16e Rencontre Patients de l'Association A.R.Tu.R.

Mercredi 10 mai 2023
À l'Institut des Maladies Génétiques IMAGINE

16e Rencontre Patients de l'Association A.R.Tu.R.

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Association pour la Recherche
sur les Tumeurs du Rein

Néphrectomie Cytoreductive dans le RCC métastatique

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Necker Enfants Malades Hôpital Universitaire

Université Paris Cité

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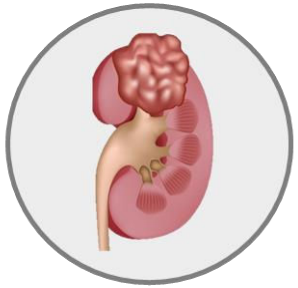
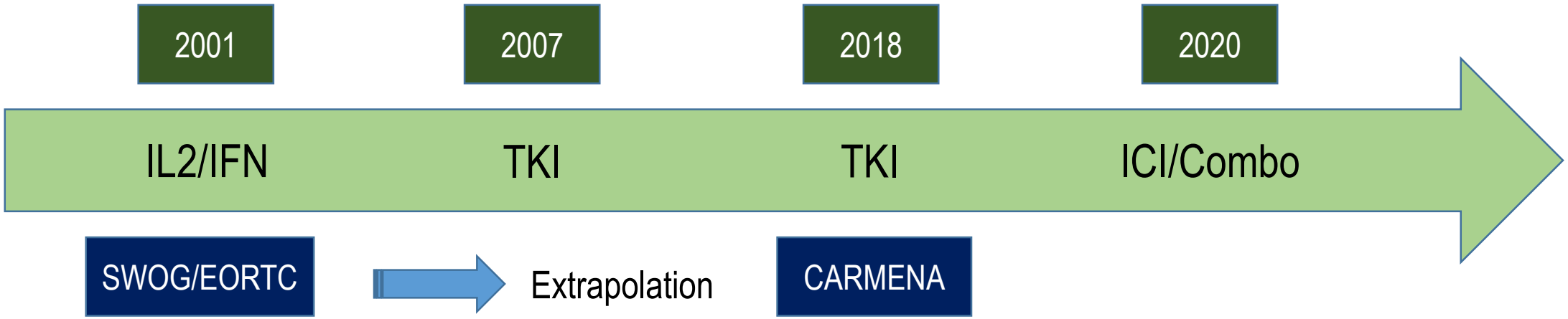
Liens d'intérêt

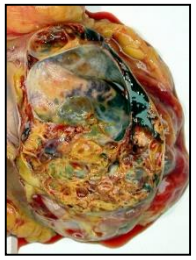
Pfizer, BMS, Roche, Ipsen, Pierre Fabre, Astellas, Janssen, Ferring, Astra Zeneca, MSD

AFU, CCAFU, ARTuR, HEGP, APHP, Université Paris Cité



Historique de la néphrectomie en situation métastatique





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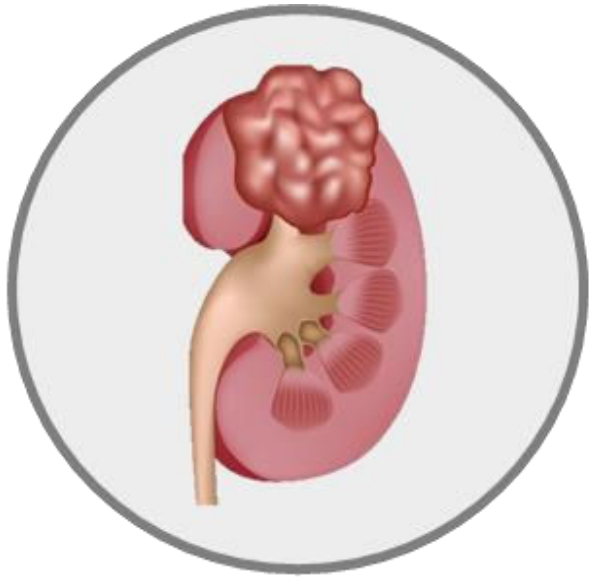
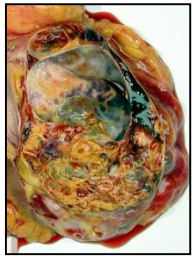
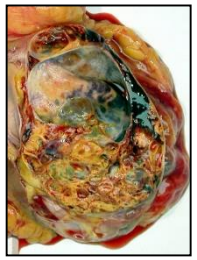
Place de la néphrectomie dans le cancer du rein métastatique



