TRIALS CLINICI IN CORSO E IN PROGRAMMAZIONE

Nuove opzioni terapeutiche in chemioterapia nella lotta al carcinoma uroteliale

---

RELATORE: R.Hurle

Istituto Clinico Humanitas, Rozzano (MI)

International Guidelines

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

[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high g
[d]CIS=carcinoma *in situ*; [e]LVI = lymphovascular invasion

American Urological Association

Table 6 – Risk group stratification

Low-risk tumours	Primary, solitary, Ta, LG/G1, < 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: • T1 tumour • HG/G3 tumour • CIS • Multiple and recurrent and large (>3 cm) Ta G1G2 tumours (all conditions must be present in this point)

eau

Immediate Instillation

LOW
&
INTERMEDIATE RISK

Brisbane W. Urology 2019
Emberbach M, Eur Urol 2018
Smith A. BJU Int 2018
Atteman M. Pharmacoeconomics 2003

Intermediate risk:

KAMAT, 2014

Low Risk
(solitary, primary low-grade Ta tumor)

Treatment:
- TURBT + single immediate post-op chemotherapeutic dose, or
- Office fulguration
- Observation/follow-up

High Risk
(any T1, high-grade and/or CIS)

Treatment:
- TURBT + BCG maintenance
- Consider cystectomy

Intermediate Risk

(histologically-confirmed multiple and/or recurrent low-grade Ta tumors)

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)

0* → **TREAT SIMILAR TO LOW RISK:**
- TURBT + single immediate post-op chemotherapeutic dose, or
- Consider office fulguration and observation
- Consider intravesical chemotherapy

1-2 → **TREAT AS INTERMEDIATE RISK:**
- TURBT plus adjuvant intravesical therapy (options include chemotherapy or BCG with maintenance [full dose, 1 year])

≥3 → **TREAT AS HIGH RISK:**
- TURBT + BCG induction + maintenance

CONSIDER PREVIOUS INTRAVESICAL TREATMENT

None
- Consider intravesical chemotherapy

Chemotherapy
- Consider BCG maintenance therapy
- Consider alternative (proven) chemotherapeutic agent

BCG
- Consider additional BCG maintenance therapy
- Consider alternative intravesical therapy

International Guidelines

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

[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high g
[d]CIS=carcinoma *in situ*; [e]LVI = lymphovascular invasion

American Urological Association

Table 6 – Risk group stratification

Low-risk tumours	Primary, solitary, Ta, LG/G1, < 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: • T1 tumour • HG/G3 tumour • CIS • Multiple and recurrent and large (>3 cm) Ta G1G2 tumours (all conditions must be present in this point)

eau

Variable increasing the risk of failure

Variable	Reference
Female sex	Fernandez-Gomez J. Eur Urol 2008
Older age	Joudi FN. J Urol 2006
Multifocality	Fernandez-Gomez J. Eur Urol 2008
Recurrent tumours	Fernandez-Gomez J. Eur Urol 2008
Associated CIS (prostatic urethra)	Palou J. Eur Urol 2012
Lymphovascular invasion	Resnick MJ. BJU Int 2011
Detectable disease at 3-months check-up cystoscopy	Solsona E. Urol 2000
Depth and multifocality of lamina propria invasion	van Rhijn BWG. Eur Urol 2012
Timing of failure	Gallagher BL. Urology 2008
Two or more prior courses of BCG	Rosevear HM. J Urol 2011

High Risk: BCG era «rules of three»

J Urol. 2003 Jan;169(1):96-100; discussion 100.

A retrospective analysis of 153 patients treated with c… …illus Calmette-Guerin for primary stage T1 grade 3 bladder c… …ssion and survival.

