UROFOCUS 2017

traitements non chirurgicaux du carcinome urothélial de vessie

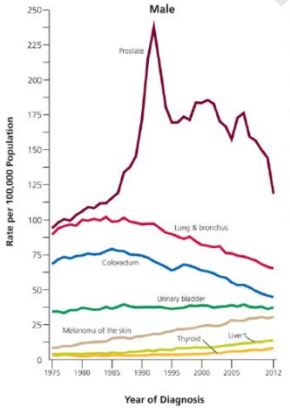
Marc COLOMBEL

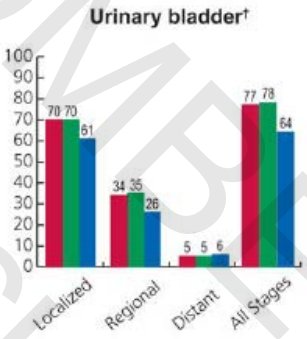
CHU Lyon

Incidence et Prevalence

(Antoni, Ferlay et al. 2017)(Miller, Siegel et al. 2016)

- 5ème cause de cancer et la 8eme cause de mortalité par cancer
- Pas d'amélioration de incidence ou de la mortalité sur les 20 dernières années
- 80% TVNIM





TVNIM 75-80%

70% Ta

20% T1

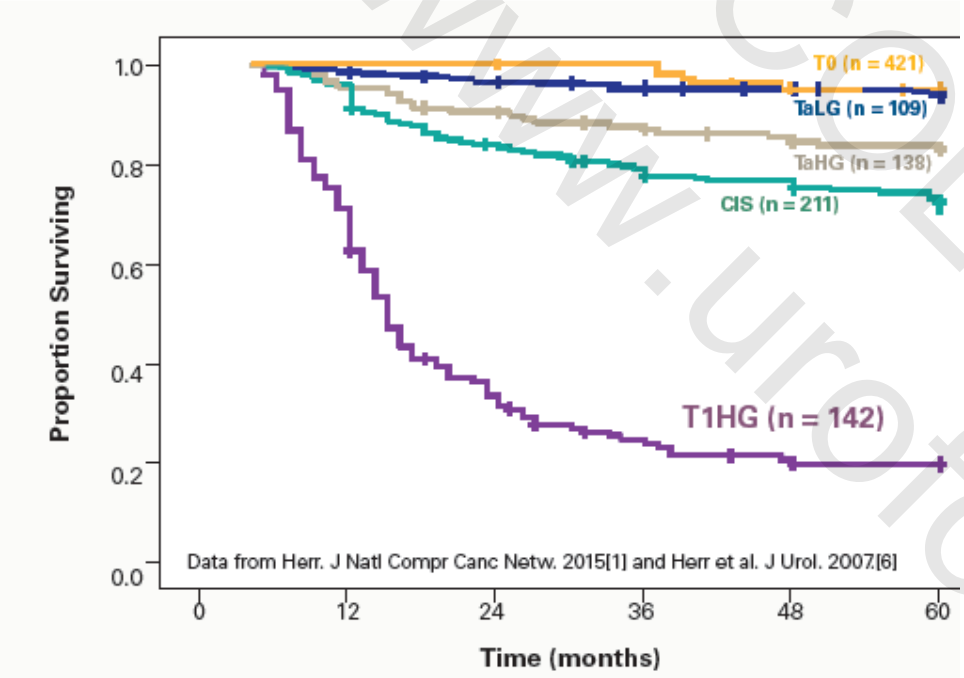
10% CIS

Coût (Yeung, Dinh et al. 2014)

Qualité de vie (Heyes, Bond et al. 2016)

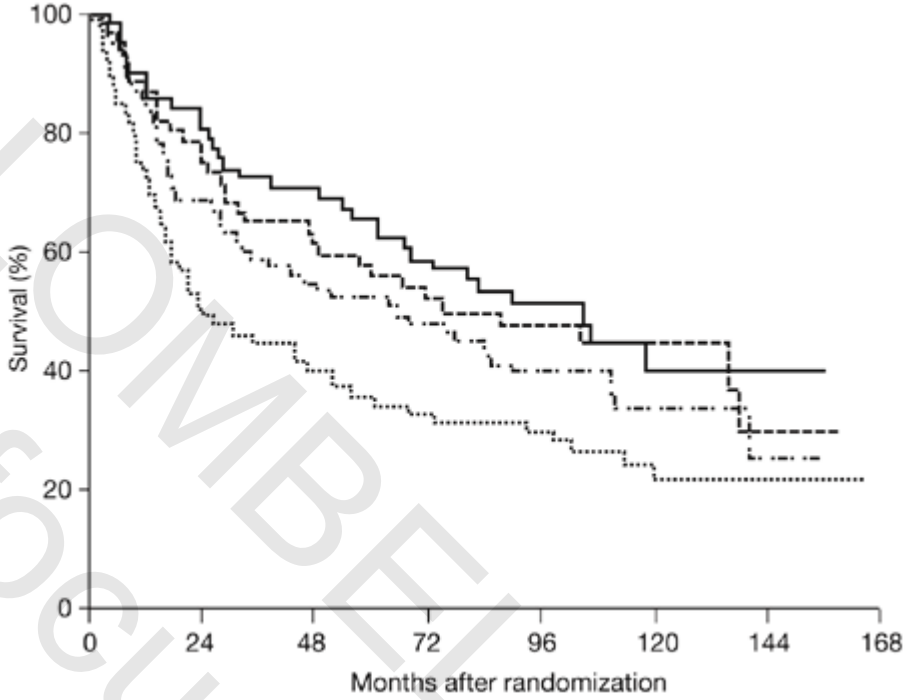
Morbidité & Survie

TVNIM



Herr, 2007 et 2015

TVIM

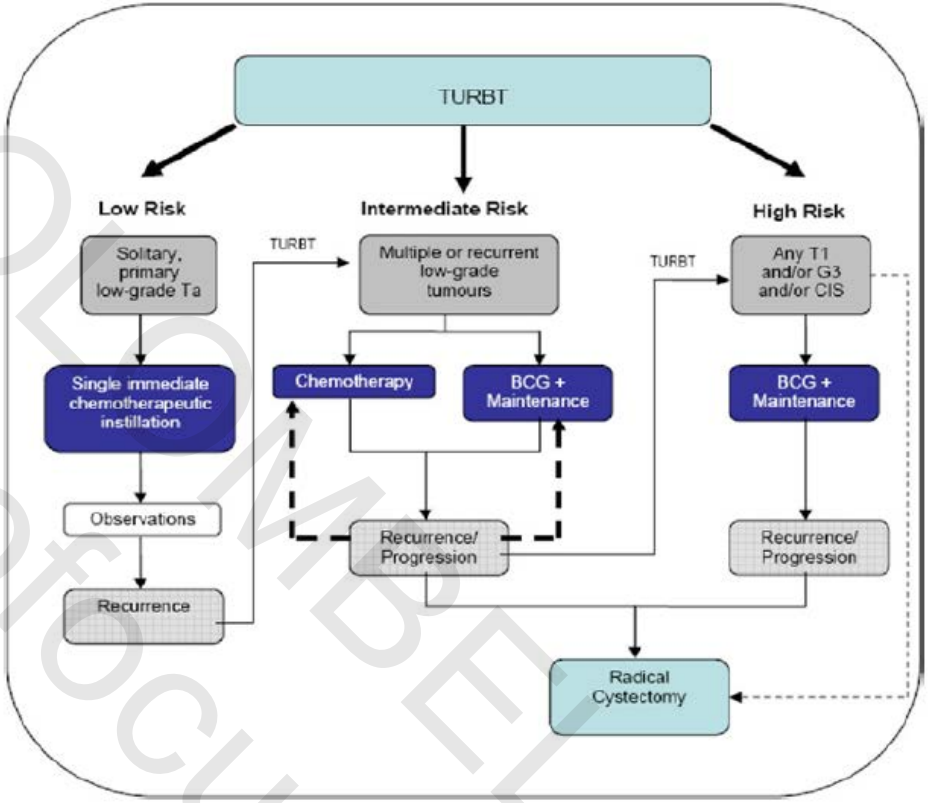


Gilbert, 2006

TVNIM=evaluation pronostique

Tables pronostiques EORTC 2007

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2–7	3	3
>8	6	3
Tumour diameter		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence per year	2	2
>1 recurrence per year	4	2
Category		
Ta	0	0
T1	1	4
Carcinoma *in situ*		
No	0	0
Yes	1	4
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23