RCC localisé



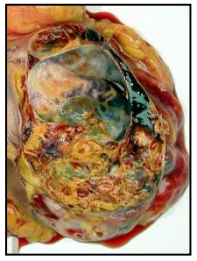
RCC d'emblée M+



+

CN immédiate (upfront CN)

+



CN différée (deferred CN)

RCC:Renal Cell Carcinoma, m:Metastatic, CN:Cytoreductive Nephrectomy

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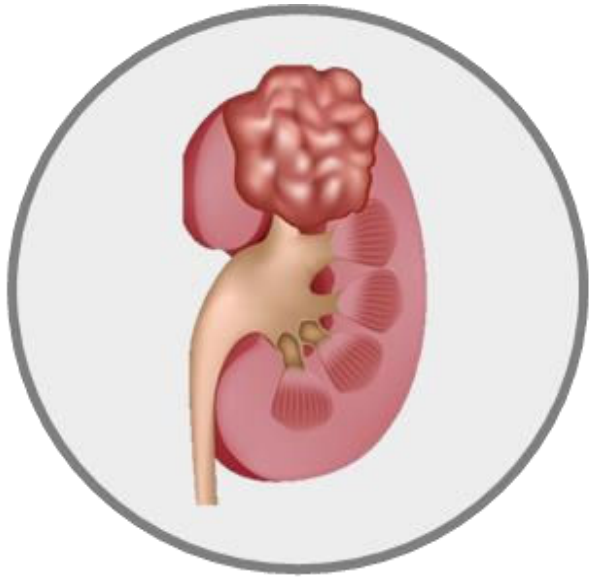
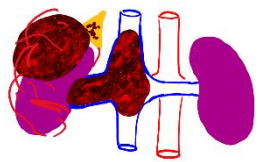
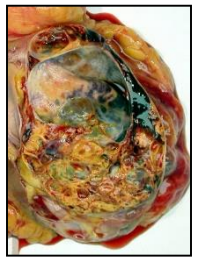
A distinguer de la place de la néphrectomie dans le cancer du rein non-métastatique mais localement avancé



RCC locallement avancé





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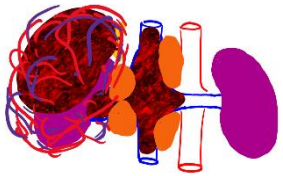
Traitement adjuvant



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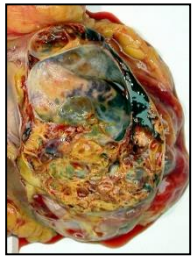

Traitement néo-adjuvant

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A ce jour il n'y a aucune étude randomisée qui évalue l'intérêt de la CN en situation métastatique traitée par immunothérapie (ICI)

CN:Cytoreductive Nephrectomy, ICI : Immune Checkpoint Inhibitor

	Year	Pts	Study	IMDC I/P (%)	TT/ICI	uCN/dCN	CN	No CN (%)	OS benefit / CN	Population
Bhindi	2020	1541	R (Cohort)	60/40	1541/0	805/85	890	651 (42)	Yes	dCN
Singla	2020	391	R (Cohort)	NA	0/391	197/24	221	170 (44)	Yes	dCN
Pieretti	2021	198	R	88/12	164/34	0/198	198	0 (0)	NA	↘IMDC, ↘>10%vol
Ghatalia	2022	1910	R (Cohort)	28/72	1155/433	605/142	747	972 (51)	Yes	uCN = dCN
Chakiryan	2022	12766	R (Cohort)	NA	12766/0	4393/612	5005	7761 (61)	No	
Teishima	2022	211	R	57/43	176/35	117/0	117	94 (45)	Yes	0-1risk F, 1met
Kato	2022	259	R (Cohort)	49/51	259/0	107/27	154	125 (48)	Yes	uCN vs noCN+dCN
Shirotake	2022	61	R	53/47	0/79	23/10	33	38 (63)	Yes	dCN
Bakouny	2023	4639	R (Cohort)	56/44	4202/437	2560/0	2560	2079 (45)	Yes	↘IMDC, ↘PS
Hahn	2023	157 (S/R)	R	54/46	43/157	89/29	118	39 (25)	No	
Bex (Surtime)	2018	99	RCT 3 neg	NA	88/0	46/34	80	19	2nd EP	dCN
Mejean (Carmena)	2018 2021	450	RCP 3	59/41	382/0	205/40	245	205	Non Inf study	1riskF + 1met and dCN