Shahin O[1], Thalmann GN, Rentsch C, Mazzucchelli L, Stud…

- Intravesical immunotherapy in the form of BCG is the only effective adjuvant therapy for high-risk NMIBC (non-muscle-invasive bladder cancer) that reduces progression of disease

…e

…3 survive without bladder

1\3 die of their disease

Definition of BCG unresponsive

BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

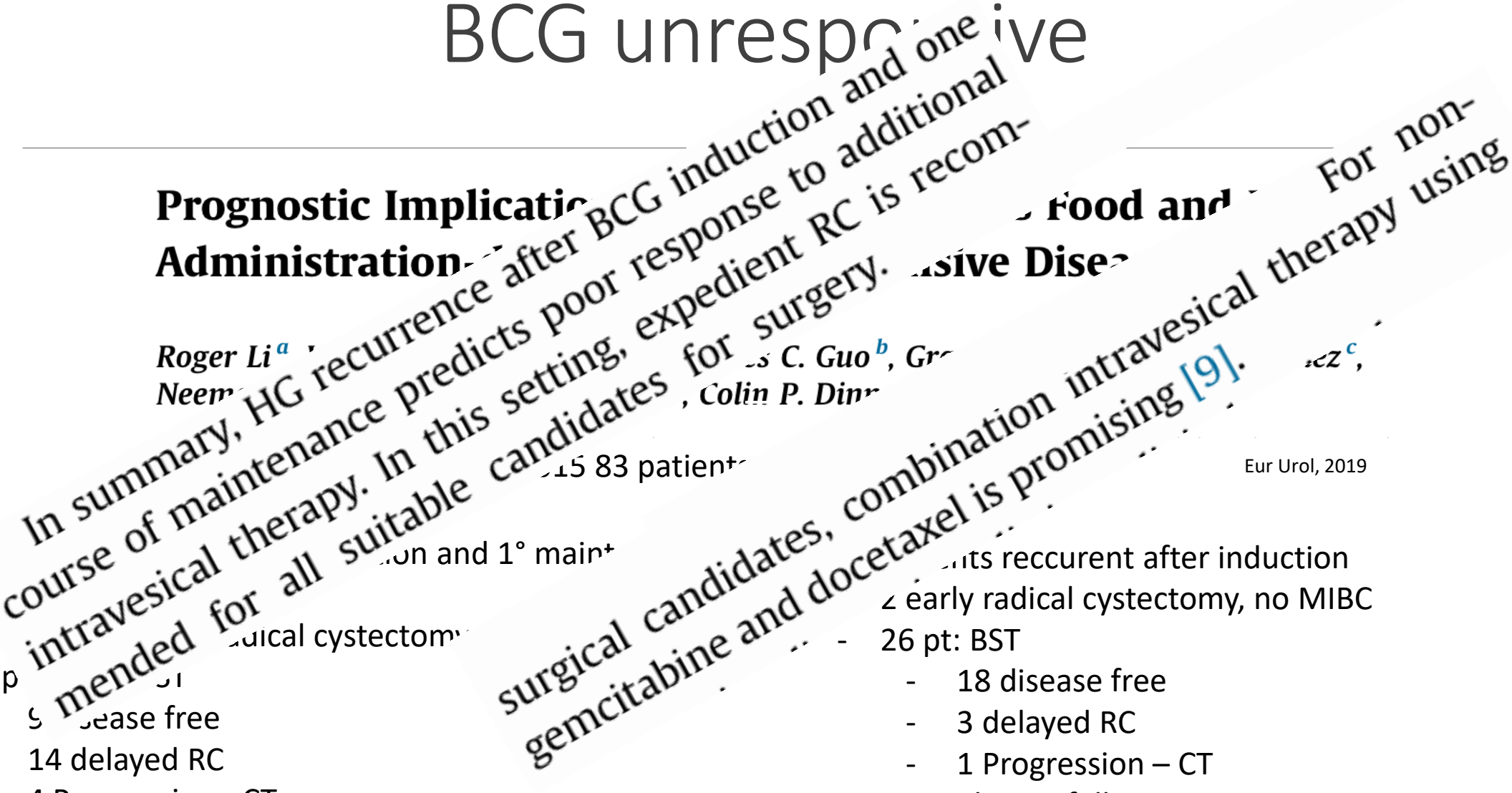
February 2018
Clinical/Medical

- ✓ Persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy
- ✓ Recurrent HG Ta/T1 disease within 6 months of completion of adequate BCG therapy
- ✓ T1 HG disease at the first evaluation following an induction BCG course