Recurrence score	Probability of recurrence at 1 yr (95% CI)	Probability of recurrence at 5 yr
0	15% (10%, 19%)	31% (24%, 37%)
1–4	24% (21%, 26%)	46% (42%, 49%)
5–9	38% (35%, 41%)	62% (58%, 65%)
10–17	61% (55%, 67%)	78% (73%, 84%)
Progression score	**Probability of progression at 1 yr (95% CI)**	**Probability of progression at 5 yr**
0	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2–6	1% (0.4%, 1.6%)	6% (5%, 8%)
7–13	5% (4%, 7%)	17% (14%, 20%)
14–23	17% (10%, 24%)	45% (35%, 55%)

Surveillance des bas grades à risque faible de récidive

- Recommandations
  - 20 à 30% récidives entre 1 et 5 ans
  - 8% récidive à 5 ans…
  - Cystoscopie à 3 mois puis tous les ans pendant 5 ans
- Futur: évaluation du risque de révidive, simplification du suivi
  - Tests
    - Arquer MCM5 (FDA)
    - Visiocyt
    - Mutations (TERT)
  - Association ECHO/cytologie

IPOP Mitomycine C 40mg

- 5% (cancer registry 2005-2012; 10 031pts)
- Récidive à 2 ans
  - IPOP: 25%
  - No IPOP: 30%

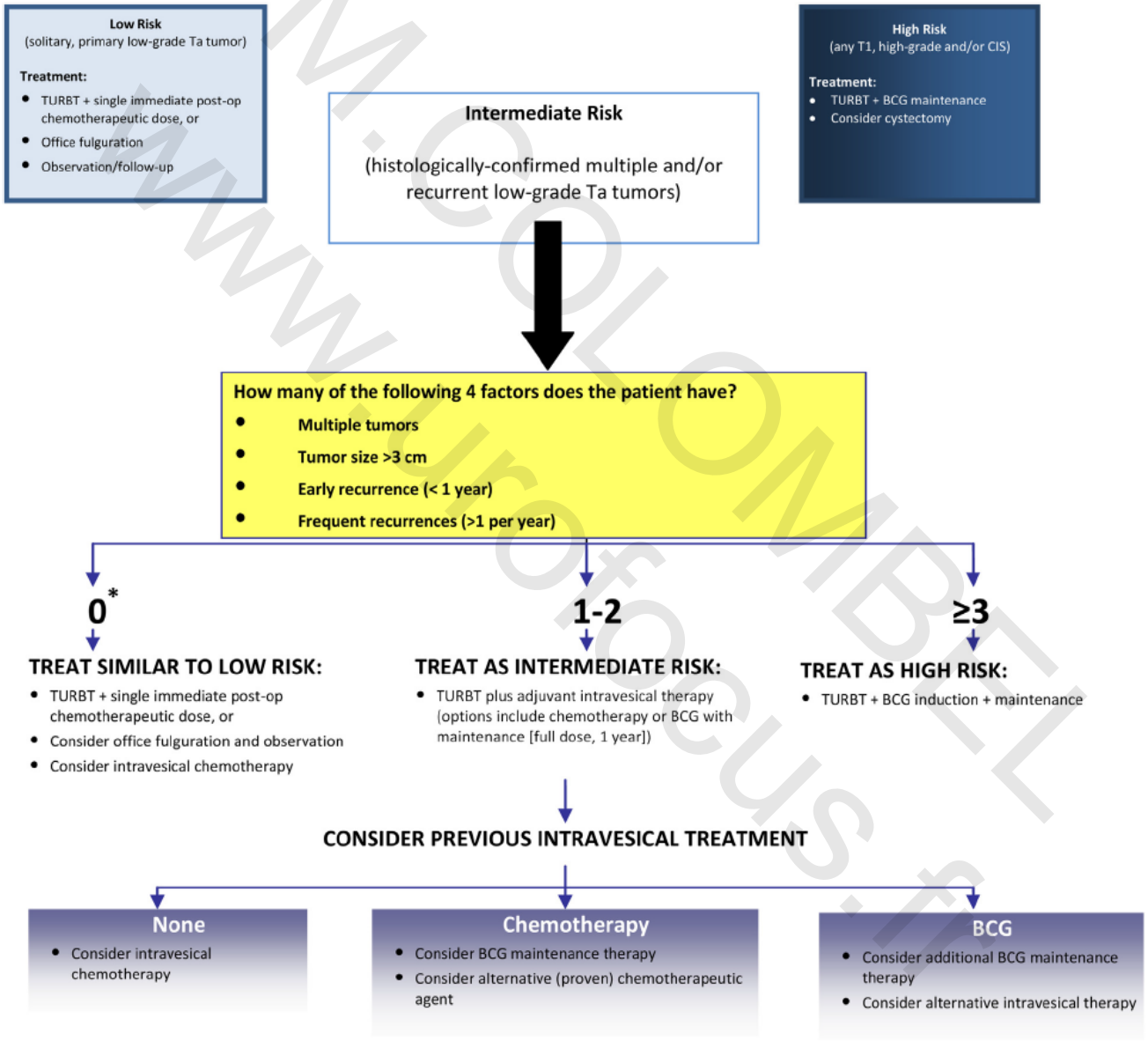
Neil Pugashetti, AUA 2017

IPOP Gemcitabine
SWOG S0337

- Instillation post opératoire 1h
- Etude randomisée; n=406 pts (13 T2; 86 HG)
- Faible toxicité
- ↘ 47% récidive des bas grades
- Non significatif pour les hauts grades

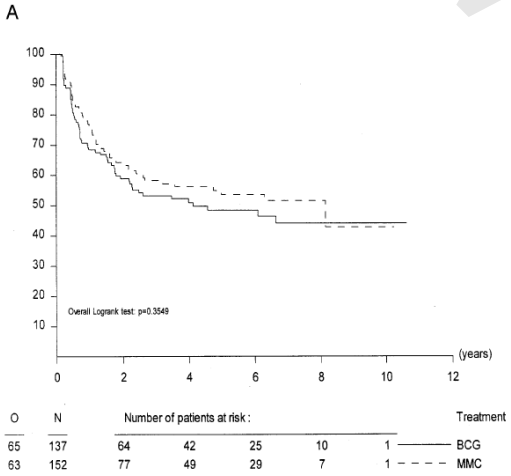
Messing, J. Urol; 2017

Risque intermédiaire

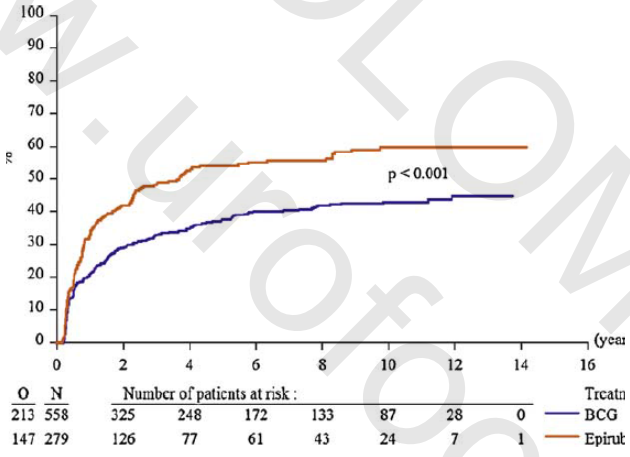


Haut risque HG et T1

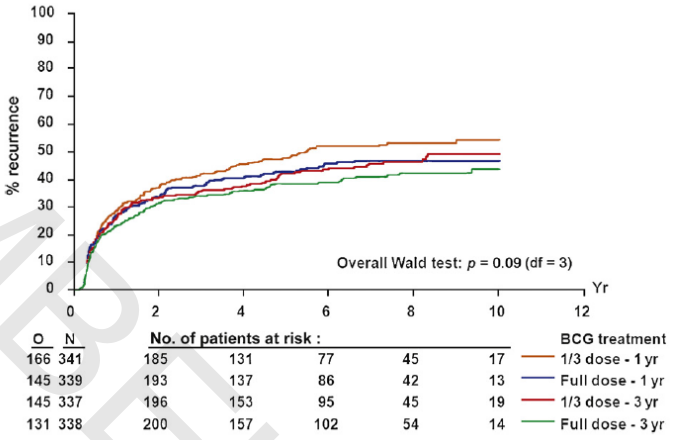
BCG avec traitement d'entretien



Witjes 1998



Sylvester 2010



Oddens 2013

TVNIM très haut risque

Contrindications au BCG

Hématurie persistante

Tuberculose active

Complications grade IV ou intolérance

Non répondeur BCG (Kamat, Colombel et al. 2017)

