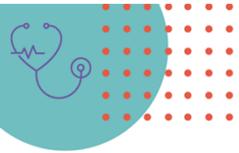


Vessie: quel traitement en adjuvant en 2023 ?

Carole IRIART, radiothérapeute CHU Grenoble-Alpes

Guillaume MORICEAU, oncologue CH Métropole Savoie, Chambéry





Conflit d'intérêt



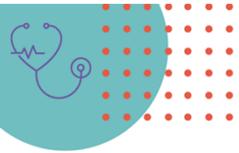
Carole IRIART

- Congrès: Janssen

Guillaume MORICEAU

- Honoraires : GSK, Pfizer, DRSC
OncoAURA
- Congrès: Pfizer



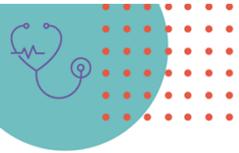


Cancer de la vessie

- Incidence: 13 000 nouveaux cas par an en France ¹
- Mortalité : 5 300 décès par an
- Survie à 5 ans:
 - 55% chez l'homme
 - 49% chez la femme

¹ Santé Publique France – chiffres 2018

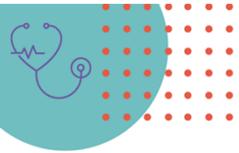




Objectifs des traitements

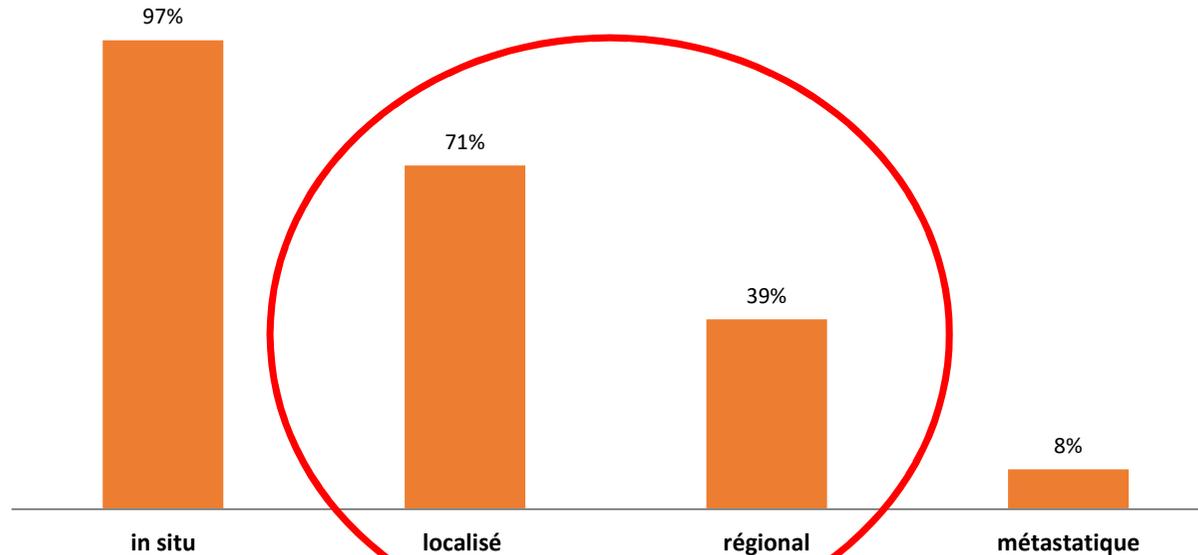
- Augmenter le taux de guérison
- Limiter les effets secondaire au long cours
- Pour un maximum de patients





Problématique-1: la maladie

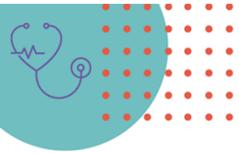
survie globale à 5 ans selon le stade au diagnostic



NCI SEER cancer stat facts: bladder cancer. <https://seer.cancer.gov/statfacts/html/urino.html>

Stein JP, LieskovskyG, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. J Clin Oncol. 2001;19:666–75.





Problématique-2 : le patient

- Patient âgé
- Terrain cardio- vasculaire (même facteur de risque)
- Insuffisance rénale/cardiaque: souvent