Pts:Patients, R:Retrospective study, IMDC I/P: Intermediate/Poor, TT:Targeted Therapy, ICI;Immune Checkpoint Inhibitor, u/dCN: upfront/deferred Cytoreductive Nephrectomy, PS:Performance Status, S:Sarcomatoid, R:Rhabdoid

Bhindi et al, Eur Urol 78, 2020; Singla et al, Urol Oncol 38, 2020; Pieretti et al, Urol Oncol 39, 2021, Ghatalia et al, J Urol 208, 2022; Chakiryan et al, JAMA Network Open 5, 2022; Teishima et al, Int Urol Nephrol 54, 2022; Kato et al, Int J Clin Oncol, 27, 2022; Shirotake et al, Anticancer Res, 42, 2022; Bakouny et al, Eur Urol, 83, 2023, Hahn et al, Eur Urol Focus, 28, 2023; Bex et al, JAMA Oncol, 13, 2018, Mejean et al, NEJM, 379, 2018, Mejean et al, 80, 2021

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Synthèse des études

10 études retrospectives dont 6 cohortes

- 7 avec ICI, TT oo combo
- IMDC : Intermédiaire > Mauvais (56% vs 44%)
- CN vs pas de CN (46% vs 54%)
- uCN >> dCN (89% vs 11%)

- Bénéfice survie globale : CN > pas de CN
- Mais le bénéfice intéressait surtout : dCN, faible IMDC, bon PS

2 études phase III dont une négative

- 2 avec sunitinib
- Carmena 59% vs 41% (I vs P IMDC)
- Surtime 89% vs 11% (I vs P MSKCC)
- CN vs pas de CN (41% vs 59%)
- uCN >> dCN (77% vs 23%)

Historical IMDC study *(Heng et al, Eur Urol, 66, 2014)*

- IMDC : Intermediaire > Mauvais (59% vs 41%)
- CN > pas de CN (59% vs 41%)

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The effect of immune checkpoint inhibitor combination therapies in metastatic renal cell carcinoma patients with and without previous cytoreductive nephrectomy: A systematic review and *meta*-analysis

Keiichiro Mori [a,b,*], Fahad Quhal [a,c], Takafumi Yanagisawa [a,b], Satoshi Katayama [a,d], Benjamin Pradere [a], Ekaterina Laukhtina [a,e], Pawel Rajwa [a,f], Hadi Mostafaei [a,g], Reza Sari Motlagh [a,h], Takahiro Kimura [b], Shin Egawa [b], Karim Bensalah [i], Pierre I. Karakiewicz [j], Manuela Schmidinger [a], Shahrokh F. Shariat [a,f,k,l,m,n,o]

International Immunopharmacology 108 (2022) 108720

Meta-analysis

Study demographics.