Au moins une cure induction et 1° cycle entretien (consolidation)

tumeur refractaire (persistance de la tumeur)

récidive de haut grade dans les 6 mois de la dernière instillation

Très haut risque de progression (HRT1G3) (Kamat, Flaig et al. 2015)

CIS diffus

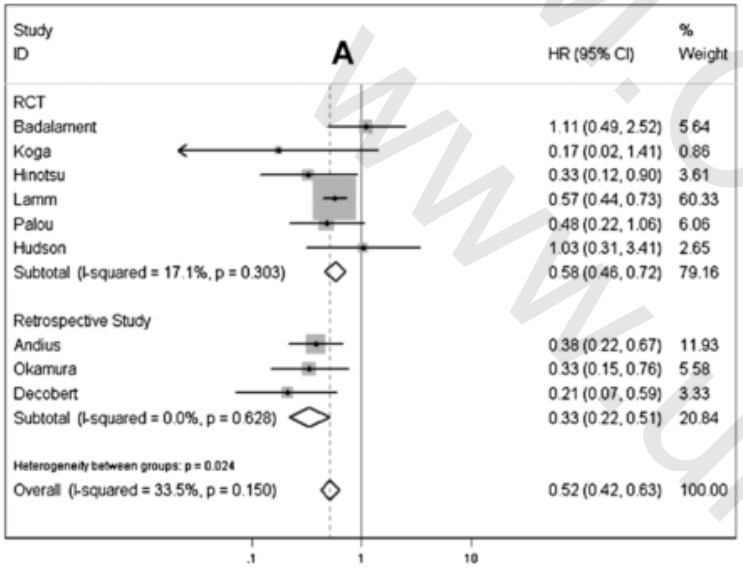
Multifocalité, résection incomplètes (2nd look positif T1G3)

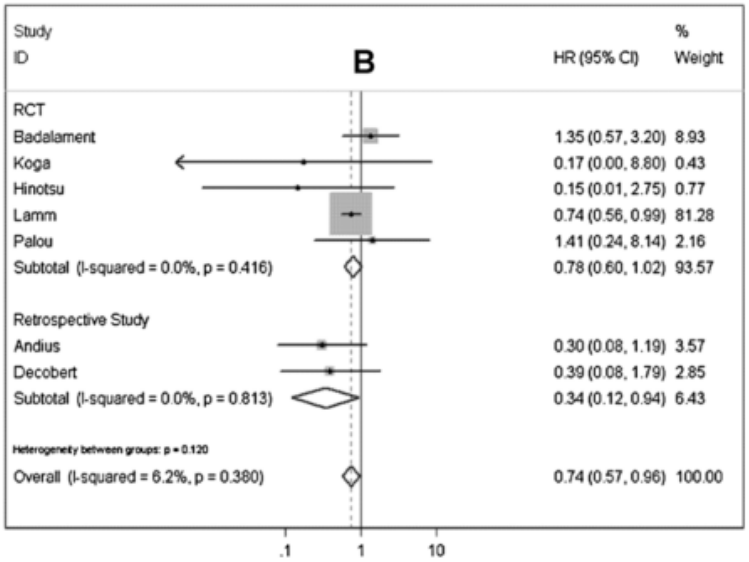
Envahissement micro vasculaire

Carcinome micro papillaire

récidive sous BCG

BCG entretien





BCG Maintenance

HR=0.516;
95% CI 0.425-0.627; P<0.0001

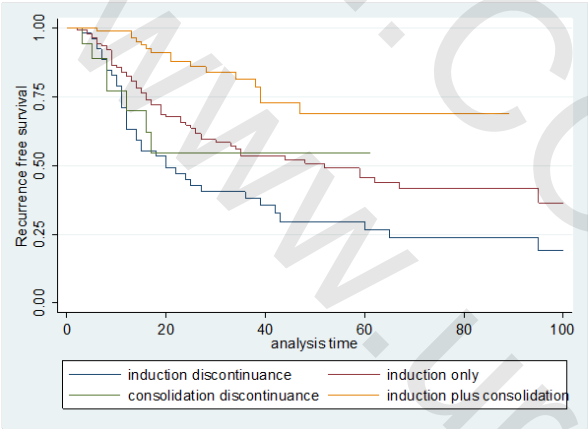
Metanalysis from (Zhu, Tang et al. 2013)

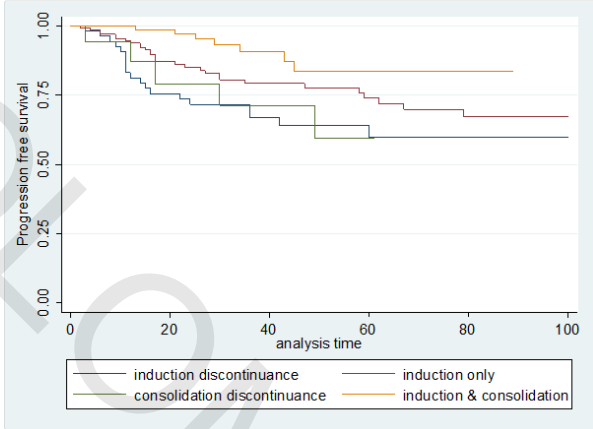
MALGRE TOUT!

- 30% pts sous traités (Snyder, Harlan et al. 2003)(Witjes, Palou et al. 2013)

- ➢ complication
- ➢ efficacité
- ➢ efficience
- ➢ organisation
- ➢ disponibilité!!!!

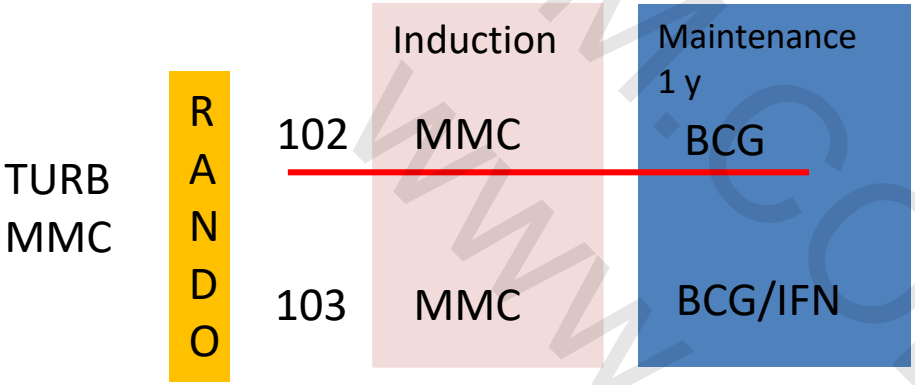
Interruption de production BCG
Impact médico économique