Traitement de référence cancer de vessie localisé

Chimiothérapie néo adjuvant avec **Cisplatine** ^{1,2,3}

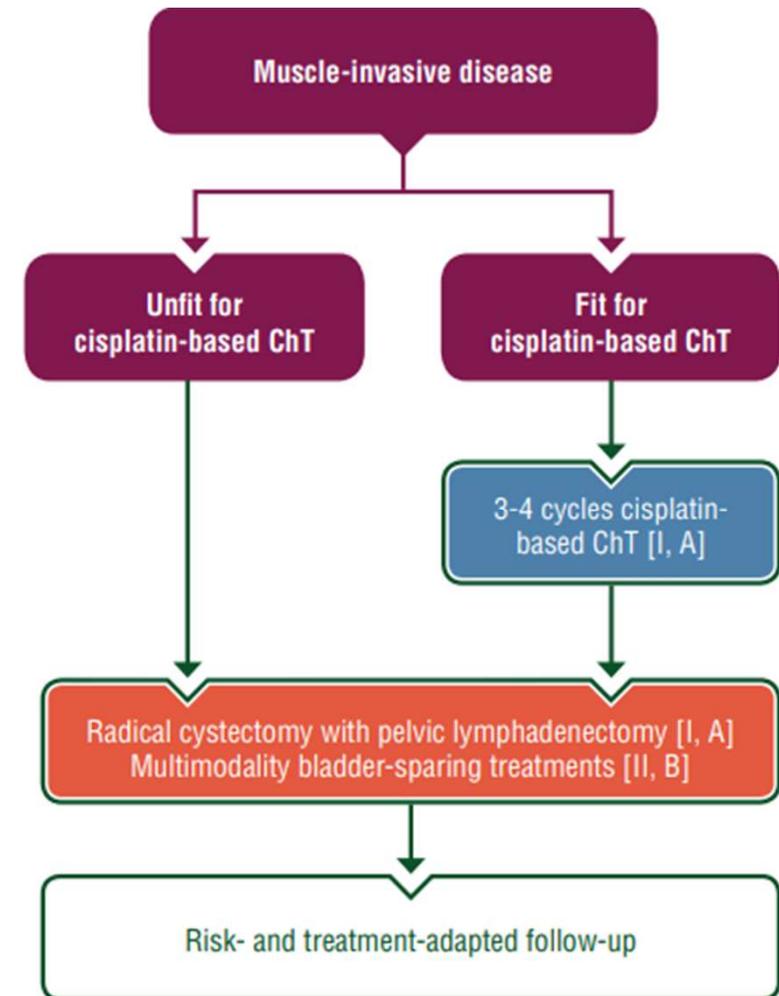
- OMS 0-1
- DFG > 60 ml/min
- Pas d'hypoacousie ni neuropathie
- Pas d'insuffisance cardiaque
- Bénéfice de 5 à 8% en survie globale ³
- **MVAC intensifié > GC ?** ⁴

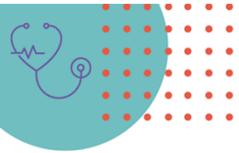
1. ESMO guidelines : Powles T et al. *Ann Oncol*. 2023

2. Recommandation CC AFU 2022-2024, www.urofrance.org

3. Yin M, et al. Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and 2016;21(6):708-15.

4. Pfister C, et al. Randomized Phase III Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Chemotherapy for Patients with Muscle-invasive Bladder Cancer. Analysis of the GETUG/AFU V05 VESPE Pathological Responses. *Eur Urol*. févr 2021;79(2):214-21.

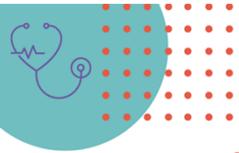




Et en post opératoire ?

