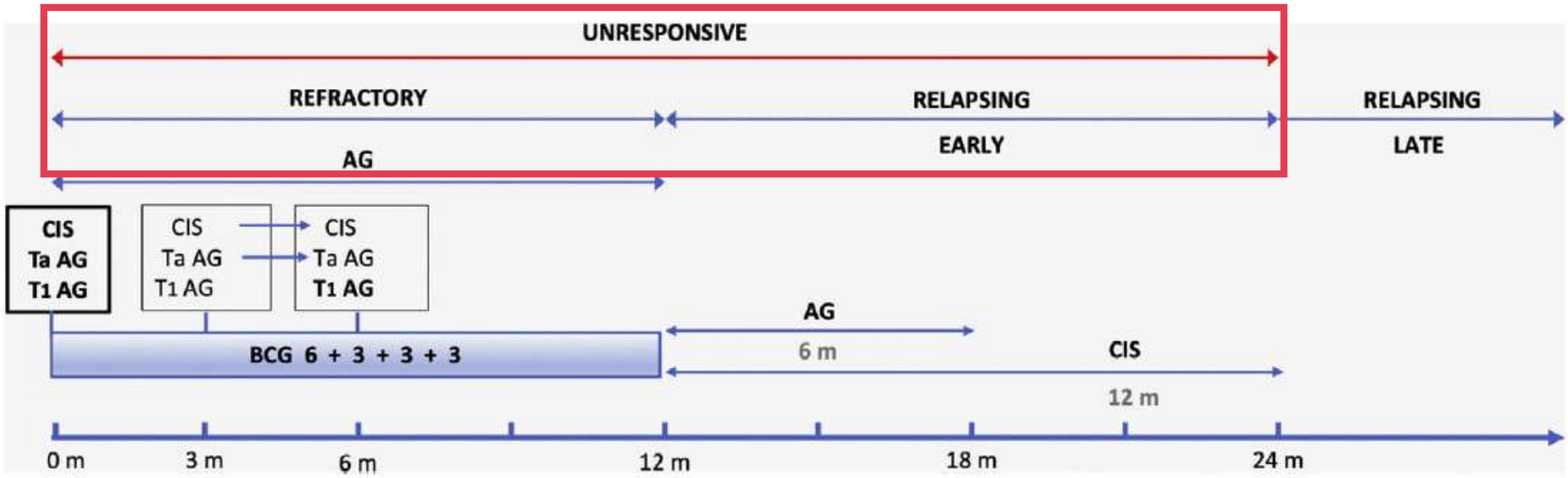
Fracaso a BCG



"Unresponsive" = NO respondedores → **NO** se van a beneficiar de > BCG

- *Refractory* → recidiva **DURANTE** tto
  - T1AG a los 3/6 meses
  - TaAG o CIS con recidiva a los 3 Y 6 meses
- *Early relapsing:*
  - Recidiva papilar **DURANTE 6 meses post-BCG**
  - *cis* **DURANTE 1er AÑO post-BCG**

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Huguet J. Actas Urol Esp 47 (2023) 395-397

Fracaso a BCG

Progresión

Recidiva AG

9.5 – 21% pacientes → ≥T2 durante o tras tto con BCG

- Peor *pronóstico* respecto a MI primarios

  - *Witjes (2011):* SCE 5a. → **55%** primarios vs **28%** progresivos
  - *Pietzak (2019):* peor resp. patológica a NeoAdy – peor SG y SCE
  - *Huguet (2005):* 95 CR

    33 progresión (SCE 5a. **34.7%**)

    62 AG recidivado → 45 NMI (SCE **90%**) vs 17 MI (SCE **38%**)

Van den Bosch S, Witges AJ. Eur Urol. 2011;60:493-500.
Pietzak EJ. Eur Urol. 2019;75:231-9,
Huguet J. Eur Urol. 2005;48:53-9

Fracaso a BCG: Progresión

CVNMI ALTO RIESGO

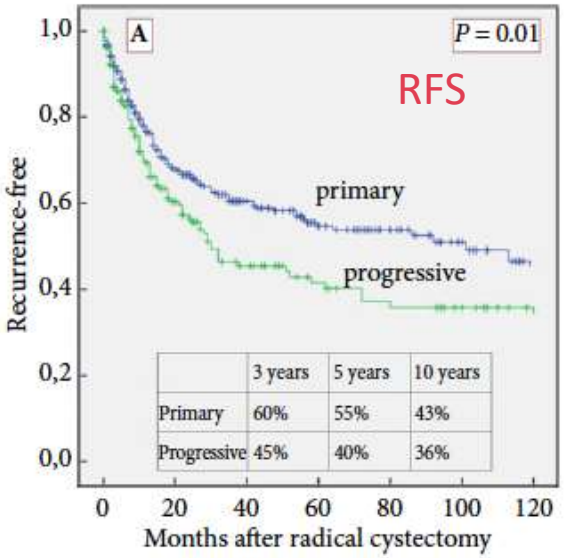
- E. obs. retrosp. unicéntrico
- N=**768 CR** → 2000– 2012
- CVMI Primario vs Progresivo
- Mediana seg → 85 meses

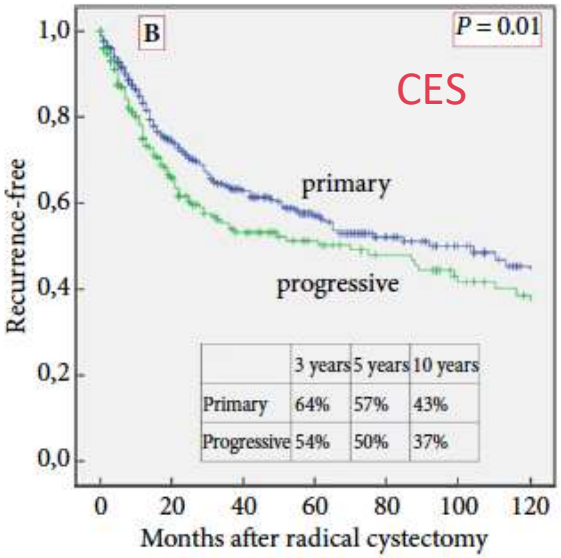
BJUI
BJU International

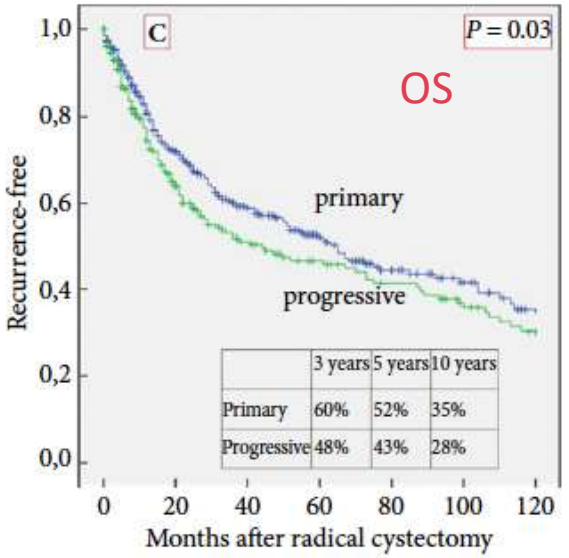
Comparing long-term outcomes of primary and progressive carcinoma invading bladder muscle after radical cystectomy

Marco Moschini*†, Vidit Sharma‡, Paolo Dell'oglio*, Vito Cucchiara*, Giorgio Gandaglia*, Francesco Cantiello†, Fabio Zattoni§, Federico Pellucchi¶, Alberto Briganti*, Rocco Damiano†, Francesco Montorsi*, Andrea Salonia* and Renzo Colombo*

*Department of Urology, Urological Research Institute, San Raffaele Scientific Institute, Vita-Salute University, Milan, †Doctorate Research Program, Magna Graecia University of Catanzaro, Catanzaro, Italy, ‡Department of Urology, Mayo Clinic Rochester, Rochester, MN, USA, §Department of Urology, University of Padua, Padua , and ¶Department of Urology, Papa Giovanni XXIII Hospital, Bergamo, Italy







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Fracaso a BCG: Progresión

CVNMI ALTO RIESGO

- R. Sistemática + Metaánalisis
- 14 estudios → **4075** casos
- CR en CVMI Primario vs Progresivo
- Peor SCE en *progresivos*