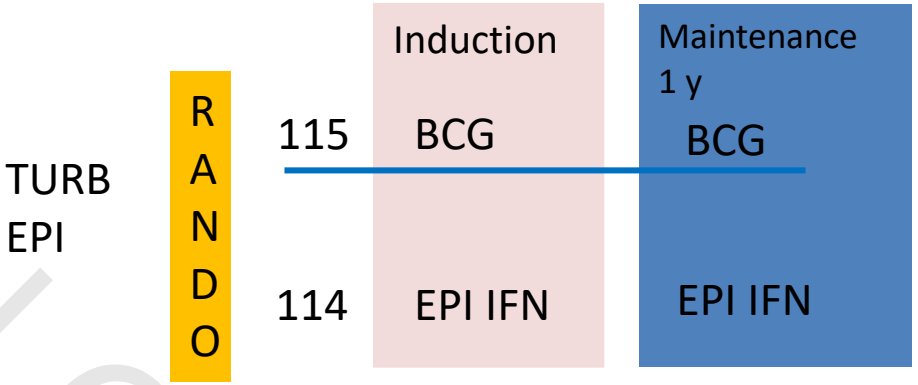


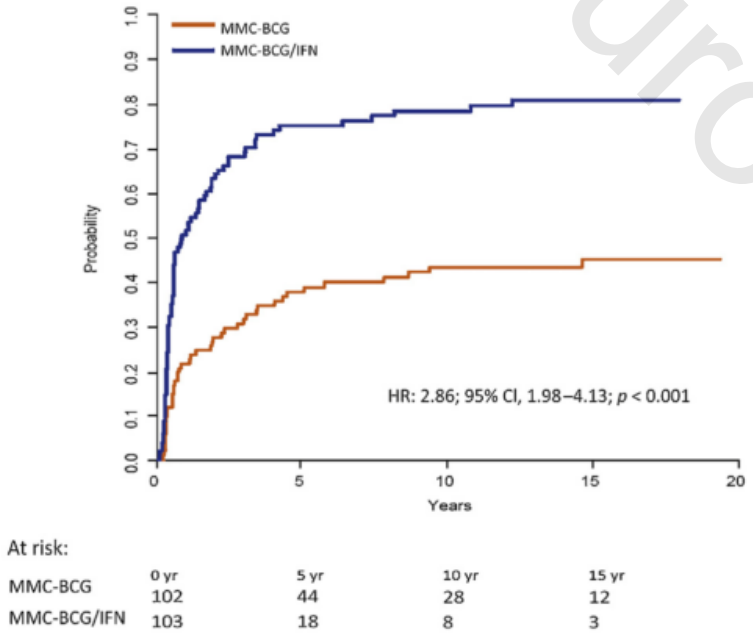


Date REUVs	Nov 2012-Sep 2014			Oct 2014- Dec 2016		
Groupe risque	Intermédiaire	Haut	Total	Intermédiaire	Haut	Total
N pts	131	60	191	140	71	211
Induction	125	51	176		61	61
Consolidation	112	50	162			
Entretien ≥ 1 an	101	46	147			
Recidive	17 (13%)	14 (23%)	31 (16%)	61 (43%)	31(43%)	92(43%)
Re BCG	16	10	26	28	20	48
Cystectomie		3	3	4	11	15
Surcout	38200 €	75640€	113840€	173320€	194820€	368140€
Surcout moyen	291€	1260€	596€	1238€	2743€	1744€

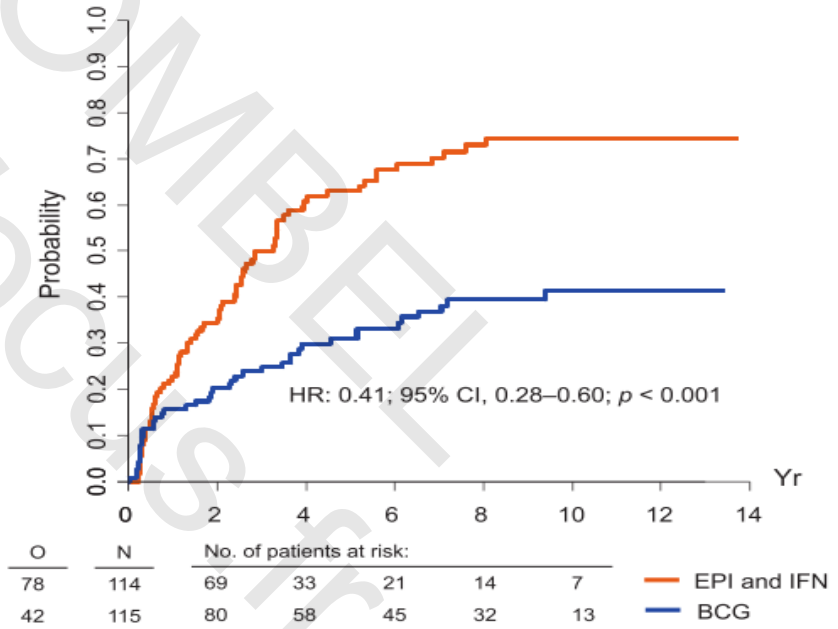
BCG = ENTRETIEN





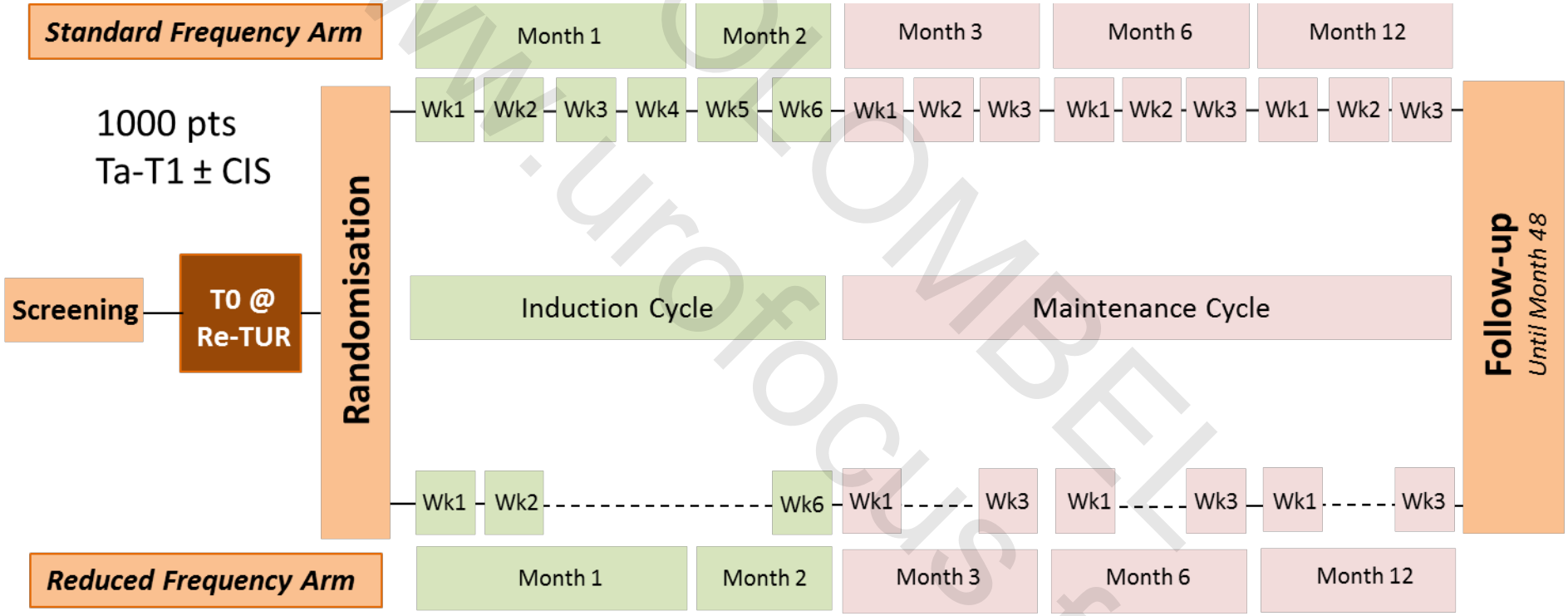


(Jarvinen, Kaasinen et al. 2012)



(Marttila, Jarvinen et al. 2016)

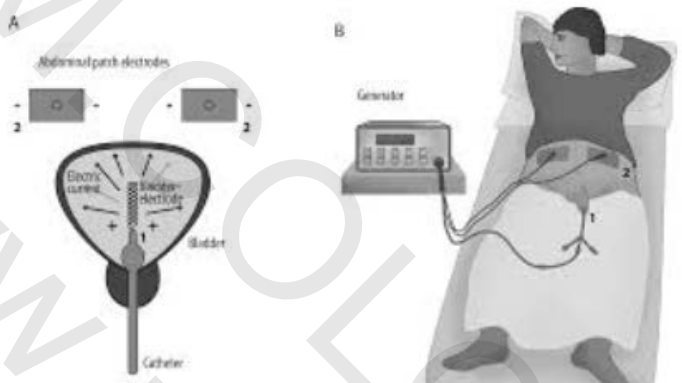
NIMBUS EAU rf



Fibroscopie fluorescence

- 304 pts (TVNIM) en surveillance, 17 centres
- ↗ 21% (vrais positifs) (Jones, AUA 2017)
- Efficient (Dansk, 2016)