Study	IMmotion151	JAVELIN Renal 101	CheckMate 214	KEYNOTE 426	CheckMate 9ER	CLEAR
Year	2019	2019	2018	2019	2021	2021
Compound	Atezolizumab plus bevacizumab	Avelumab plus axitinib	Nivolumab plus ipilimumab	Pembrolizumab plus axitinib	Nivolumab plus cabozantinib	Pembrolizumab plus lenvatinib
Control	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Number (treatment/control)	178/184	442/444	425/422	432/429	323/355	355/357
Age (treatment/control)	62/59	62/61	62/61	62/61	62/61	64/61
Male (treatment/control)	67%/79%	72%/78%	74%/71%	71%/75%	77%/71%	72%/77%
Poor risk (treatment/control)	11%/11%19vs20	12%/10% 72vs71	21%/21% 91vs89	13%/12% 56vs52	19%/21% 61vs68	9%/10% 32vs32
Nephrectomy (treatment/control)	84%/83%	80%/80%	80%/76%	83%/83%	69%/71%	74%/77%
PD-L1 positivity	100%/100%	61%/65%	26%/29%	59%/62%	26%/25%	30%/33%
Median OS (treatment/control)	34.0/32.7	NRE/NRE	NRE/26.0	NRE/35.7	NRE/NRE	NRE/NRE
Median PFS (treatment/control)	11.2/7.7	13.3/8.4	11.6/8.4	15.4/11.1	16.6/8.3	23.9/9.2
Median ORR (treatment/control)	43%/35%	51%/26%	42%/27%	60%/40%	56%/27%	71%/36%
Subsequent treatment	44%/55%	21%/39%	39%/54%	54%/69%	19%/33%	33%/58%
Median follow up	15 months	10.8/8.6 months	25.2 months	30.6 months	18.1 months	26.6 months

Abbreviation: NR (not reported), NRE (not reached), ORR (objective response rate), OS (overall survival), PD-L1 (programmed death ligand 1), PFS (progression free survival)

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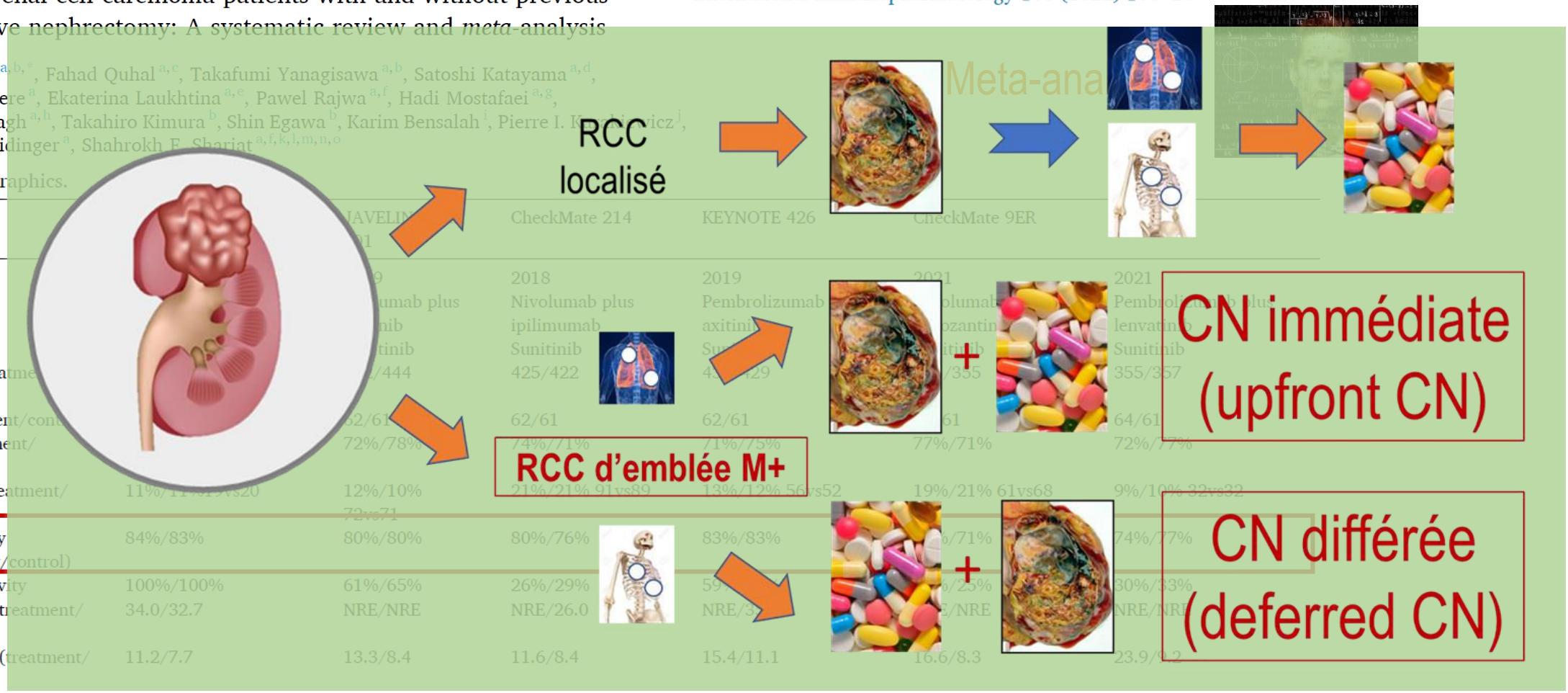