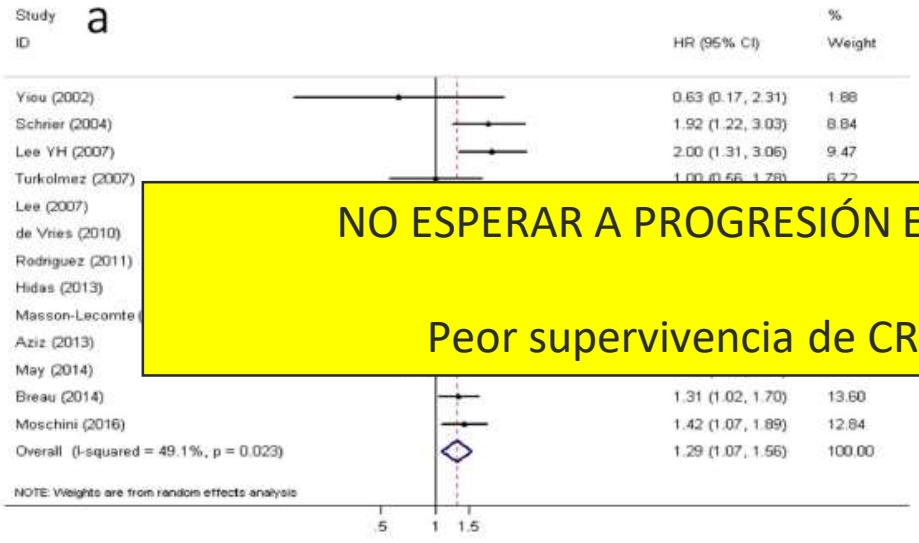
SCIENTIFIC REPORTS

OPEN

l: 2 February 2017
d: 2 May 2018
d online: 15 May 2018

Oncological Outcome of Primary and Secondary Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-analysis

Peng Ge[1], Li Wang[2], Meng Lu[1], Lijun Mao[1], Wang Li[1], Rumin Wen[1], Jian Lin[3,4], Junqi Wang[1] & Jiacun Chen[1]



NO ESPERAR A PROGRESIÓN EN CVNMI CON FRACASO A BCG

Peor supervivencia de CR diferida respecto a precoz

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Manejo del fracaso a BCG

Table 7.3: Treatment options for the various categories of BCG failure

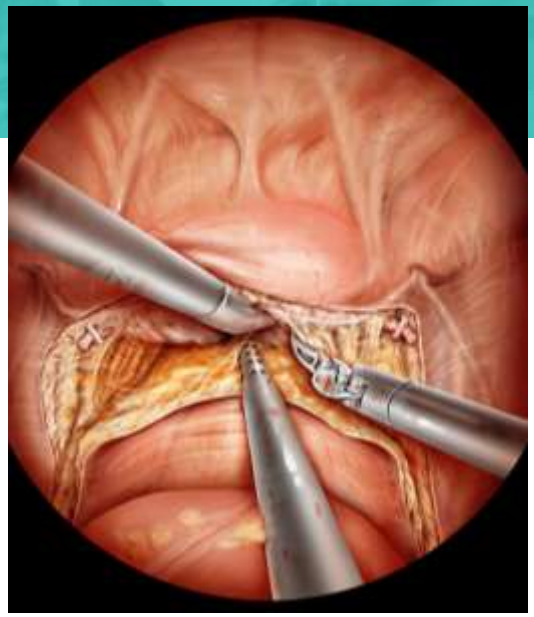
Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC).
	2. Enrolment in clinical trials assessing new treatment strategies.

7.9.4 ***Summary of evidence - treatment failure of intravesical therapy***

Summary of evidence	LE
Prior intravesical chemotherapy has no impact on the effect of BCG instillation.	1a
Treatments other than RC must be considered oncologically inferior in patients with BCG-unresponsive tumours.	3

intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.
	2. Radical cystectomy.

Cistectomía precoz



1. ***Subestadificación*** → **27-51%** CVMI en CR

2. ***Progresión*** → Peor supervivencia progresivos vs primarios

3. ***Efectividad*** → CR precoz < CVMI → DFS a 5a **>80%** (*cis* incluso >)

Huguet J. Eur Urol. 2005;48:53-9
Moschini M. BJU Int. 2016;117:604
Stein, J.P. J Clin Oncol. 2001;19:666

Cistectomía precoz

… y cuándo???

CUANTO ANTES

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Cistectomía precoz

2007 → ***Retrosp. unicéntrico***
MSKCC
CR tras BCG *(cT1 tras BCG)*

- Por *progresión* (hist.)
- *Recidiva* (cont.)

SCE a 5a

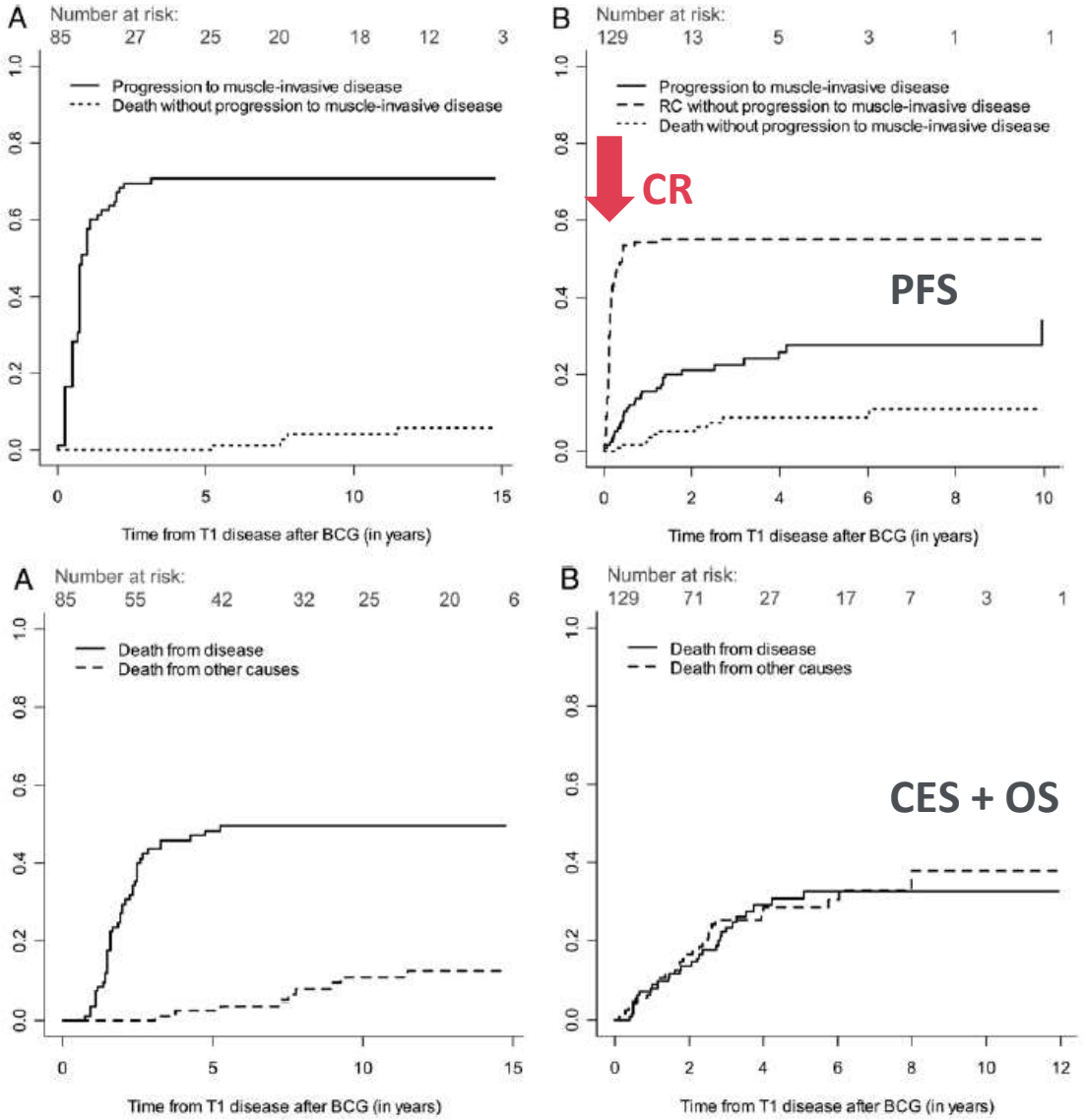
- Hist. → 52%
- Cont. → 69%

Treatment Paradigm Shift May Improve Survival of Patients With High Risk Superficial Bladder Cancer

THE JOURNAL of UROLOGY

Ganesh V. Raj,* Harry Herr, Angel M. Serio, Sherri M. Donat, Bernard H. Bochner, Andrew J. Vickers and Guido Dalbagni†

From the Departments of Urology (GVR, HH, AMS, SMD, BHB, GD) and Biostatistics (AJV), Memorial Sloan-Kettering Cancer Center, New York, New York