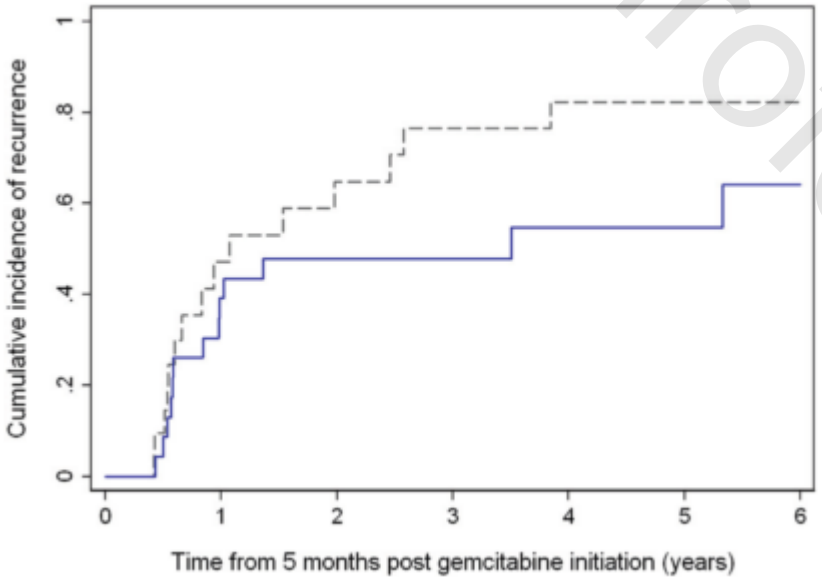
EMDA-MMC



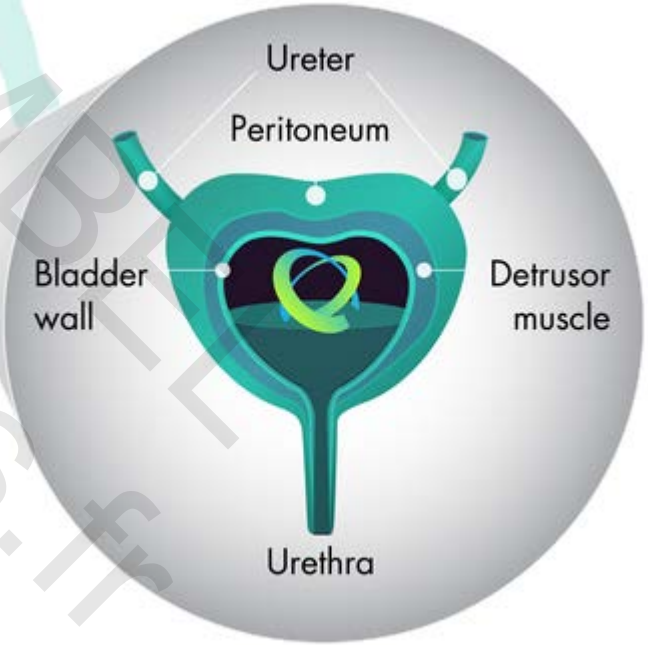
- Meta analyse Cochrane 2017
- 672 pts (3 etudes; même PI)
- EMDA MMC versus BCG: résultats incertains!!
- EMDA MMC versus MMC; RR 0,65
- EMDA MMC versus BCG entretien: HR 0,51

Chimiothérapie intravésicale GEMCITABINE

- Phase II
- 2000/100ml 2/semaine; 3 semaines
- 20 à 50% BCG refractaireaprès



Sternberg, 2013



www.tarisbiomedical.com

HORIZON 2020

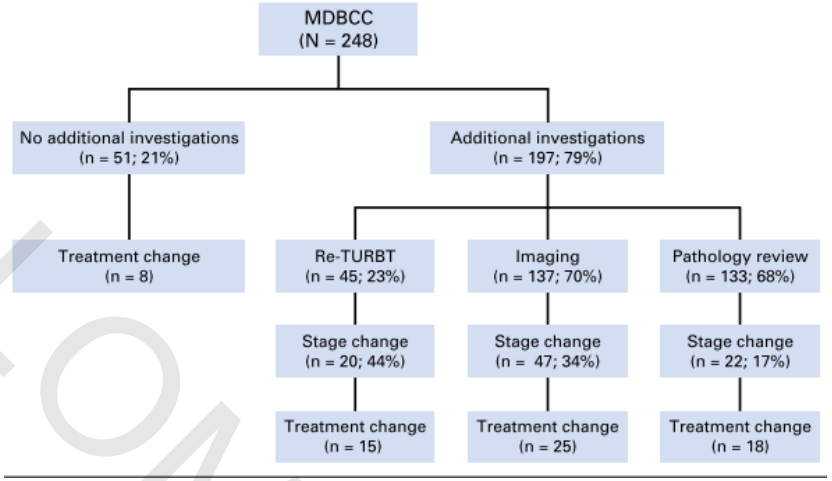
- Therapie génique: Phase II CG0070, oncolytic adenovirus, for BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC)
- Thérapie ciblées: EGFR & EGF2, positif traité par photoimmunotherapy (PIT)

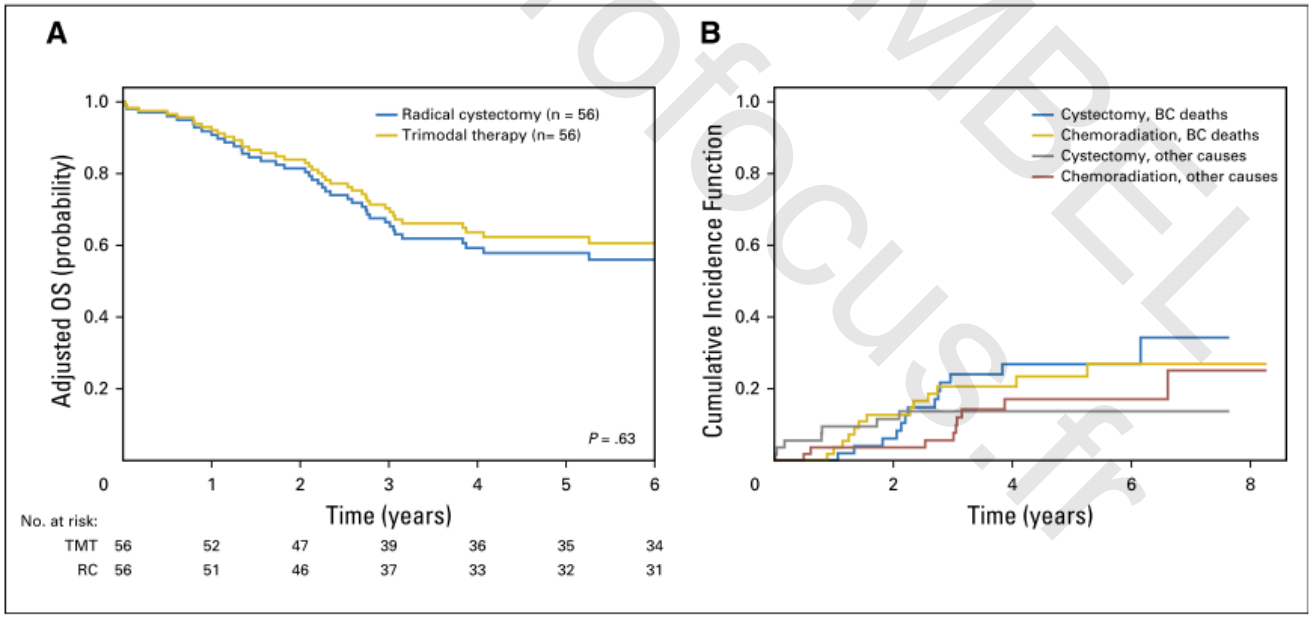
TVIM

RADIO CHIMIOTHERAPIE

TRIMODAL
REU- CT-RT

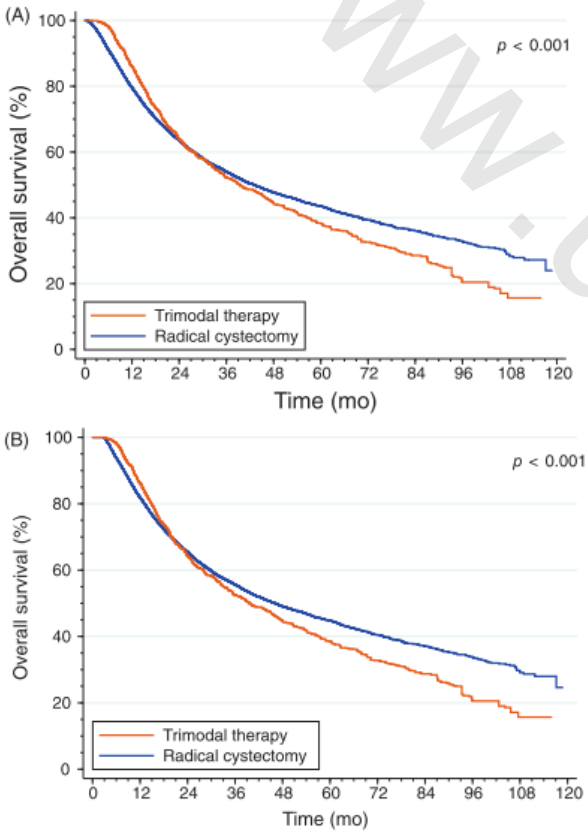
Propensity score analyse
33% reclassés
10% cystectomie