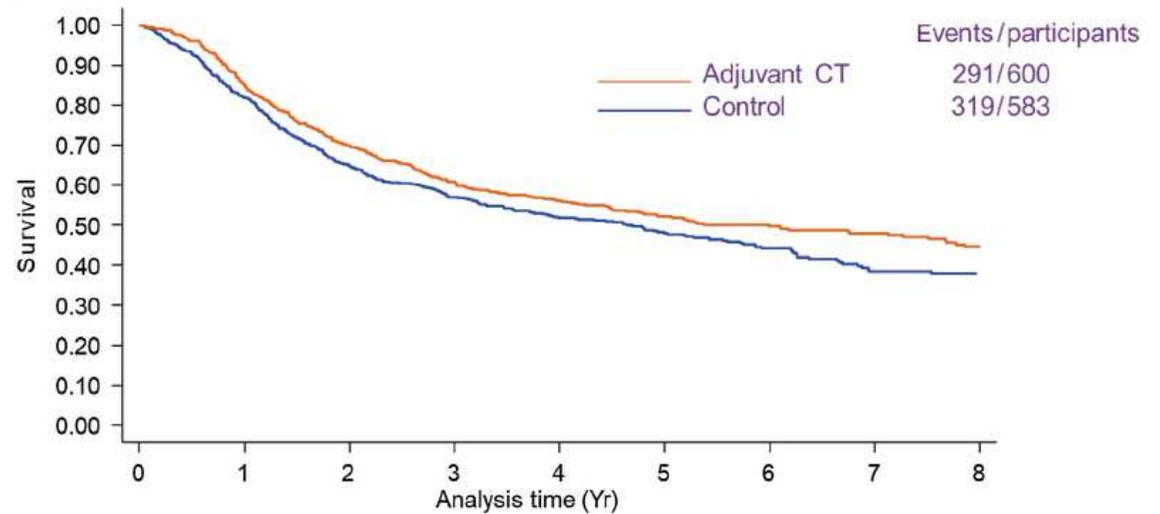
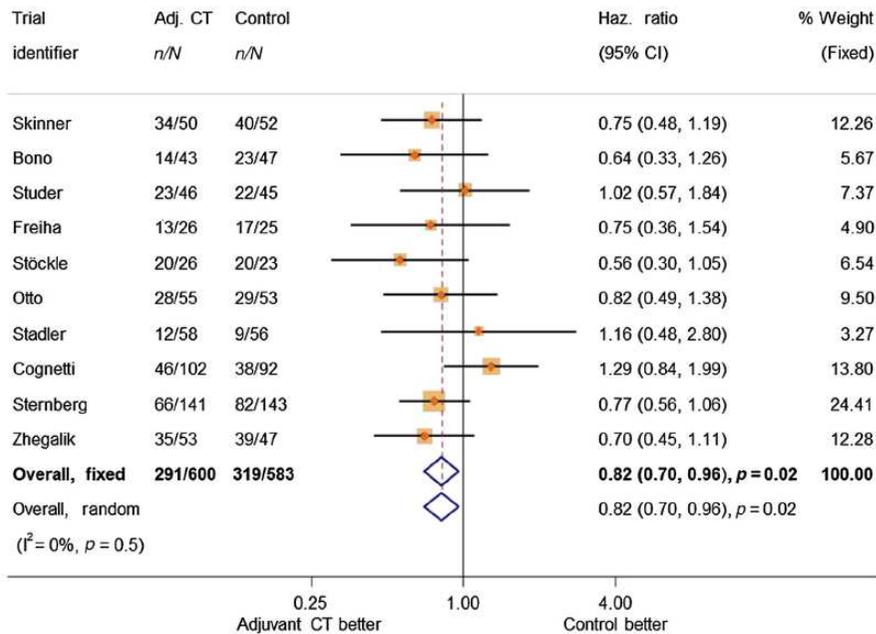
- Chimiothérapie
- Immunothérapie
- Radiothérapie





Chimiothérapie adjuvante: Cisplatine

- Bénéfice absolu en survie globale : 6% à 5 ans



Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis of Individual Participant Data from Randomised Controlled Trials. Eur Urol. janv 2022;81(1):50-61.

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Bénéfice à 5 ans de la chimiothérapie adjuvante



- **survie globale** : +6%
 - + 9% après ajustement sur l'âge, sexe, stade pT et stade pN
- **survie sans récurrence** : +11% à 5 ans
- **Contrôle local** : +11 %
- **Survie sans métastase**: + 8%

Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis of Individual Participant Data from Randomised Controlled Trials. Eur Urol. janv 2022;81(1):50-61.





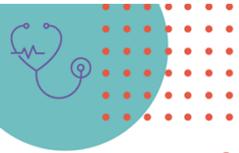
Bénéfice à 5 ans de la chimiothérapie adjuvante



	Chirurgie + CT adjuvante	Chirurgie seule +/- CT à rechute
Survie globale (%)	56	50
Survie globale ajustée (%)	59	50
Survie sans récurrence	61	50
Survie sans métastases	58	50
Contrôle local	71	60

Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis of Individual Participant Data from Randomised Controlled Trials. Eur Urol. janv 2022;81(1):50-61.