BCG unresponsive

The management of BCG unresponsive NMIBC has been identified as an **unmet clinical need** by the FDA

BCG unresp ive



Prognostic Implicati **Food and**
Administration- **sive Dise**

Roger Li [a] *s C. Guo* [b], *Gr* *ez* [c],
Neem *, Colin P. Din*

In summary, HG recurrence after BCG induction and one course of maintenance predicts poor response to additional intravesical therapy. In this setting, expedient RC is recommended for all suitable candidates for surgery. For non-surgical candidates, combination intravesical therapy using gemcitabine and docetaxel is promising [9].

Eur Urol, 2019

55 15 83 patient

with on and 1° maint

- 16 dical cystectomy
- 39 p
  - 9 ease free
  - 14 delayed RC
  - 4 Progression - CT

its reccurent after induction

2 early radical cystectomy, no MIBC

- 26 pt: BST
  - 18 disease free
  - 3 delayed RC
  - 1 Progression – CT
  - 4 lost in follow up

Critical Issues

- ✓ The current definitions take into account the timing of failure
- ✓ They not reflect the type of BCG schedule administered or the primary indication for BCG.
- ✓ Published differing outcomes for patients who receive just induction BCG compared with a maintenance schedule.

Critical Issues

- ✓ Comparing salvage therapies in patients failing BCG has been hindered by the lack of standard definitions and studies that combined different classes of BCG-failure
- ✓ Given the high risk of disease recurrence, a placebo-controlled arm is not ethical in BCG unresponsive disease, so experimental single armed trials with new agents are now being conducted

Mukherjee N. Urol Oncol 2018

BCG unresponsive: intravesical therapy

FDA validated

Table 1 | **Results of intravesical chemotherapy after BCG failure**

Agent	Outcomes	Studies
Valrubicin	18–21% disease free at 6 months	Steinberg *et al.*[42]
	16% disease free at 12 months	Dinney *et al.*[43]
Gemcitabine	21–28% disease free at 12 months	Dalbagni *et al.*[45]
	21% disease free at 24 months	Dalbagni *et al.*[46]
Docetaxel	40% disease free at 12 months	Laudano *et al.*[50]
Abraxane	36% disease free at 12 months	McKiernan *et al.*[52]

- No salvage medical or intravesical treatments have been shown to have durable efficacy in true BCG-unresponsive patients, although some show efficacy in select subgroups of patients

Gemcitabine in BCG unresponsive ICH Experience

8 weekly instillation 2000mg Gemcitabine

ICH PROTOCOL	
Start	2011-ongoing
N°Pt.	33
CR	15(45%)
DFS 12m	10 (30%)
DFS 24m	7 (21)
NR	18(55%)

OUTCOME	
Died	6 othes causes , 7 for disese
Alive M+/N+	7
Alive NED	11 (5 after recurrence NMIBC)