Kulkarni, 2017

TRIMODAL
National Cancer Data Base
n: 1257 vs 11586



Bénéfice: pts plus âgés

Sélection, sélection, sélection

TVIM

CHIMIOTHERAPIES

HIGH DOSE INTENSITY CT

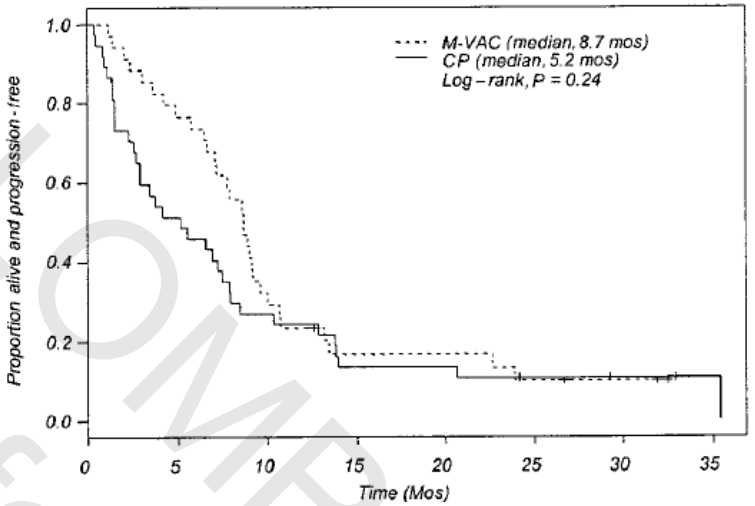
- EORTC 30924
  - HD-M-VAC versus M-VAC, 265 pts
  - CR: 21% vs 9%
  - PR: 41% vs 41%
  - 5 y survival 21,8 % vs 13,5
- HE 16/03
  - HD-M-VAC versus HD-GC
  - CR: 11% vs 10,2%
  - PR::49% vs 55%
  - 3 y survival 27% vs 26%

EORTC Genito-Urinary Cancer Group. Eur J Cancer. 2006 Jan;42(1):50-4
Bamias A, Ann Oncol. 2013 Apr;24(4):1011-7

CARBOPLATIN FOR PATIENTS UNSUITABLE FOR CISPLATIN BASED CT

Parameter	M-VAC arm No.	M-VAC arm %	CP arm No.	CP arm %
No. of eligible patients	41		39	
Male	34	83	27	69
Median age (yrs)	64		65	
Race, White	36	88	39	100
ECOG performance status				
0	18	45	13	34
1	18	45	18	47
2	4	10	7	18
Unknown	1		1	
Bone and or liver metastases	12	29	13	33
Risk factors (based on Bajorin et al.[6])				
0	14	34	11	28
1	23	56	23	59
2	4	10	5	13
Creatinine (median mg/dL)	1.2 (0.5–1.6)		1.0 (0.5–1.5)	

Toxicity type	M-VAC (n = 43) Grade 3 (%)	M-VAC (n = 43) Grade 4 (%)	M-VAC (n = 43) Grade 5 (%)	CP arm (n = 41) Grade 3 (%)	CP arm (n = 41) Grade 4 (%)	CP arm (n = 41) Grade 5 (%)
Anemia	33	5	—	5	—	—
Neutropenia	44	23	—	29	—	—
Febrile neutropenia	7	—	2	5	—	—
Thrombocytopenia	19	2	—	10	—	—
Dyspnea	14	—	—	2	—	—
Mucositis	9	—	—	—	—	—
Emesis	12	—	—	2	—	—
Nausea	16	—	—	7	—	—
Thrombosis/embolism	5	2	—	—	—	—
Fatigue	19	5	—	10	—	—
Neuropathy-sensory	2	—	—	15	—	—



Petrioli R, **Cancer**. 1996 Jan 15;77(2):344-51.
Dreicer R, **Cancer**. 2004 Apr 15;100(8):1639-45.

SECOND LINE CT, CR≈0; PR≈10-15%
MS<12 MONTHS

Study	Agent	Patient No.	PS	Visceral Metastases, %	CR, %	PR, %	ORR, %	MS, mo
Witte 1997[38]	Ifosfamide	56	—	—	9	11	20	Not reported
Witte 1998[34]	Topotecan	44	—	—	0	9	9	6.3
Dodd 2000[35]	Pyrazoloacridine	14	≥80%* (86%)	57	0	0	0	9
Roth 2002[36]	Piritrexim	35	0/1† (100%)	35	0	7	7	7
Moore 2003[75]	Oxaliplatin	18	—	—	0	6	6	Not reported
Paz-Ares 1998[51]	Pemetrexed	31	—	—	0	29	29	9.5
Sweeney 2006[52]	Pemetrexed	47	0/1† (95%)	43	6	21	28	9.6
Galsky 2006[53]	Pemetrexed	13	—	61.5	0	8	8	Not reported
Lorusso 1998[76]	Gemcitabine	35	0/1† (40%)	—	13	10	23	5
McCaffrey 1997[40]	Docetaxel	30	—	32	0	13	13	9
Vaughn 2002[41]	Paclitaxel	31	0/1† (87%)	77	0	10	10	7.2
Culine 2006[31]	Vinflunine	51	≥80%* (98%)	49	0	18	18	6.6
Petrylak 2007[56]	Vinflunine	114‡	≥80%* (86%)	49	0	14.9	14.9	8.3
Wulfing 2005[63]	Lapatinib	59	—	—	0	3	3	4.5
Gomez-Abuin 2007[62]	Bortezomib	20	—	—	0	0	0	Not reported

IMMEDIATE VERSUS DEFERED

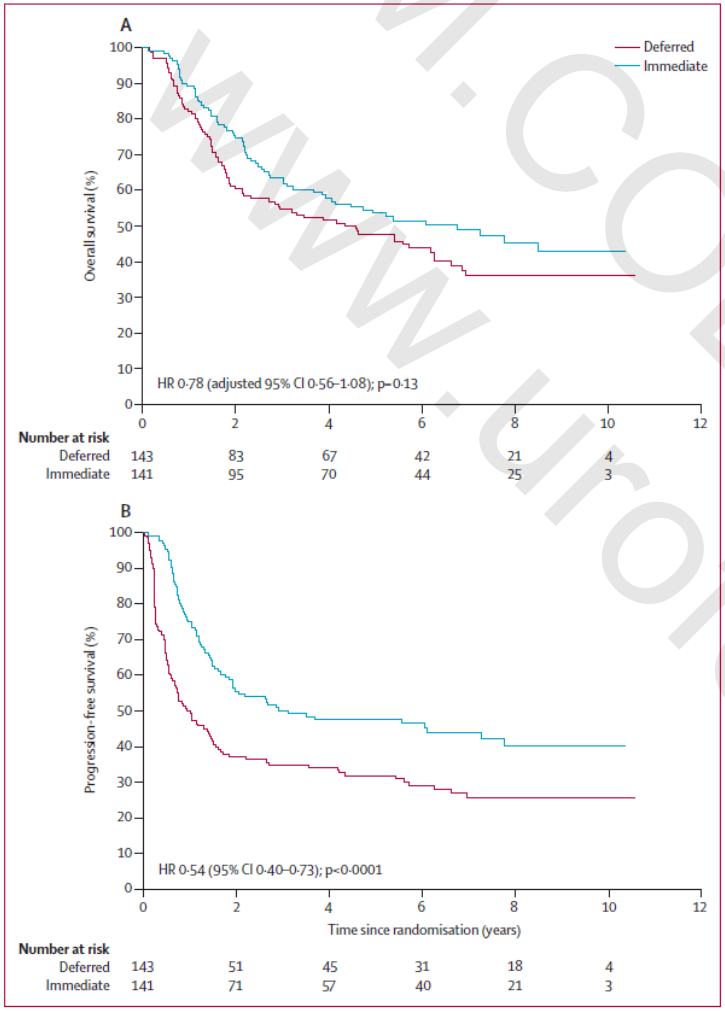
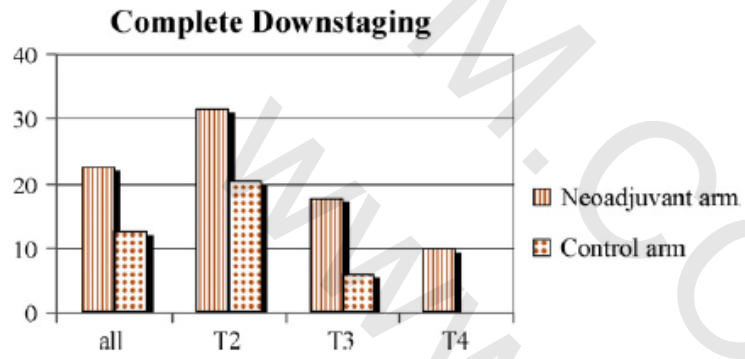
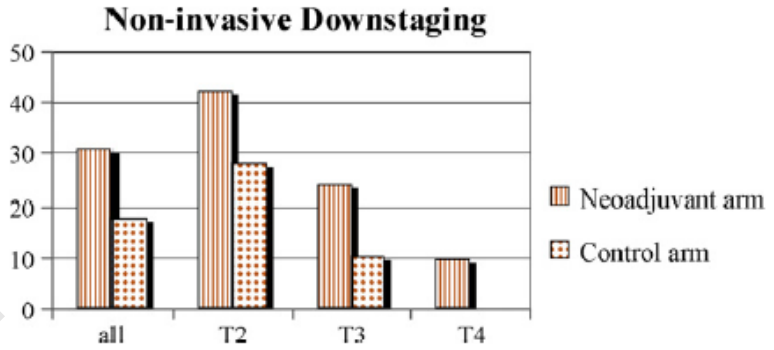