Cistectomía precoz

				Early cystectomy	Delayed cystectomy	*p*-value
Author	**Ref**	**N**	**Cohort**	**Definitions**	**Cancer-specific survival**	**Cancer-specific survival**	
Herr and Sogani [63]	121	90	High-risk NMIBC who underwent at least one course of BCG	Early RC: within 2 years of initial BCG	15 yr: 69%	15 yr: 26%	0.001
				Delayed RC: after 2 years of initial BCG			
				Early RC: within 1 year of initial BCG	15 yr: 75%	15 yr: 34%	0.001
				Delayed RC: after 1 year of initial BCG			
Denzinger et al. [35]	122	105	High-grade T1	Early RC: average 4 weeks after initial TURBT	1o yr: 78%	10 yr: 51%	<0.01
				Delayed RC: after induction BCG, on average 11 months after initial TURBT			
Hautmann et al. [56]	123	223	High-grade T1	Early RC: within 90 days of initial TURBT	10 yr: 79%	10 yr: 65%	NA
				Delayed RC: if progression after induction BCG			
De Berardinis et al. [33]	124	152	High-risk NMIBC	Early RC: within 60 days of re-TURBT	10 yr: 78%	10 yr: 78%*	0.98
				Delayed RC: after induction and maintenance BCG, with signs of progression			
Stöckle et al. [131]	125	73	High-grade T1	Early RC: immediately following initial TURBT	5 yr: 90%	5 yr: 62%	0.001
				Delayed RC: after recurrence			
Jäger et al. [67]	126	278	High-grade T1	Early RC: within 5–12 months of initial TURBT	10 yr: 79%	10 yr: 61%	NA
				Delayed RC: after 12 months of initial TURBT			
Thalmann et al. [135]		121	High-grade T1	Early RC: within 3 months of initial TURBT	5 yr: 69%	5 yr: 80%*	0.3
				Delayed RC: after induction BCG, with signs of recurrence, median time to RC of 13 months			

*Comparison of early cystectomy versus those treated with BCG (deferred cystectomy and including those who did not progress)

Lee, D.J., Chang, S.S. (2018). The Role and Importance of Timely Radical Cystectomy for High-Risk Non-muscle-Invasive Bladder Cancer. In: Daneshmand, S., Chan, K. (eds) Genitourinary Cancers . Cancer Treatment and Research, vol 175. Springer, Cham.

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Cistectomía precoz

Bladder Cancer

Patient Preferences for Treatment of Bacillus Calmette-Guérin–unresponsive Non–muscle-invasive Bladder Cancer: A Cross-country Choice Experiment

Hannah Collacott[a,*], *Nicolas Krucien*[a], *Sebastian Heidenreich*[a], *James W.F. Catto*[b,c], *Ola Ghatnekar*[d]

[a] *Evidera, London, UK;* [b] *Department of Oncology, University of Sheffield, Sheffield, UK;* [c] *Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK;* [d] *Ferring Pharmaceuticals, Copenhagen, Denmark*

Results and limitations: Most of the 107 participants (average age 63 yr) never selected RC (89%) as their preferred option in the choice experiment. Preferences were most affected by time to RC (RAI 55%), followed by risk of progressing to MIBC (RAI 25%), medication administration (RAI 12%), and the risk of serious side effects (RAI 8%). To increase the time to RC from 1 yr to 6 yr, patients accepted a 43.8% increase in the risk of progression and a 66.1% increase in the risk of serious side effects.

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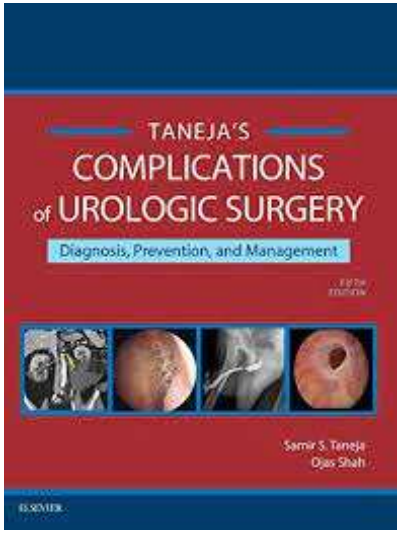
Collacot H. Eur Urol OpenSci. 2023;49:92-99

Cistectomía precoz

- **49-69%** alguna complicación en los 90 DPO
  - **13-22%** Clavien-Dindo III/IV
- **1-10%** *mortalidad* POI
- FR > importante → *Comorbilidad*
- También complicaciones *tardías*



McKiernan, J.M., Anderson, D.B (2018). Complications of Radical Cystectomy and Urinary Diversion. In: Taneja, S.S., Shah, O.(eds) Taneja's Complications of Urologic

Cistectomía precoz

Table 41.1 Summary of 90-Day Radical Cystectomy Complications Based on Institutional Cohorts Using Contemporary Reporting Methods

Complication Years	Shabsigh[5] 1995–2005	Takada[12] 1997–2010	Schiavina[11] 1995–2009	Novara[7] 2002–2006	Hautmann[3] 1986–2008
Number	1142	928	404	358	1013[c]
Overall	64%	68%	52%	49%	58%
Minor[a]	51%	51%	34%	36%	36%
Major[a]	13%	17%	17%	13%	22%
By organ system					
Gastrointestinal	29%	26%	15%	17%	15%
Infectious	25%	30%	11%	7%	24%
Wound	15%	21%	5%	7%	9%
Genitourinary	11%	15%	8%	7%	17%
Cardiac	11%	<1%	8%	8%	-
Pulmonary	9%	1%	6%	5%	-
Bleeding	9%	<1%	6%	16%	-
Thromboembolic	8%	<1%	4%	4%	-
Neurologi	5%	2%	3%	3%	-
Miscellaneous	3%	3%	9%	1%	-
Surgical	1%	<1%	1%	0%	-
Reoperation[b]	14%	11%	7%	10%	-
Return to OR	3%	9%	-	-	-
IR procedure	11%	3%	-	-	-
Mortality	3%	2%	5%	3%	2%

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McKiernan, J.M., Anderson, D.B (2018). Complications of Radical Cystectomy and Urinary Diversion. In: Taneja, S.S., Shah, O.(eds) Taneja's Complications of Urologic