Combo Therapy

Gemcitabine 1g / Mitomycin C 40mg

<u>Lightfoot 2014</u>

48% 1-year DFS
38% 2-year DFS
Administered sequentially
Induction 6 wk MNT 1 yr

<u>Cockerill 2015</u>

37% 2-year DFS

Administered sequentially
Induction 6–8 wk No MNT

BCG unresponsive

78%

88%

Combo Therapy

Gemcitabine 1g / Docetaxel 37,5mg

Steinberg 2015

54% 1-year DFS
34% 2-year DFS
Administered sequentially
Induction 6 wk MNT 24 mo

Milbar 2017

42% 1-year DFS
24% 2-year DFS
Administered sequentially
Induction 6 wk MNT 24mo

BCG unresponsive

82%

66%

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Naive

Category	Phase	Enroll.	Title	Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	III	120	Neoadjuvant Short-term Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in NMIBC	Mitomycin C	Oct. 2020	NCT03348969
Cytotoxic therapy	II	82	CALIBER - A Phase II Randomised Feasibility Study of Chemoresection and Surgical Management in Low Risk Non-Muscle Invasive Bladder Cancer	Mitomycin C	Sept. 2018	NCT02070120
Cytotoxic therapy	III	500	A Randomized, Single-Dose, Double-Blind, Placebo-Controlled Phase 3 Study of Qapzola™ (Apaziquone) as a Chemotherapy Adjuvant to Transurethral Resection of Bladder Tumors in Patients with Low- To-Intermediate-Risk NMIBC (CONQUER)	Apaziquone	Dec. 2022	NCT03224182 CONQUER
Cytotoxic therapy	II	54	Evaluation of Immediate Preoperative Instillation (IPOI) of Mitomycin C Compared to Early Postoperative Instillation (IPOP) in Non-muscle Invasive Bladder Cancer	Mitomycin C	Jan. 2018	NCT02075060

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Denmark
P.I. Jensen
Condition: Recurrent NMIBC Ta LG or HG
Status: Active, not recruiting

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Naive

Category	Phase	Enroll.	Title	Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	III	120	Neoadjuvant Short-term Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in NMIBC	Mitomycin C	Oct. 2020	NCT03348969
Cytotoxic therapy	II	82	CALIBER - A Phase II Randomised Feasibility Study of Chemoresection and Surgical Management in Low Risk Non-Muscle Invasive Bladder Cancer	Mitomycin C	Sept. 2018	NCT02070120
Cytotoxic therapy	III	500	A Randomized, Single-Dose, Double-Blind, Placebo-Controlled Phase 3 Study of Qapzola™ (Apaziquone) as a Chemotherapy Adjuvant to Transurethral Resection of Bladder Tumors in Patients with Low- To-Intermediate-Risk NMIBC (CONQUER)	Apaziquone	Dec. 2022	NCT03224182 CONQUER
Cytotoxic therapy	II	54	Evaluation of Immediate Preoperative Instillation (IPOI) of Mitomycin C Compared to Early Postoperative Instillation (IPOP) in Non-muscle Invasive Bladder Cancer	Mitomycin C	Jan. 2018	NCT02075060

NIH U.S. National Library of Medicine
ClinicalTrials.gov

UK, multicenter
P.I. Mostafid
Condition: NMIBC LG
Status: Active, not recruiting

82pt, 2:1 RCT
- Chemoresection
- TURBT * early instillation (3 mo cystoscopy follow up + biopsy)

Chemoresection: MMC 40mg, 4 once weekly

- Primary outcome: CR with chemoresection
- Secondary outcome: compliace, salvage surgical rate, PFS

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Naive

Category	Phase	Enroll.	Title	Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	III	120	Neoadjuvant Short-term Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in NMIBC	Mitomycin C	Oct. 2020	NCT03348969
Cytotoxic therapy	II	82	CALIBER - A Phase II Randomised Feasibility Study of Chemoresection and Surgical Management in Low Risk Non-Muscle Invasive Bladder Cancer	Mitomycin C	Sept. 2018	NCT02070120
Cytotoxic therapy	III	500	A Randomized, Single-Dose, Double-Blind, Placebo-Controlled Phase 3 Study of Qapzola™ (Apaziquone) as a Chemotherapy Adjuvant to Transurethral Resection of Bladder Tumors in Patients with Low- To-Intermediate-Risk NMIBC (CONQUER)	Apaziquone	Dec. 2022	NCT03224182 CONQUER
Cytotoxic therapy	II	54	Evaluation of Immediate Preoperative Instillation (IPOI) of Mitomycin C Compared to Early Postoperative Instillation (IPOP) in Non-muscle Invasive Bladder Cancer	Mitomycin C	Jan. 2018	NCT02075060

NIH U.S. National Library of Medicine
ClinicalTrials.gov

France, multicenter
P.I. Irani
Condition: Primary or recurrent paillary aspect NMIBC

54pt,
- IPOI: 1h before TURBT
- IPOP: post op within 24h

- Primary outcome: PFS 12 mo.