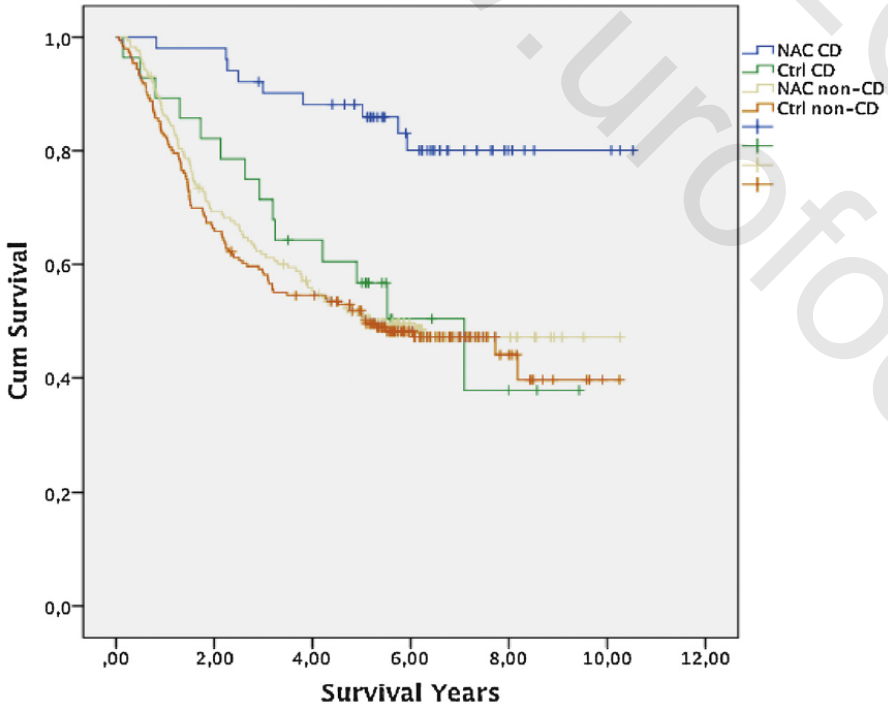
Figure 2: **Kaplan-Meier survival curves**
(A) Overall survival. (B) Progression-free survival. HR=hazard ratio.

Sternberg CN, Lancet Oncol. 2015 Jan;16(1):76-86

DOWNSTAGING=MARKER OF OS







Nordic Urothelial **Cancer** Group.
Eur Urol. 2012 Jun;61(6):1229-38.

OBJECTIF PT0

Difficile !!!

	Nordic I[7]	Nordic II[6]	SWOG[5]	MRC[8]	Totals
No. NC/control intent to treat	151/160	155/154	153/154	491/485*	950/953
No. RC/total No. (%):	264/311 (85)	271/309 (88)	250/307 (81)	494/561 (88)	1,267/1,488 (85)
NC	130/151 (86)	132/155 (85)	126/153 (82)	245/284 (86)	633/743 (85)
Control	134/160 (84)	139/154 (90)	124/154 (81)	249/277 (90)	643/745 (86)
No. NC pts treated (% intent to treat)†	108 (72)	103 (66)	131 (87)‡	392 (80)	734 (77)
No. pT0/total No. (%):					
NC	33/130 (25)	37/140 (26)	48/126 (38)	67/206 (33)	185/602 (31)
Control	17/134 (13)	16/139 (12)	18/124 (15)	26/211 (12)	77/605 (13)
Notes	—	Includes laparotomy in 8 pts but not RC	—	Pathology data missing on 68 pts overall	—

Neo adjuvant CT: CR: 31%
Control:CR: 13%

→ Absolute difference of 18%

Lavery HJ, J Urol. 2014 Apr;191(4):898-906

CHIMIOSENSIBILITE TCC

- Metastatic/Advanced Disease: HD-MVAC/GC

- CR: 11-25%
- OS: 20-30% @ 2 years

- Localized/Advanced : HD-MVAC

- CR: 20%
- **OS: >80% @ > 5years**

Bladder cancer Chemosensitivity to (cysplatin) CT= 20%

ICUD guidelines

CYSTECTOMIE: traitement de référence	B
Taux de toxicité et mortalité “acceptable”	B
Résultats modestes en méta analyse	B
Utiliser M-VAC	B
Bénéfice cT3, Nx	B
Adjuvant CT ≥T3 or N1-2	C

Différenciation glandulaire ou épidermoide n’est pas un facteur de résistance

Eur Urol. 2013 Jan;63(1):45-57

SELECTION DES PATIENTS POUR NACT?

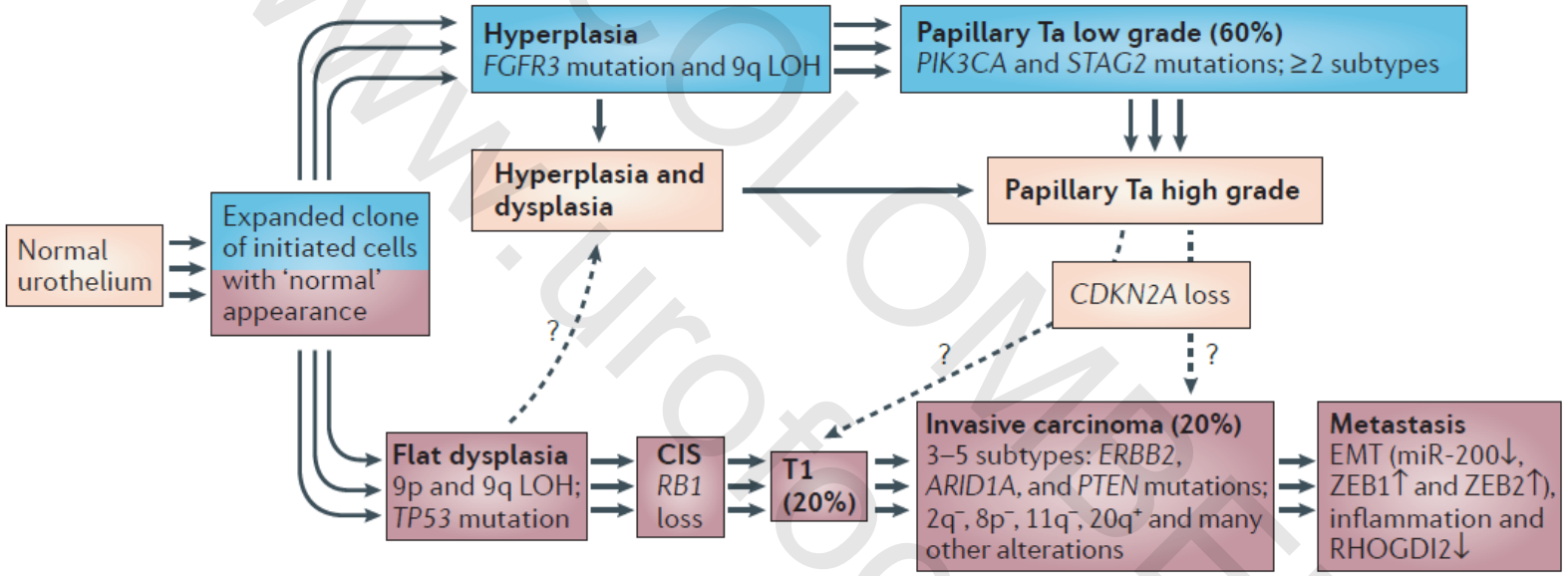
30-40% ineligible (fonction rénale)
Stagging preop inaproprié
Réponse impredictible