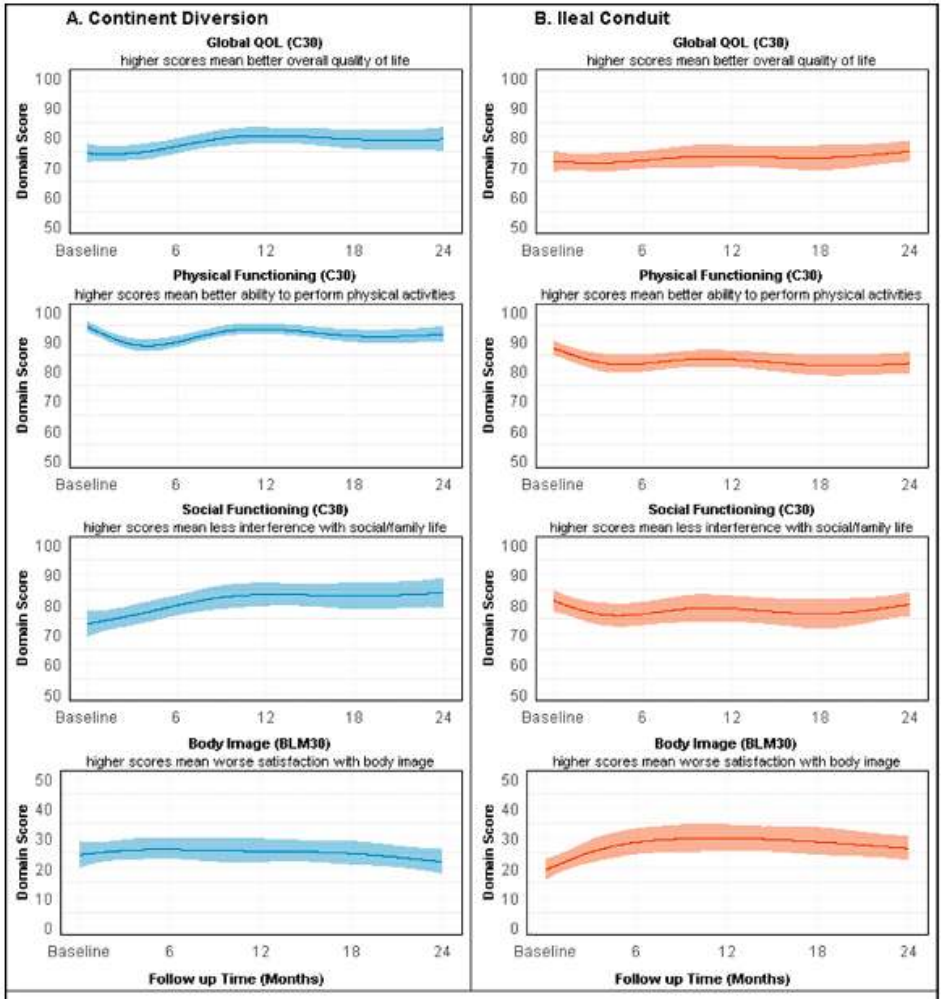
Cistectomía precoz

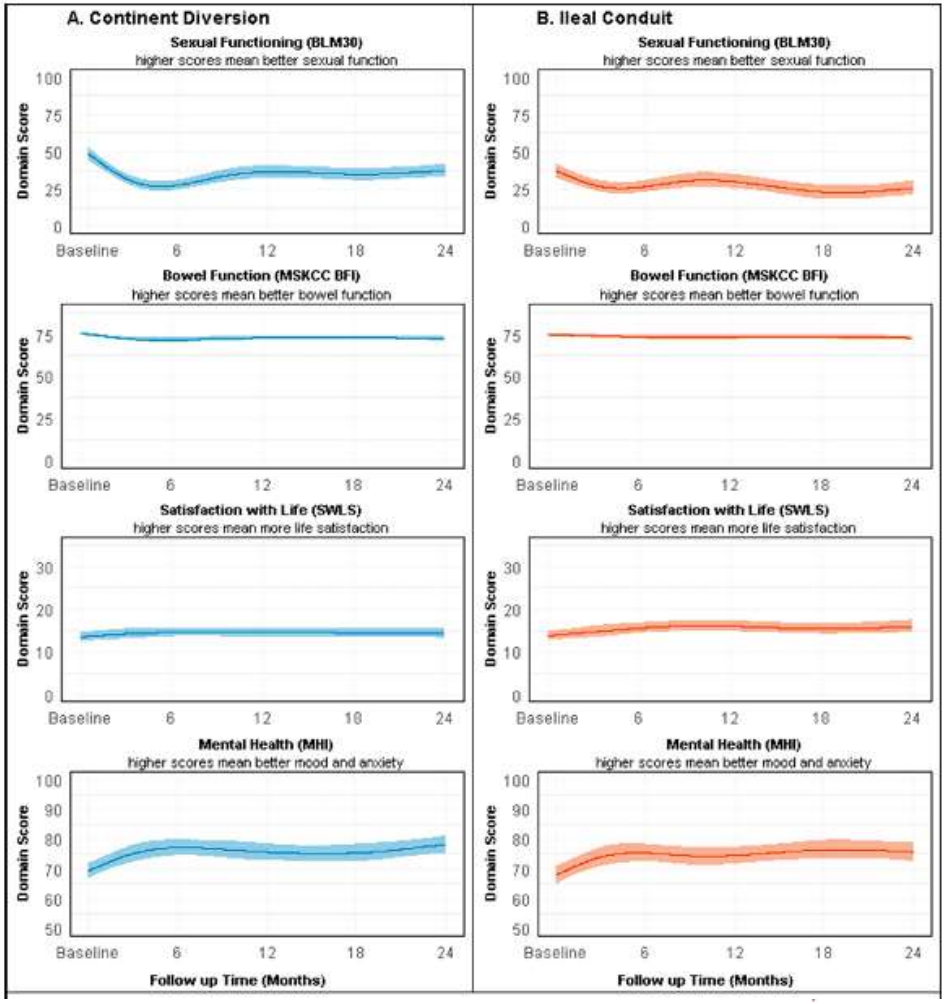
Bladder Cancer

Health-related Quality of Life for Patients Undergoing Radical Cystectomy: Results of a Large Prospective Cohort

Matthew B. Clements[a], Thomas M. Atkinson[b], Guido M. Dalbagni[a], Yuelin Li[b], Andrew J. Vickers[c], Harry W. Herr[a], S. Machele Donat[a], Jaspreet S. Sandhu[a], Daniel S. Sjoberg[c], Amy L. Tin[c], Bruce D. Rapkin[d], Bernard H. Bochner[a,]*

[a] Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [b] Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [c] Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [d] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA





Clements, M.B. Eur Urol. 2022;81(3):294-304

Cistectomía precoz

Surgical Oncology

A systematic review and meta-analysis of quality of life outcomes after radical cystectomy for bladder cancer

Linda S. Yang [a], Bernard L. Shan [b], Leonard L. Shan [a], Peter Chin [c], Spencer Murray [c], Nariman Ahmadi [c], Akshat Saxena [c,*]

[a] Melbourne Medical School, The University of Melbourne, Melbourne, Victoria, Australia
[b] Monash University, Department of Medicine, The Wollongong Hospital, NSW, Australia
[c] Department of Urology, The Wollongong Hospital, NSW, Australia

- *RS + Metanálisis* de 29 estudios → n = **3754**
- Derivaciones **continentes** vs **no continentes** ***(no dif. significativas)***

Conclusions: QOL after radical cystectomy is comparable after either continent or incontinent urinary diversion. Post-operative QOL may improve, but urinary and sexual dysfunction remains inferior to the general population. Patient choice is key to selection of reconstruction method.

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Yang, L.S.,Surg Onc.2016;25(3):281-297

Manejo del fracaso a BCG

GUIDELINES

Table 7.3: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Ra[illegible]RC)
	2. Enrolment in clinical trials assessing new treatment strategies.
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG relapsing: TaT1 HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to a patient's individual situation.
	2. Bladder-preserving strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.
	2. Radical cystectomy.

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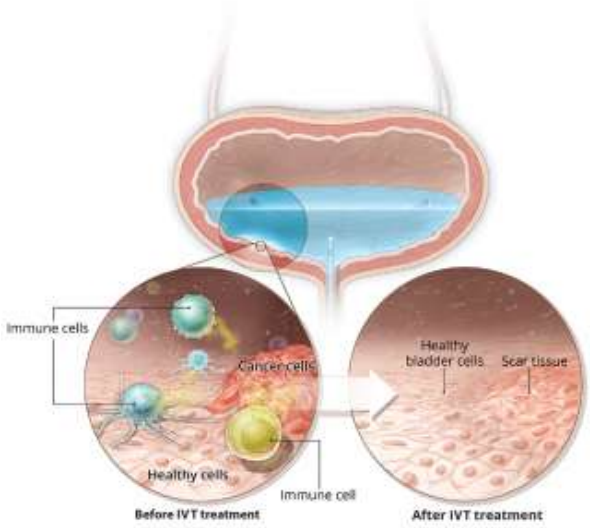
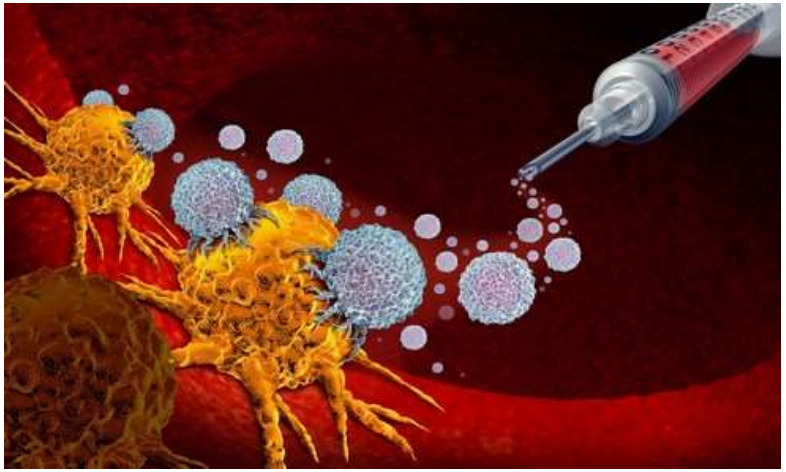
Estrategias de preservación vesical