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Naive

Category	Phase	Enroll.	Title	Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	I, II	16	A Phase 1/2a Pilot Study of Intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer	TSD-001	Sept. 2018	NCT03081858
Cytotoxic therapy	III	300	A Prospective, Open-label Randomized Clinical Trial of a Single Bladder Instillation of Mitomycin C vs. Gemcitabine vs. No Additional Treatment Immediately After Transurethral Resection of Bladder Tumor (TURBT)	Mitomycin C Gemcitabine	April 2019	NCT02695771
Cytotoxic therapy	II	78	The Effectiveness and Safety of Neoadjuvant Intravesical Mitomycin-C Instillation in Non-muscle Invasive Bladder Cancer Patients: Prospective, Randomized, Phase II Study	Mitomycin C	Dec. 2021	NCT03058757
Cytotoxic therapy	III	120	Open clinical trial to evaluate the efficacy of intravesical instillation of hyaluronate added to early instillation of mitomycin vs early instillation of mitomycin in patients suffering from low risk not muscle-infiltrating bladder cancer	Hyaluronate Chondroitin sulfate	n.d.	EUCTR2016-003813-92

NIH U.S. National Library of Medicine
ClinicalTrials.gov

USA, multicenter
P.I. Ofelein
Condition: NMIBC Ta LG
Status: Recruiting

- Proliposomal intravesical Paclitaxel

Escalation dose of Paclitaxel every 2 wks for 6 wks:

- 25mg – 50mg – 75mg – 100mg – 150mg
- Until DLT

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Naive

Category	Phase	Enroll.	Title	Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	I, II	16	A Phase 1/2a Pilot Study of Intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer	TSD-001	Sept. 2018	NCT03081858
Cytotoxic therapy	III	300	A Prospective, Open-label Randomized Clinical Trial of a Single Bladder Instillation of Mitomycin C vs. Gemcitabine vs. No Additional Treatment Immediately After Transurethral Resection of Bladder Tumor (TURBT)	Mitomycin C Gemcitabine	April 2019	NCT02695771
Cytotoxic therapy	II	78	The Effectiveness and Safety of Neoadjuvant Intravesical Mitomycin-C Instillation in Non-muscle Invasive Bladder Cancer Patients: Prospective, Randomized, Phase II Study	Mitomycin C	Dec. 2021	NCT03058757
Cytotoxic therapy	III	120	Open clinical trial to evaluate the efficacy of intravesical instillation of hyaluronate added to early instillation of mitomycin vs early instillation of mitomycin in patients suffering from low risk not muscle-infiltrating bladder cancer	Hyaluronate Chondroitin sulfate	n.d.	EUCTR2016-003813-92

NIH U.S. National Library of Medicine
ClinicalTrials.gov

USA, multicenter
P.I. Humphrey
Condition: NMIBC

3 arms:
- MMC immediate instillation
- Gemcitabine 2000mg immediate inst.
- No intervention

- Primary outcome: adverse events
- Secondary. Outcome: bladder stones

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Naive

Category	Phase	Enroll.	Title	Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	I, II	16	A Phase 1/2a Pilot Study of Intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer	TSD-001	Sept. 2018	NCT03081858
Cytotoxic therapy	III	300	A Prospective, Open-label Randomized Clinical Trial of a Single Bladder Instillation of Mitomycin C vs. Gemcitabine vs. No Additional Treatment Immediately After Transurethral Resection of Bladder Tumor (TURBT)	Mitomycin C Gemcitabine	April 2019	NCT02695771
Cytotoxic therapy	II	78	The Effectiveness and Safety of Neoadjuvant Intravesical Mitomycin-C Instillation in Non-muscle Invasive Bladder Cancer Patients: Prospective, Randomized, Phase II Study	Mitomycin C	Dec. 2021	NCT03058757
Cytotoxic therapy	III	120	Open clinical trial to evaluate the efficacy of intravesical instillation of hyaluronate added to early instillation of mitomycin vs early instillation of mitomycin in patients suffering from low risk not muscle-infiltrating bladder cancer	Hyaluronate Chondroitin sulfate	n.d.	EUCTR2016-003813-92