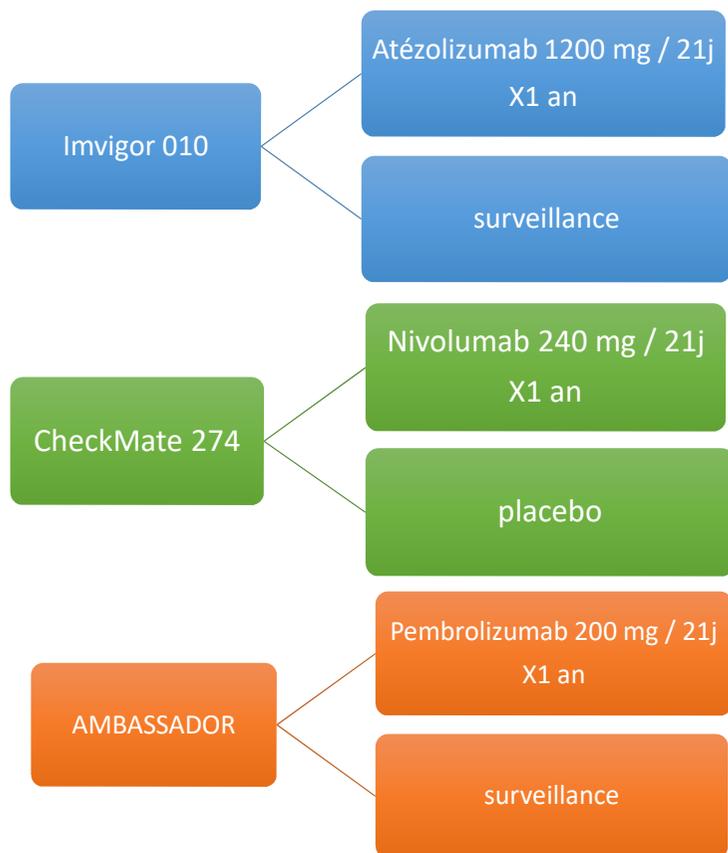
chimiothérapie adjuvante : toxicités

- Toxicités +/- bien rapportées dans les études
- Connues
 - Cytopénie
 - Nausées/vomissement
 - Neuropathie / acouphènes
 - Insuffisance rénale
- Rarement définitives

Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis of Individual Participant Data from Randomised Controlled Trials. Eur Urol. janv 2022;81(1):50-61.



Immunothérapie adjuvante



Critère principal
Survie sans maladie (DFS)

DFS NEGATIVE ¹

Critère principal
Survie sans maladie (DFS)
- Tous
- PDL1 +

DFS POSITIVE ²

Co- Critère principaux
Survie sans maladie (DFS) et survie globale (OS)