FUSIÓN



TERAPIA INTRAVESICAL



TRATAMIENTO SISTÉMICO

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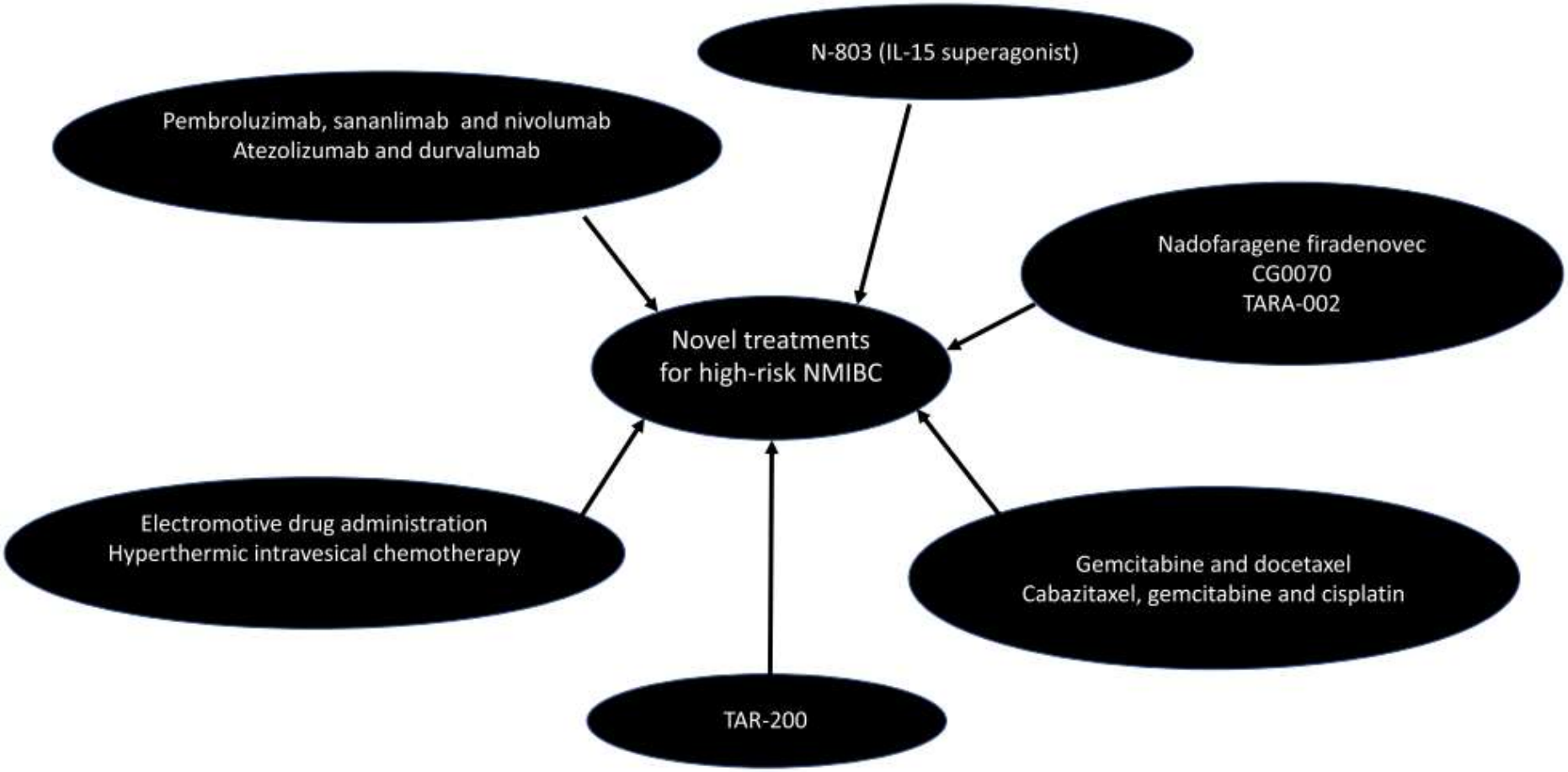
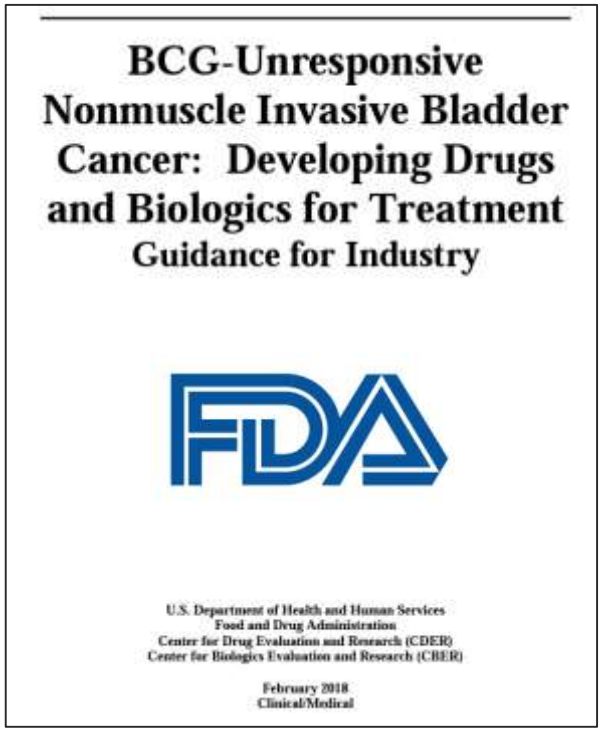
Estrategias de preservación vesical



Estrategias de preservación vesical

- **Diseño experimental**:
  - Ensayo **fase II**
  - Brazo *único*



- **Desenlaces de interés:**
  - CR inicial a los 6 meses en cis → **40-50%**
  - Respuesta duradera **≥30%** a los 18-24 meses

Estrategias de preservación vesical

- ***Variables de interés*** → CR no es tan relevante
  - Diferenciar **PFS y HG-RFS**
  - Evitar *progresión* → **SCE <40%** a los 5a
  - Cistectomía de rescate?
- **NO** *brazo de comparación*
- **NO** *estudios comparativos* → NO se puede concluir cuál es mejor
- Importante separar pacientes **cis** vs **papilar** vs **papilar+cis**
- Importante ***seguimiento*** planteado
  - biopsias confirmatorias, intervalos, pruebas dx…
- Definición ***refractariedad*** BCG

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Estrategias de preservación vesical

BCG Failure

- Freedom from high-risk recurrence at 1 year (for papillary disease)
- CR at 6 months (for CIS)

- Freedom from high-risk recurrence at 6 months and at 2 years (for papillary disease)
- CR at 12 months (for CIS)
- Time to progression
- Disease worsening
- Disease-specific survival
- OS
- Toxicity
- QOL

Minimum 2 years: 1 year of active treatment followed by a minimum of 1 year of monitoring and follow-up

Mandatory:
- Cystoscopy every 3 months
- Cytology every 3 months for CIS
- Appropriate upper-tract evaluation at end of study

Recommended:
- Cytology every 3 months for papillary disease

BCG refractory or unresponsive CIS:
- Initial CR rate of 50% at 6 months
- Durable response rate of 30% at 12 months and 25% at 18 months

BCG refractory or unresponsive papillary disease:
- Recurrence-free rate of 30% at 12 months and 25% at 18 months

- CIS: 20 CR per 40 patients
- Papillary: 10 recurrence-free patients per 33 patients

· JUNE 1, 2016

CAL ONCOLOGY

REVIEW ARTICLE

efinitions, End Points, and Clinical Trial Designs for
on–Muscle-Invasive Bladder Cancer: Recommendations
om the International Bladder Cancer Group

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

BCG refractory or unresponsive CIS:
- Initial CR rate of 50% at 6 months
- Durable response rate of 30% at 12 months and 25% at 18 months

BCG refractory or unresponsive papillary disease:
- Recurrence-free rate of 30% at 12 months and 25% at 18 months

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Estrategias de preservación vesical

	Pembro KN-057	Atezo SWOGS1605	N803+BCG QUILT 3032	Nadrofaragene Firadenovec	HIVEC	Gem/Doce	Erdafitinib
12 months DFS	43.5%	53%	57%	43.8%	78%	~70%	77% (chemo 41%)
24 months DFS	34.9%	18 months 49%	48%	N/A	57.5%	58%	N/A
Patients	132	55	77	35	134	34	49
Setting	Phase 2 Single arm	Phase 2	Phase 2/3 Single arm	Phase 3 Single arm	Retrospective	Retrospective	Rand
REF	ASCO-GU 2023	Black Eur Urol 2023	ASCO 2022	Dinney 2021	Brummelhuis 2021	Steinberg 2020	ESMO 2023

QT Intravesical

- ***Mitomicina C*** → CR **19%** (4/21) a 3a
- ***Valrubicina*** → CR a 6 meses **18%** **(FDA: *cis refractario a BCG)***
- ***Gemcitabina*** → CR **47%** a 3 meses – RFS 21% a 2ª (cis + papilar+-cis)
- ***Docetaxel*** → 2 años CR **59%** - RFS 1a 40% - RFS 3a 25%

Malmstrom et al. J Urol 1999;161:1124-7;2.
Dinney et al. Urol Oncol 2013;31:1635-42.
Skinner et al. J Urol 2013;190:1200.
Barlow et al. J Urol 2013;189:834.

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QT Intravesical: Secuenciación

THE JOURNAL of UROLOGY

- ***Retrosp. Multicéntrico***
- N=**276***
- Gem/Doc I + M
- Mediana seg. ***11 meses:***
  - HG-RFS **60%/46%** cis – **69%/52%** pap.
  - PFS **97%**
- EA **40.6%** → *9.4% afect. tto*

105 (38%) criterios refractariedad BCG:

- HG-RFS → 50%cis – 58%pap
- Estado ref. no asociación con HG-RFS

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

Ryan L. Steinberg, Lewis J. Thomas, Nathan Brooks, Sarah L. Mott, Andrew Vitale, Trafford Crump, Mounica Y. Rao, Marcus J. Daniels, Jonathan Wang, Supriya Nagaraju, William C. DeWolf, Donald L. Lamm, Max Kates, M. Eric Hyndman, Ashish M. Kamat,* Trinity J. Bivalacqua, Kenneth G. Nepple and Michael A. O'Donnell†,‡

From the Department of Urology, University of Texas Southwestern, Dallas (RLS), MD Anderson Cancer Center, Houston (NB, SN, AMK), Texas, Department of Urology, Cleveland Clinic Foundation, Cleveland, Ohio (LJT), Department of Urology (AV, KGN, MAO) and Holden Comprehensive Cancer Center (SLM, KGN, MAO), University of Iowa, Iowa City, Iowa, Department of Urology, University of Calgary, Calgary, Alberta, Canada (TC, MEH), University of Arizona School of Medicine (MAR, DLL) and BCG Oncology (DLL), Phoenix, Arizona, Department of Urology, Johns Hopkins University, Baltimore, Maryland (MJD, MK, TJB), and Beth Israel Deaconess Medical Center, Boston, Massachusetts (JW, WCD)

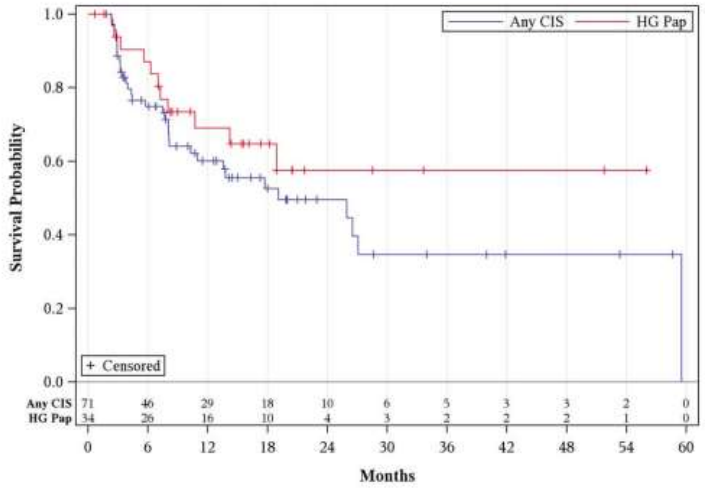

Figure 2. High grade bladder recurrence-free survival for BCG unresponsive cases.