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Multicenter
Condition: Recurrent NMIBC LG
Status: Active, not recruiting

120pt, RCT (MEDAC MMC)
- 60 pt intervention group (neoadjuvant chemoresection 3 instillation weekly for 3 wks, follow up with cystoscopy at 4 wks)
- 60 control group TURBT + adjuvant

- Primary outcome: 2 year RR
- Secondary outcome: Tumor response rate

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Unresponsive

Category	Phase	Enroll.	Title		Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	III	88	A Phase 3 Study to Evaluate the Efficacy and Safety of Intravesical Nanoxel®M (Docetaxel-PM) In Bacillius Calmette-Guerin Refractory Non-Muscle Invasive Bladder Cancer	F	Docetaxel-PM Mitomycin-C	Dec. 2020	NCT02982395
Cytotoxic therapy	I	24	A Phase I Trial for the Use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment of BCG-Refractory Non-muscle Invasive Urothelial Carcinoma of the Bladder	U	Cabazitaxe Gemcitabine Cisplatin	May 2020	NCT02202772
Drug delivery	III	106	A Multicenter, Single-Arm Study Evaluating the Efficacy of Synergo® Radiofrequency-Induced Thermochemotherapy Effect (RITE) With Mitomycin C (Synergo® RITE + MMC) in CIS Non-Muscle Invasive Bladder Cancer (NMIBC) Bacillus Calmette-Guérin (BCG)-Unresponsive Patients with or without Papillary NMIBC	U	Synergo RITE + MMC	Dec. 2024	NCT03335059

Korea
P.I. Ku,SAMIANG
Condition: Ta, T1 refractory BCG
Status: Active

88pt, RCT
- Experimental arm 75mg Nanoxel
- Comparative arm: MMC 40ml

- Primary outcome: RFR 1 yr

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Unresponsive

Category	Phase	Enroll.	Title		Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	III	88	A Phase 3 Study to Evaluate the Efficacy and Safety of Intravesical Nanoxel®M (Docetaxel-PM) In Bacillius Calmette-Guerin Refractory Non-Muscle Invasive Bladder Cancer	F	Docetaxel-PM Mitomycin-C	Dec. 2020	NCT02982395
Cytotoxic therapy	I	24	A Phase I Trial for the Use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment of BCG-Refractory Non-muscle Invasive Urothelial Carcinoma of the Bladder	U	Cabazitaxe Gemcitabine Cisplatin	May 2020	NCT02202772
Drug delivery	III	106	A Multicenter, Single-Arm Study Evaluating the Efficacy of Synergo® Radiofrequency-Induced Thermochemotherapy Effect (RITE) With Mitomycin C (Synergo® RITE + MMC) in CIS Non-Muscle Invasive Bladder Cancer (NMIBC) Bacillus Calmette-Guérin (BCG)-Unresponsive Patients with or without Papillary NMIBC	U	Synergo RITE + MMC	Dec. 2024	NCT03335059

NIH U.S. National Library of Medicine
ClinicalTrials.gov

USA, multicenter
P.I. Mckerninan
Condition: BCG refractory NMIBC
Status: Active

24 pt, RCT
5 arms:
- GC 2000mg + CARBAZETAXEL 2.5mg 1wk for 6 wks
- GC 2000mg + CARBAZETAXEL 5mg 1wk for 6 wks
- GC 2000mg + CARBAZETAXEL 5mg + CDDP 66mg 1wk for 6 wks
- GC 2000mg + CARBAZETAXEL 5mg + CDDP 80mg 1wk for 6 wks
- GC 2000mg + CARBAZETAXEL 5mg + CDDP 100mg 1wk for 6 wks

- Primary outcome: adverse events 6wks, complete response at 6 wks

Nuove Opzioni Terapeutiche in Chemioterapia nella Lotta al Carcinoma Uroteliale: BCG Unresponsive