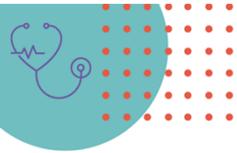
DFS POSITIVE *

1. Bellmunt, Joaquim et al. The Lancet Oncology, Volume 22, Issue 4, 525 – 537

2. Bajorin et al. N Engl J Med 2021;384:2102-14.DOI: 10.1056/NEJMoa2034442

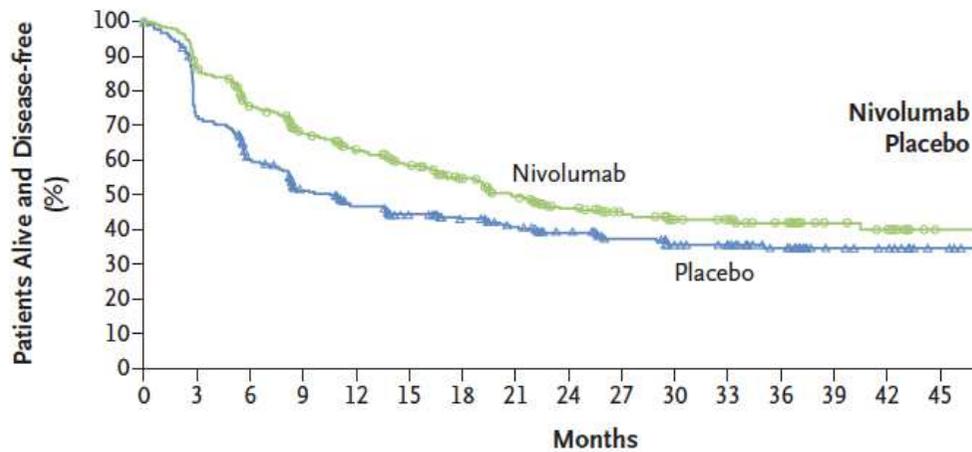
* Non publié





Immunothérapie adjuvante

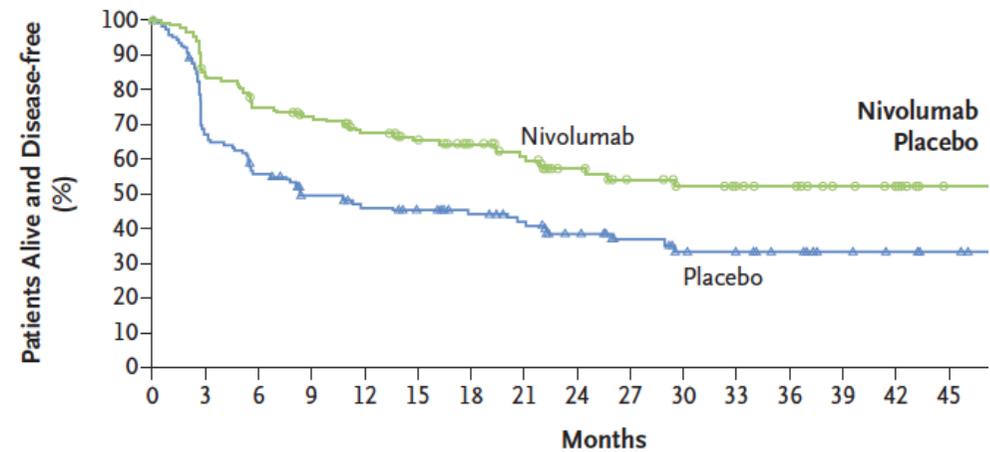
Intention-to-Treat Population



	médiane de survie globale
Nivolumab	21 mois
Placebo	11 mois

HR 0,70 (98,31% CI: 0,54-0,89)
P<0,001

Patients with a PD-L1 Expression Level of $\geq 1\%$



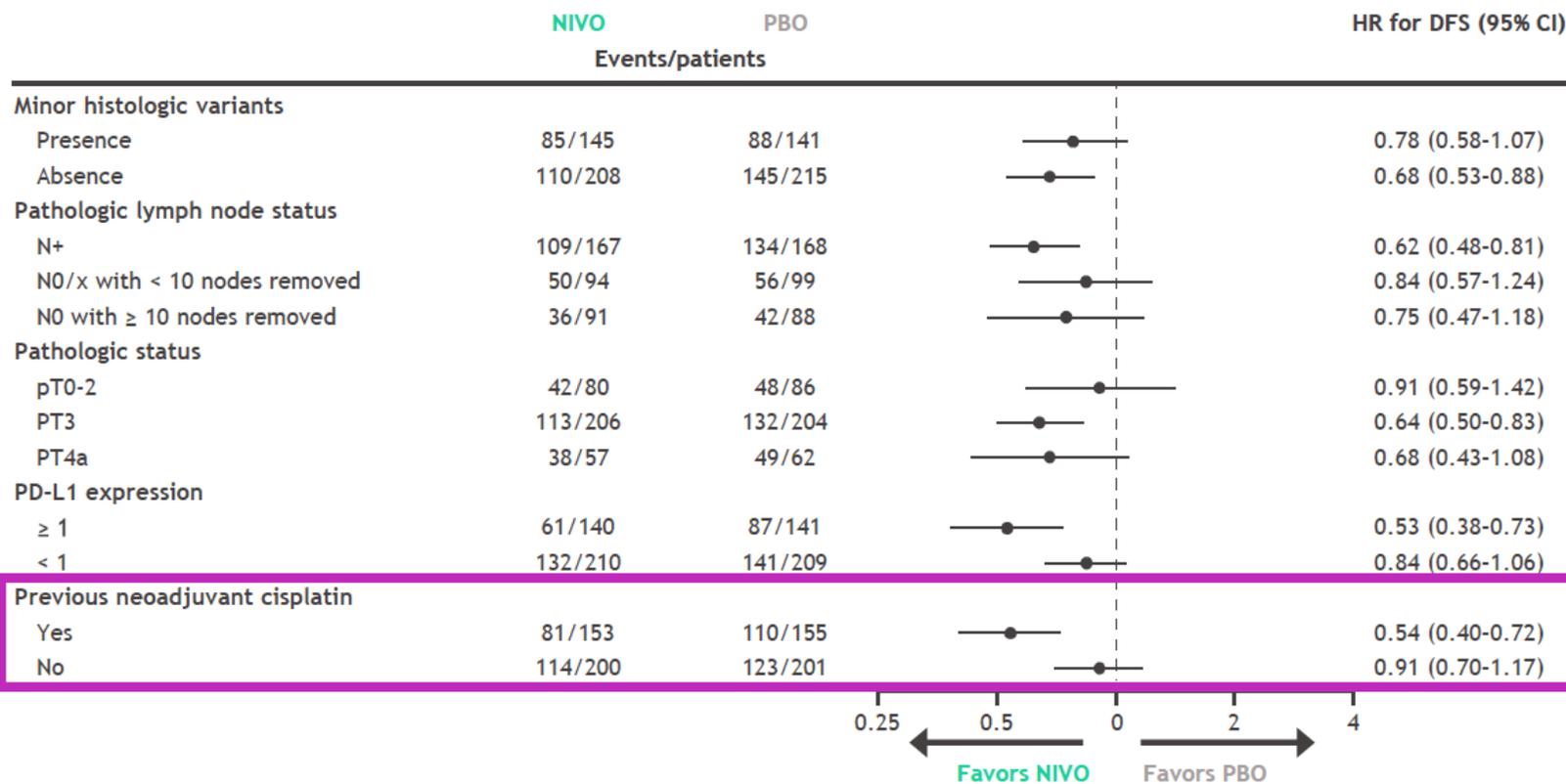
	médiane de survie globale
Nivolumab	Non atteinte
Placebo	11 mois