Stadification moléculaire

TVIM

IMMUNOTHERAPIES

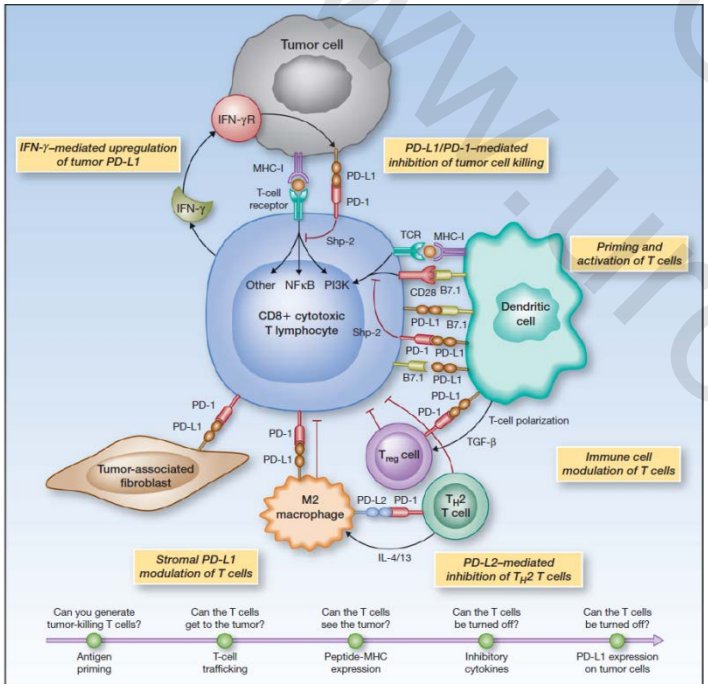
Molecular Pathways of Bladder TCC

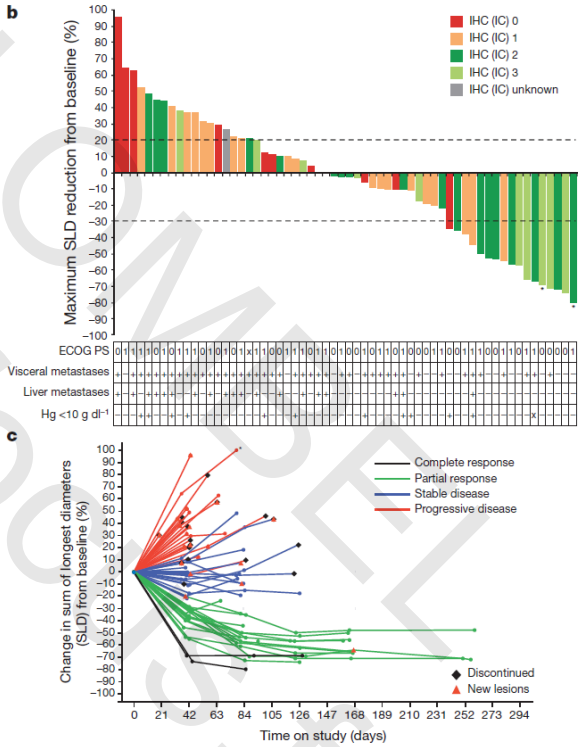


Knowles MA, Hurst CD.
Nat Rev **Cancer**. 2015 Jan;15(1):25-41

Targeting PD-L1/PD-1 pathway

MPDL3280A (anti-PD-L1)
Phase I; 68 pts ; < 5% grade 3-4 tox
2nd line CT

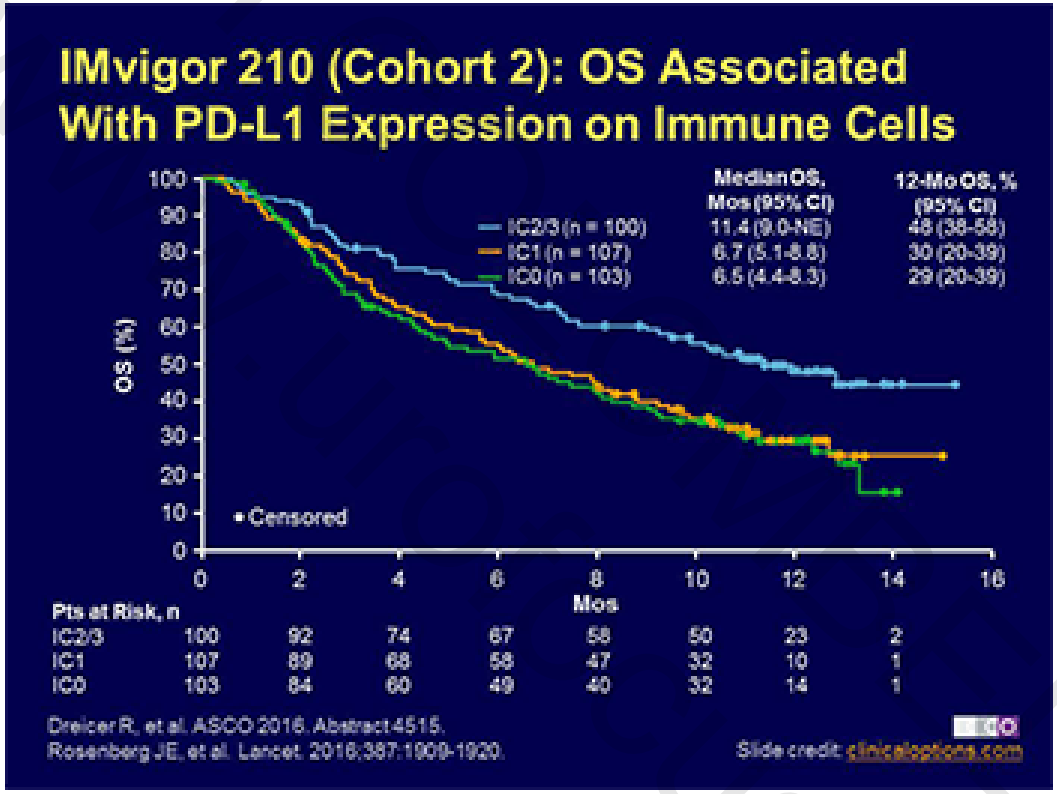




Chen DS; Clin Cancer Res. 2012

Powles T; Nature. 2014

Etude IM VIGOR (ATEZOLIZUMAB)

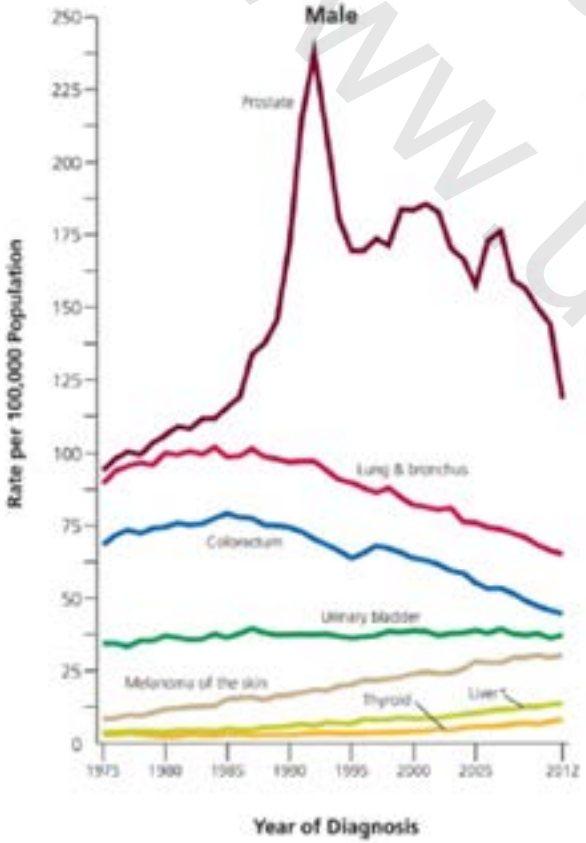


23% RR et RC , durable, FDA accepté en 1st-ligne pour les patients inéligibles au cisplatine

IMMUNOTHERAPIE 2017

Immuno modulateur	Application clinique	Statut
Atezolizumab	M+ ou >T3	FDA approved
Nivolumab	M+ Cysplat resistant	FDA approved
Durvulamab	M+ ou >T3	PhI/II
Atezolizumab	M+ première ligne	PhI/II
Atezolizumab	SWOG 1605 BCG resistant	PhII en cours

CONCLUSIONS



OBJECTIFS

RYTHME
EFFICIENCE
MULTI DISCIPLINARITE
INNOVATION
COMPLIANCE