Category	Phase	Enroll.	Title		Interventions	Completion date	Trial ID (acronym)
Cytotoxic therapy	III	88	A Phase 3 Study to Evaluate the Efficacy and Safety of Intravesical Nanoxel®M (Docetaxel-PM) In Bacillius Calmette-Guerin Refractory Non-Muscle Invasive Bladder Cancer	F	Docetaxel-PM Mitomycin-C	Dec. 2020	NCT02982395
Cytotoxic therapy	I	24	A Phase I Trial for the Use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment of BCG-Refractory Non-muscle Invasive Urothelial Carcinoma of the Bladder	U	Cabazitaxe Gemcitabine Cisplatin	May 2020	NCT02202772
Drug delivery	III	106	A Multicenter, Single-Arm Study Evaluating the Efficacy of Synergo® Radiofrequency-Induced Thermochemotherapy Effect (RITE) With Mitomycin C (Synergo® RITE + MMC) in CIS Non-Muscle Invasive Bladder Cancer (NMIBC) Bacillus Calmette-Guérin (BCG)-Unresponsive Patients with or without Papillary NMIBC	U	Synergo RITE + MMC	Dec. 2024	NCT03335059

USA, multicenter
P.I. Ruinsky
Condition: CIS NMIBC unresponsive to BCG
Status: Active

NIH U.S. National Library of Medicine
ClinicalTrials.gov

ONCOFID: Overview

Oncofid-P-B* is a conjugate of paclitaxel and Hyaluronic Acid (HA) for the treatment of NMIBC by intravesical instillation

- Conjugation of paclitaxel with HA:
  - Confers tumor targeted activity (CD44)
  - Improves paclitaxel solubility
  - Reduces paclitaxel Toxicity
  - Confers muco-adhesive properties

Phase I study

PI: R Hurle

EU Multicenter study

ICH experience

ONCOFID, registered as EUDRACT 2016-004144-11 European registry

Oncofid-P-B: clinical overview

- A Phase 1 multiple escalating dose (150-750 mg, 6 weeks) in 16 BCG refractory CIS patients completed
  - 60% CR at EoT
- A Phase 2 (600 mg, 6 weeks + 6+6 months) in 60 Ta G1-G2 patients (marker lesion) completed
  - 45% CR at EoI (naïve 60%)
  - DFS 15.7 months
- Good efficacy and excellent safety (17 DRAEs, G1-G2)/591 instillations) led to test Oncofid-P-B administered **weekly for 12 consecutive weeks** in BCG unresponsive CIS patients

Oncofid-P-B 12-week study

Trial design:

Open label, multicenter, multinational, Phase 1 study*, to evaluate the **safety** and **efficacy** of Oncofid-P-B in 20 patients with CIS ±Ta/T1 who **are unresponsive* or intolerant to BCG** and unwilling or unfit for cystectomy

Materials & Methods

Treatment Schedule:

- **12 consecutive weekly** instillations (intensive phase) followed, in CR patients, by 12 monthly instillations (maintenance phase)

Primary end-point:

- Overall safety profile

Secondary endpoints:

- Efficacy after the intensive phase and after the entire treatment period
- Compliance (drug time retain)
- Rate of discontinuation
- Systemic absorption

The **complete response** (CR) is defined as a negative cystoscopy including biopsy of the urothelium and negative cytology.

Results

Descriptive analysis	
N° patients enrolled	21*
N° patients treated	20
Mean age	72,8 (SD 7,58; 65-83)
Sex	16 M, 5 F
Race	All white caucasian
Diagnosis	17 pure CIS 4 CIS + Ta

Safety Results

During the induction phase, seven mild-moderate (G1- G2) DRAEs including haematuria, proteinuria, nausea and urticaria were reported

There were no DRSAEs or withdrawals due to treatment

In all plasma samples analysed, the drug concentration was always below the LOQ

Efficacy Results

15 out of 20 patients (75%) reached a CR at the end of intensive phase

None of the non-responders developed disease progression

Conclusion

Excellent safety profile of Oncofid-P-B

Favorable preliminary efficacy data,

It confirming its potential as therapeutic option in BCG unresponsive CIS patients, also with a prolonged treatment schedule, and deserves further clinical evaluation

Thank You for Your Attention

rodolfo.hurle@humanitas.it