HR 0,53 (98,87% CI: 0,34-0,84)
P<0,001

Bajorin et al. N Engl J Med 2021;384:2102-14.DOI: 10.1056/NEJMoa2034442

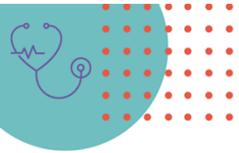


Immunothérapie adjuvante



Bajorin et al. N Engl J Med 2021;384:2102-14.DOI: 10.1056/NEJMoa2034442



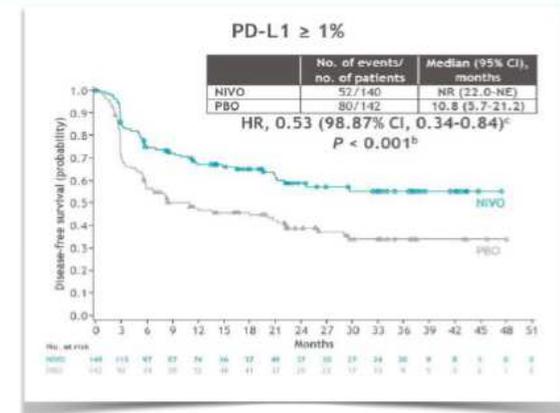
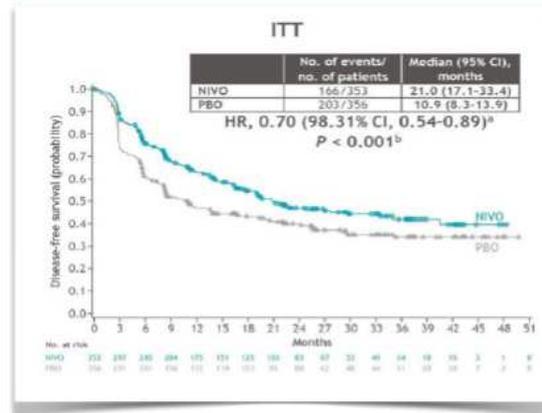


Immunothérapie adjuvante

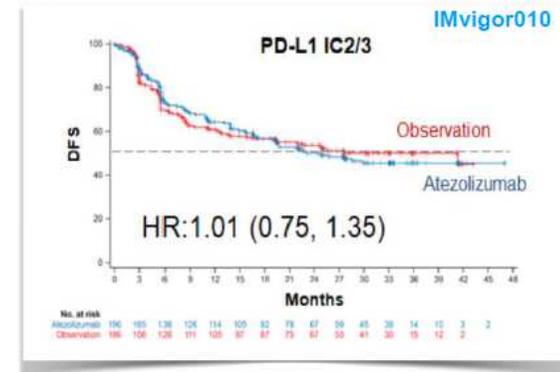
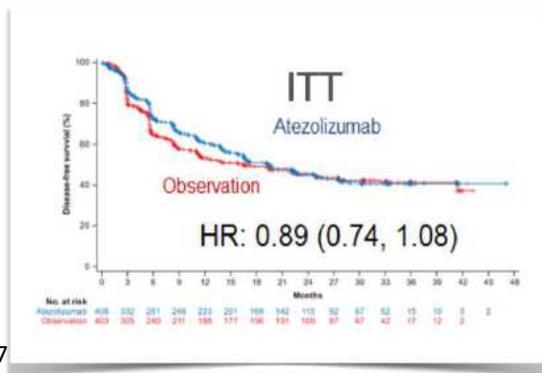
Nivolumab²

Disease-free survival

CheckMate 274



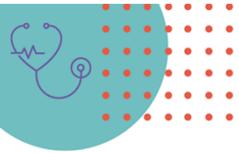
Atezolizumab¹



1. Bellmunt, Joaquim et al. The Lancet Oncology, Volume 22, Issue 4, 525 - 537
 2. Bajorin et al. N Engl J Med 2021;384:2102-14.DOI: 10.1056/NEJMoa2034442

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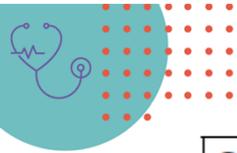


Immunothérapie adjuvante

- 2 études positives (anti PD1)
- 1 étude négative (anti PDL1)
- **Survie globale immature**
- Effets secondaires classiques de l'immunothérapie
- Parfois prolongés voire définitifs

=> Non (encore) recommandé





Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting in patients with high-risk MIBC who have or have not received NAC have demonstrated conflicting results with the CheckMate 274 study demonstrating an improvement in DFS with adjuvant nivolumab and the IMvigor 010 study failing to show an improvement in DFS with adjuvant atezolizumab.	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	2b

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

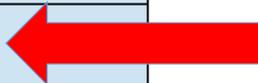


Tableau de recommandation 2

Recommandations : traitements périopératoires			Niveau
Situation néoadjuvante	FIT	Chimiothérapie MVAC ou HD-MVAC	Fort
		ou GC	Moyen
	UNFIT	Pas de chimiothérapie néoadjuvante	Fort
Situation adjuvante (tumeur ypT2-T4 et/ou ypN+)	Exposé à une chimiothérapie néoadjuvante	Immunothérapie Nivolumab (si PD-L1 $\geq 1\%$)	Moyen
	Non exposé à une chimiothérapie néoadjuvante et FIT	Chimiothérapie MVAC ou HD-MVAC ou GC	Moyen
Situation adjuvante (tumeur pT3-T4 et/ou pN+)	FIT	MVAC ou GC	Moyen
	UNFIT	Immunothérapie Nivolumab (si PD-L1 $\geq 1\%$)	Moyen