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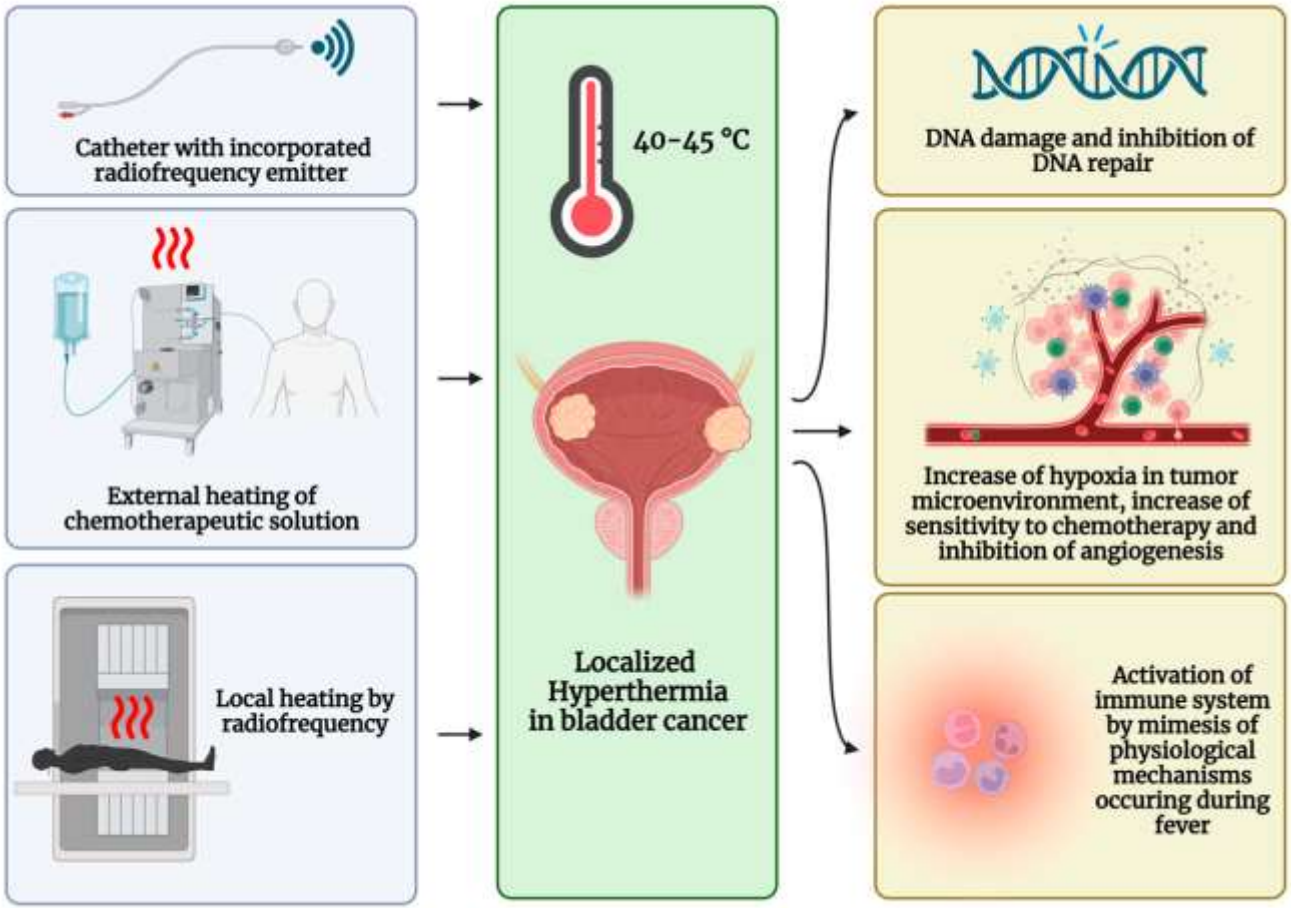
Quimiohipertermia



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Claps, F. BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer: Current Treatment Landscape and Novel Emerging Molecular Targets. *Int. J. Mol. Sci.* **2023**, *24*, 12596.

Quimiohipertermia: RITE

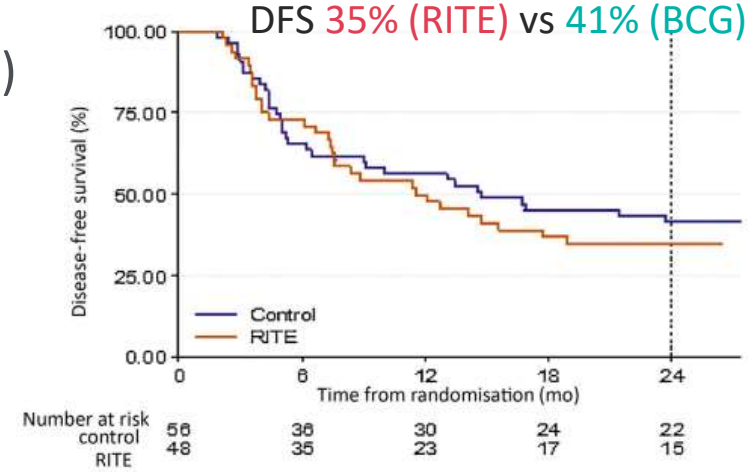
- EC fase III (n=**104**)
- Fracaso ***al menos 1 ciclo inducción*** BCG
- 1:1 → RITE : Tto estándar (reBCG)

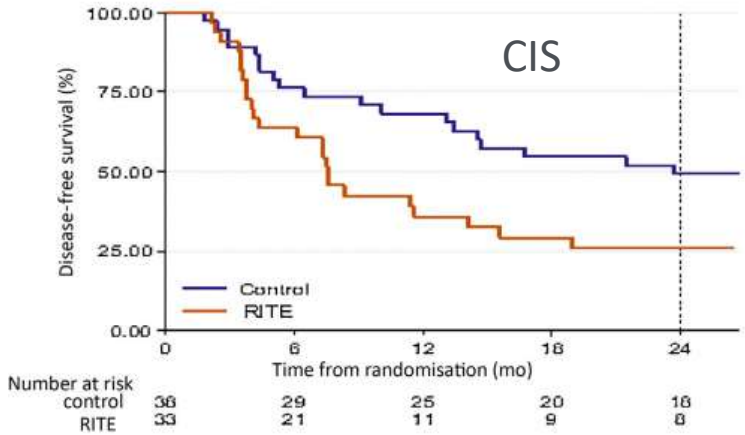
Platinum Priority – Bladder Cancer
Editorial by XXX on pp. x–y of this issue

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

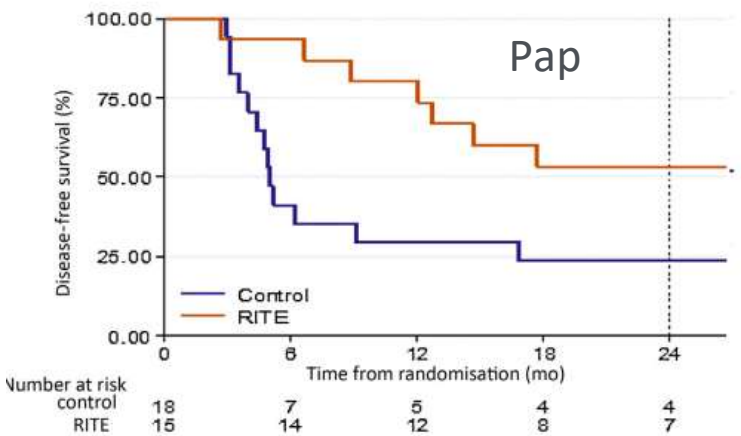
Wei Shen Tan [a,b], Anesh Panchal [c], Laura Buckley [c], Adam J. Devall [c], Laurence S. Loubière [c], Ann M. Pope [c], Mark R. Feneley [b], Jo Cresswell [d], Rami Issa [e], Hugh Mostafid [f], Sanjeev Madaan [g], Rupesh Bhatt [h], John McGrath [i], Vijay Sangar [j], T.R. Leyshon Griffiths [k], Toby Page [l], Dominic Hodgson [m], Shibendra N. Datta [n], Lucinda J. Billingham [c,1], John D. Kelly [a,b,1,]*

DFS 35% (RITE) vs 41% (BCG) a 2a **(p=0.49)**





DFS 26% (RITE) vs 49% (BCG) a 2a (**p = 0.01**)



DFS 53% (RITE) vs 24% (BCG) a 2a **(p=0.1)**

Quimiohipertermia: HIVEC

- Resultados similares a RITE en tumores papilares
- Aparentemente mejores resultados en *cis:*

  - ***Anastay (2023)*** → Observacional **n=116** (36 cis)

    RFS 2a 19.9%/43.7% (p=0.52)

    PFS 2a 71.8%/88.8% (p=0.32)

  - ***Piipers (2022)*** → Observacional **n=56**

    HR-RFS **1a** (53%) **2a** (35%) *no dif cis vs pap*

  - ***De Jong (2018)*** → post-hoc

    No dif en RFS cis vs p

NECESIDAD DE ESTUDIOS PROSPECTIVOS Y COMPARATIVOS (RCT)

- Buen perfil de seguridad y tolerancia

Anastay V. *Cancers (Basel).* 2023 Feb 24;15(5):1455.

de Jong J.J. *Bladder Cancer.* 2018;4:395–401.