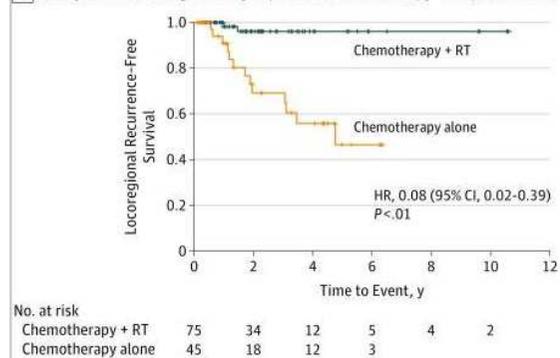
Radiothérapie adjuvante

- 20 à 30% de récurrence locorégionale tout stade confondu après cystectomie.
- Essai de phase II randomisé
- N=120 patients
- pT3 min et/ou N+
- 4 cycles GEMZAR+CDDP
- RTE: 45Gy, bifrac 1,5Gy/fr, 3 semaines conform
- SSRL à 2 ans passe de 69% à 96% à 2 ans

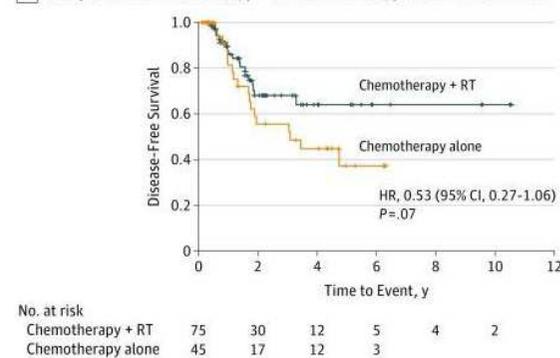
Mais:

- Essai égyptien, 64% de c. urothélial, 46% c. épidermoïde.
- Pas de chimio néoadjuvante, pas d'IMRT.
- Zaghoul MS, et. Al; Adjuvant Sandwich Chemotherapy Plus Radiotherapy vs Adjuvant Chemotherapy Alone for Locally Advanced Bladder Cancer After Radical Cystectomy: A Randomized Phase 2 Trial. JAMA Surg. 2018 Jan 17;153(1):e174591. doi: 10.1001/jamasurg.2017.4591. Epub 2018 Jan 17. PMID: 29188298; PMCID: PMC5833621.

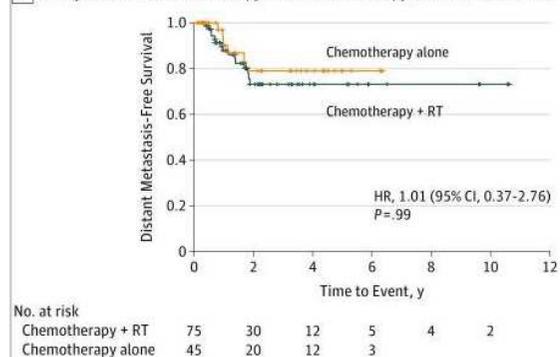
A Two-year LRFS was significantly improved for chemotherapy + RT (96% vs 69%)



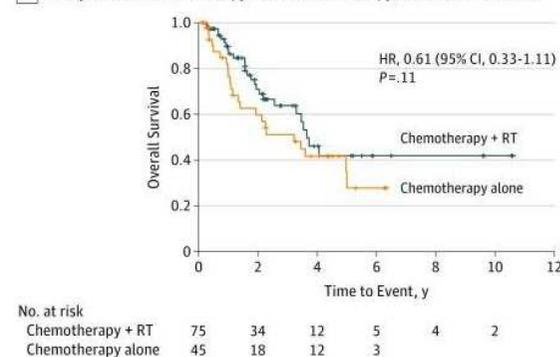
B Two-year DFS for chemotherapy + RT vs chemotherapy alone was 68% vs 56%



C Two-year DMFS for chemotherapy + RT vs chemotherapy alone was 73% vs 79%



D Two-year OS for chemotherapy + RT vs chemotherapy alone was 71% vs 60%



Radiothérapie adjuvante: guidelines EAU 2023 muscle-invasive and metastatic bladder cancer