Pijpers O.M. *Urol. Oncol.* 2022;40:62.e13–e20.

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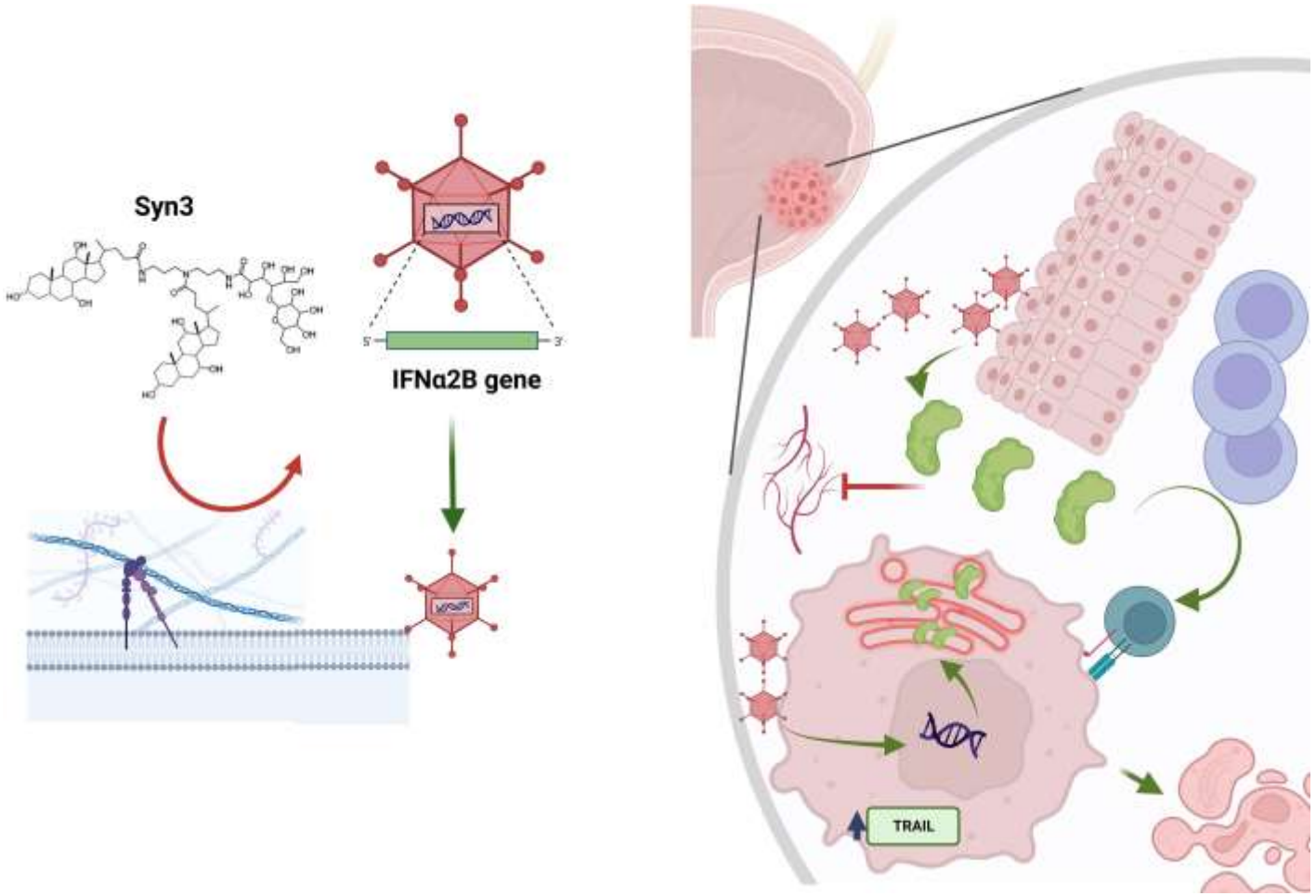
Nadofaragene firadenovec



Martini A, Tholomier C, Mokkapati S and Dinney CPN (2023) Interferon gene therapy with nadofaragene firadenovec for bladder cancer: from bench to approval. *Front.*

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Nadofaragene firadenovec

THE LANCET Oncology

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 J 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

- EC *fase III single-arm*
- n = **151** → 103/**68%** (*cis+-pap*) 48/**32%** (*pap*)
- 75mL NF ($3x10^{11}$ part/ml) intravesical ***cada 3 meses***
- *Cistoscopia + citología* **cada 3 meses**
- *Biopsias* de confirmación a los **12 meses**
- Mediana seguimiento ***19.7 meses*** *(IQR 16-24.8)*

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Nadofaragene firadenovec

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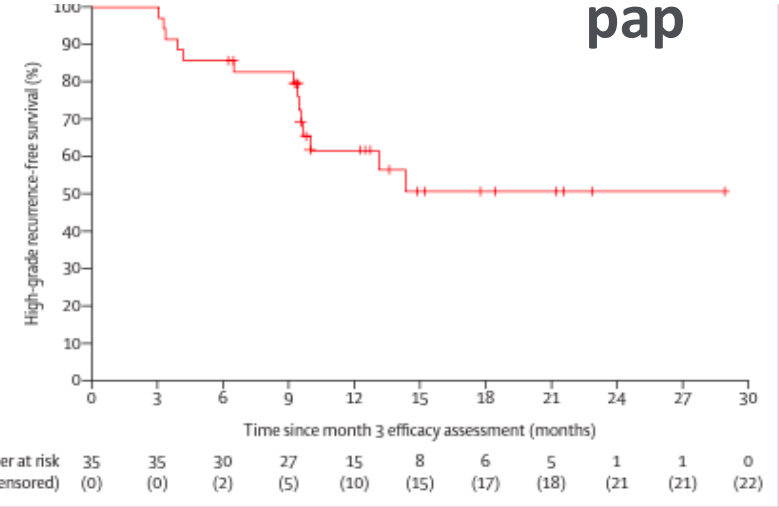
	Carcinoma in situ cohort (n=103)	High-grade Ta or T1 cohort (n=48)	All patients (n=151)
Patients with complete response at month 3 *	55 (53·4%; 43·3–63·3)	35 (72·9%; 58·2–84·7)	90 (59·6%; 51·3–67·5)
Duration of complete response † or high-grade recurrence-free survival ‡, months	9·69 (9·17-NE)	12·35 (6·67-NE)	7·31 (5·68–11·93)
Patients who were free from high-grade recurrence			
Month 6	42 (40·8%; 31·2–50·9)	30 (62·5%; 47·4–76·0)	72 (47·7%; 39·5–56·0)
Month 9	36 (35·0%; 25·8–45·0)	28 (58·3%; 43·2–72·4)	64 (42·4%; 34·4–50·7)
Month 12	25 (24·3%; 16·4–33·7)	21 (43·8%; 29·5–58·8)	46 (30·5%; 23·2–38·5)

pap



- Tasa EA > *grado II* → **4%**
- CFS a los 2a → **64.5%** *(no dif.)*
- *Progresión* → **5% cis – 6% pap**