7.2.3 Summary of evidence and guidelines for pre- and post-operative radiotherapy

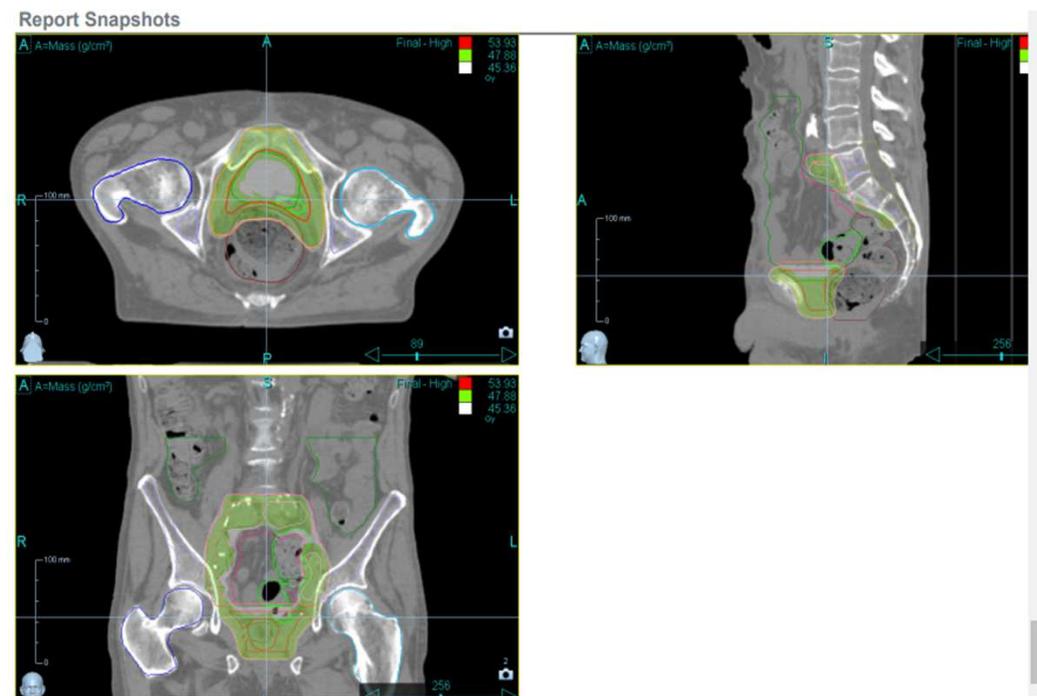
Summary of evidence	LE
No contemporary data exists to support that pre-operative RT for operable MIBC increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45–50 Gy in fractions of 1.8–2 Gy, results in down-staging after 4 to 6 weeks.	2
Limited evidence supports the safe use of pre- and post-operative RT in case a neobladder is planned or <i>in situ</i> .	3
Limited high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after RC.	3
Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival following cystectomy for locally-advanced bladder cancer (pT3b–4, or node-positive).	2a

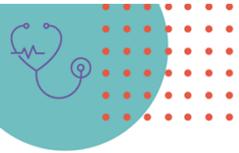
Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong
Consider offering adjuvant RT in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak



Radiothérapie adjuvante, GETUG AFU 30 en cours BLADDER -ART

- Essai randomisé de phase II, chimio adj possible avant
- Unicancer, P. Sargos
- 50,4 Gy, 28fr 1,8Gy
- Rando 3:1
- Critère de jugement I: PRFS à 3 ans
- stades pN0-2, M0 par imagerie, pT3a, pT3b, pT4a, pT4b; pTX-pN1-2 et pTx-pNx-R1 (classification TNM) sont éligibles. Carcinome urothélial >50%, néovessies exclues

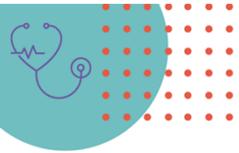




En conclusion

TRAITEMENT	Survie globale	Survie sans récurrence	Contrôle local	Survie sans métastases
Chimiothérapie	Oui	Oui	Oui	Oui
Immunothérapie	immature	Oui (2 études) Non (1 étude)	?	oui
Radiothérapie	?	?	Oui	?



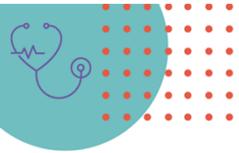


En conclusion

TRAITEMENT	Survie globale	Survie sans récurrence	Contrôle local	Survie sans métastases
Chimiothérapie	Oui	Oui	Oui	Oui
Immunothérapie	immature	Oui (2 études) Non (1 étude)	?	oui
Radiothérapie	?	?	Oui	?

Le CISPLATINE résiste encore en 2023 ...
.... Mais pour combien de temps ?

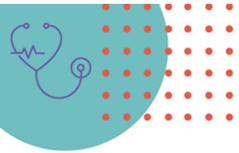




Et demain , la fin du CISPLATINE ?

- Immunothérapie : données de SG ?
- Anticorps conjugués: enfortumab vedotin
- **Association ADC / IO** va remonter les lignes
- Thérapies ciblées pour altération FGFR 2/3 : erdafitinib





Merci de votre attention