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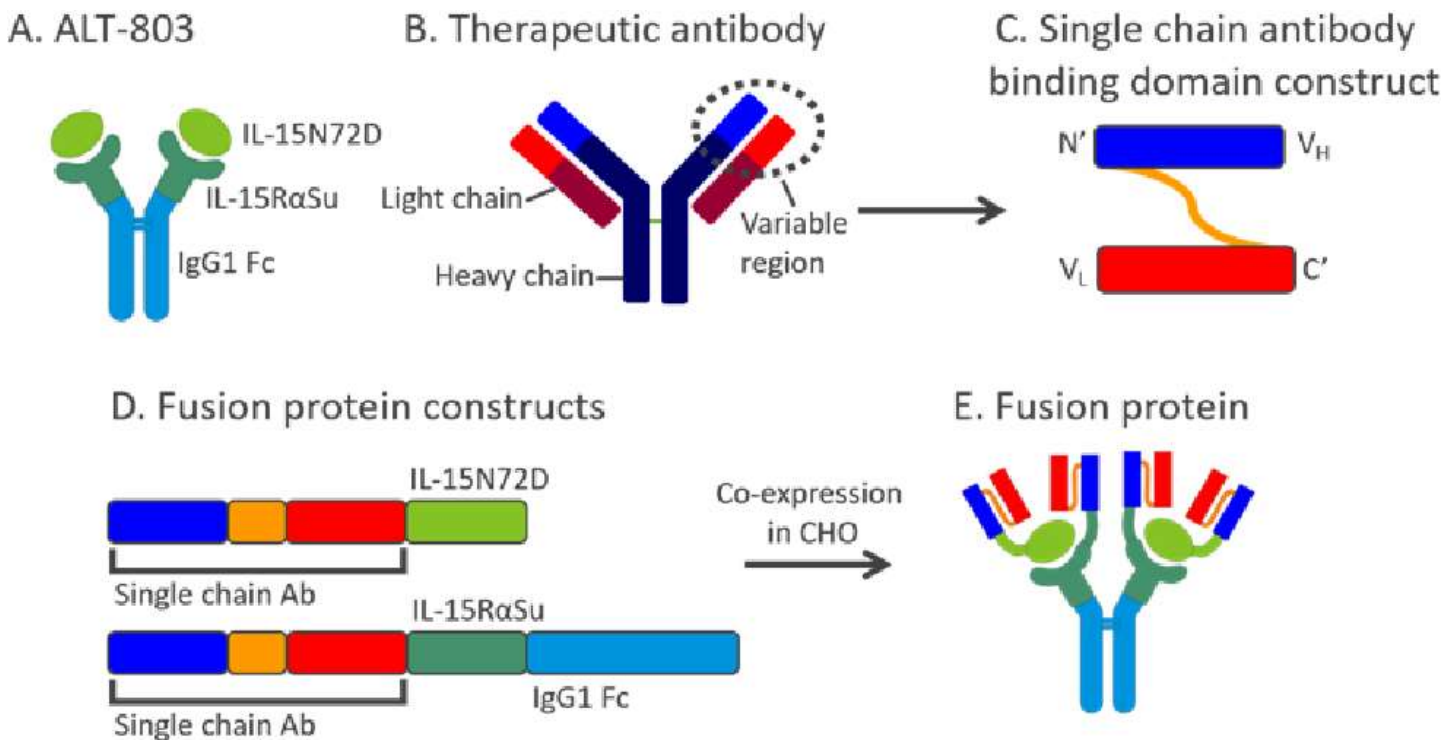
NAI (N-803) – Ensayo QUILT



Alter, S., Rhode, P.R., Jeng, E.K., BioScience, H.C., Miramar, & Florida (2018). Targeted IL-15-based Protein Fusion Complexes as Cancer Immunotherapy Approaches.

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Grupo quirónsalud

NAI (N-803) – Ensayo QUILT

- EC fase III single – arm
- *3 cohortes* de tratamiento (**n=171**)
  - **A (n=84): cis +- pap** → Iv **N-803 + BCG**
  - **B (n=77): pap** → Iv **N-803 + BCG**
  - **C (n=10): cis +- pap** → Iv **N-803**

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

- I + M similar esquema SWOG 8507
- *Cistoscopia + citología* **/ 3 meses hasta 24 meses – /6 meses a partir de mes 24**
- *Biopsias* de confirmación a los **12 meses**
- Mediana de *seguimiento*: 23.9 meses (*cis*) – 20.7 meses (pap)

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NAI (N-803) – Ensayo QUILT


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- ***Cis (cohorte A):***
  - *Respuesta completa* → **71%** (inicial 78% - tras ReI 22%)
  - *CR* a 3 meses **(55%)** – 6 meses (56%) - 12 meses (45%) – 18 meses **(33%)**
  - *Mediana de duración* **26,6 meses**
  - *PFS* a 24 meses (84.7%) *OS* (94.3%) *DSS* (100%)
  - *Cist. radical* → 7% (4/58 resp) 11 meses – 33% (8/24 no resp) 7.8 meses

- ***Ta/T1 AG (cohorte B):***
  - *Mediana DFS* → **19,3 meses**
  - *DFR* a 12 meses **(55.4%)** – 16 meses (51.1%) - 18 meses **(48.3%)**
  - *Cist. radical* → **7%**

EA grado > II → **20%**

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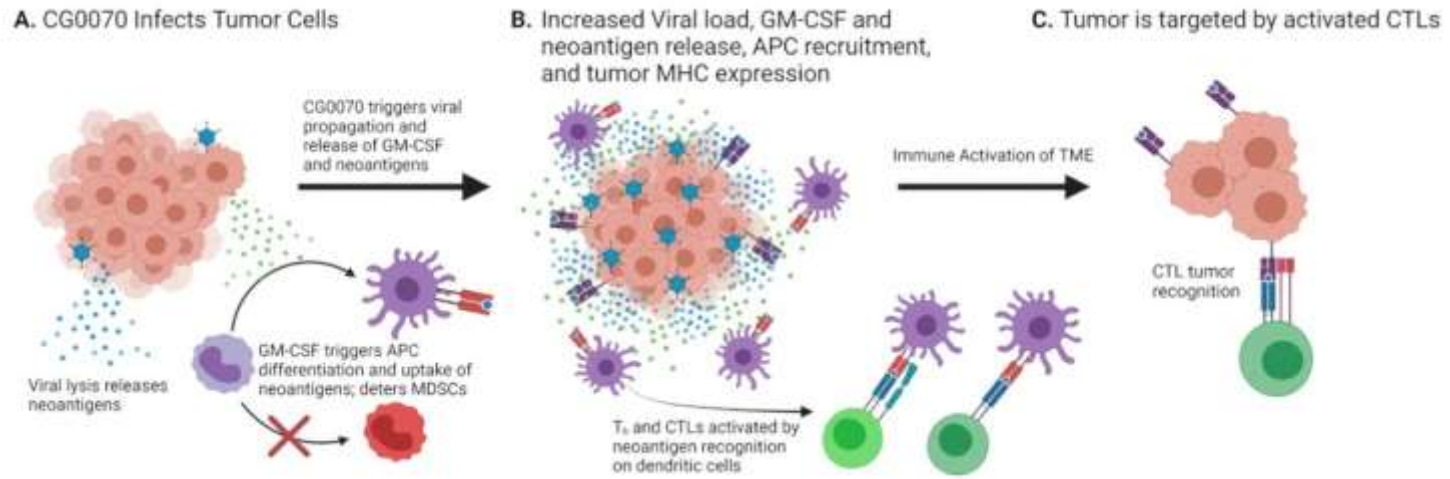
Lo último

CG0070 + Pembrolizumab (CORE-1)

AUA 2023
CHICAGO ✶ APR 28-MAY 1

- *Virus oncolítico* → E2F (promotor) + GM-CSF (transgen)
- Instilaciones vesicales similar SWOG
- EC fase II (**CORE-1:** + Pembrolizumab) → cis +- pap
  - CR 85% → 82% 6m - 81% 9m - 68% 12m
- EC fase III (**BOND-003:** CG0070 mt) *en marcha*
  - BOND-002: CR 65% - 44% 6m - 28% 12m

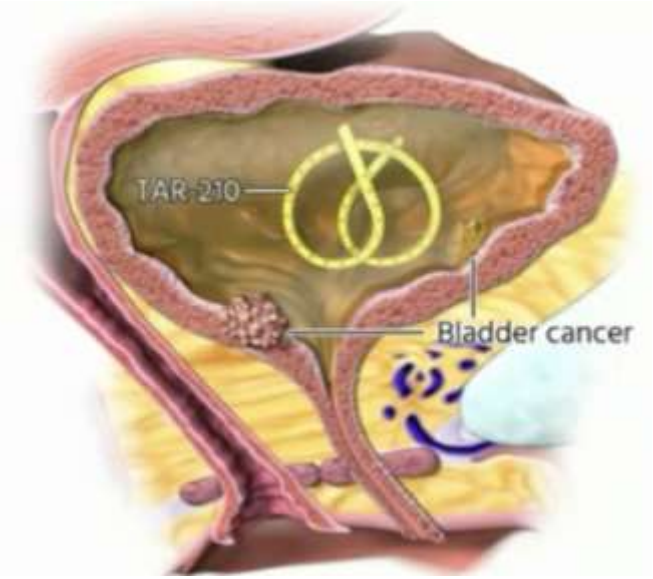


Lo último

Erdafitinib intravesical (TAR-210)

MADRID 2023 ESMO congress

- ITK FGFR *mutación en FGFR*
- EC fase I → 2 cohortes
  - Cohorte 1: NMIBC HG Pap (no cis) BCG previa/refract.
- Fase *escalada de dosis*
- Mediana exposición tto → **3.7 - 4.3 meses**
- *Libres recurrencia* → **82%** (n=11)



Conclusiones

- Cistectomía radical ***tratamiento de elección***
- C. radical **PRECOZ** → *SCE directamente proporcional a precocidad*
- Múltiples EPV estudiadas → NINGUNA superior a CR
- Resultados clínicos aceptables y *duración mantenida*
- > Sencillo y barato que CR
- Perfil de seguridad y tolerancia vs CR
- Ventana de ***oportunidad***
  - bajo riesgo de progresión
  - mínimo retraso para CR en fracasos

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GRACIAS

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