Study demographics.

Study						
Year		2019	2018	2019	2021	2021
Compound		umab plus inib	Nivolumab plus ipilimumab	Pembrolizumab axitinib	olumab ozantin	Pembrolizumab plus lenvatinib
Control		tinib	Sunitinib	Sunitinib	itinib	Sunitinib
Number (treatment/control)		/444	425/422	429	/355	355/357
Age (treatment/control)		62/61	62/61	62/61	61	64/61
Male (treatment/control)		72%/78%	74%/71%	71%/75%	77%/71%	72%/77%
Poor risk (treatment/control)	11%/11%,13vs20	12%/10% 72vs71	21%/21% 91vs89	13%/12% 56vs52	19%/21% 61vs68	9%/10% 32vs32
Nephrectomy (treatment/control)	84%/83%	80%/80%	80%/76%	83%/83%	/71%	74%/77%
PD-L1 positivity	100%/100%	61%/65%	26%/29%	59	/25%	30%/33%
Median OS (treatment/control)	34.0/32.7	NRE/NRE	NRE/26.0	NRE/3	/NRE	NRE/NRE
Median PFS (treatment/control)	11.2/7.7	13.3/8.4	11.6/8.4	15.4/11.1	16.6/8.3	23.9/
Median ORR (treatment/control)	43%/35%	51%/26%	42%/27%	60%/40%	56%/27%	71%/36%
Subsequent treatment	44%/55%	21%/39%	39%/54%	54%/69%	19%/33%	33%/58%
Median follow up	15 months	10.8/8.6 months	25.2 months	30.6 months	18.1 months	26.6 months

Abbreviation: NR (not reported), NRE (not reached), ORR (objective response rate), OS (overall survival), PD-L1 (programmed death ligand 1), PFS (progression free survival)

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Etudes "pivotales" sous ICI : patients mRCC traités avec la tumeur primaire en place

Trial	Number and % of patients treated with primary tumour in place	Patients treated with the primary tumour in place (ICI combination versus sunitinib)		Subgroup analyses (hazard ratios with 95% confidence intervals)	
		ICI combination	sunitinib	PFS	OS
CM 214	187/847 (22 %)	84	103	NA	0.63 (0.42-0.94)
CM 9ER	196/651 (30.1 %)	101	95	0.63 (0.43-0.92)	0.79 (0.48-1.29)
Javelin 101	75/660 (11.4 %)	37	38	0.63 (0.31-1.29)	NA
Keynote 426	146/861 (16.9 %)	NA	NA	NA	NA
Clear	175/712 (24.6%)	93	82	0.44 (0.28-0.68)	0.52 (0.31-0.86)

mRCC, metastatic renal cell carcinoma
ICI, Immune checkpoint inhibitors
CM, Checkmate

A. Méjean, A. Bex, Cytoreductive Nephrectomy: Still Necessary in 2021, Eur Urol Open Sci. 2022 Jan 6;36:49-50

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Study	NIH Trial number	Primary outcomes	Estimated Enrollment
Nivo With or Without Beva or Ipil Before Surgery in Treating Patients With mRCC That Can Be Removed by Surgery	NCT02210117 Phase 1	Safety and tolerability of therapy with nivolumab or nivo + beva or nivo + ipi in (mRCC) in the context of presurgical or prebiopsy therapy	105 pts MDAnderson May 21, 2020
Peri-op Pembro ± Axi + CN and/or MET	NTC04370509 Phase 2	Proportion of participants with >= 2-fold increase in the number of tumor-infiltrating immune cells (TIICs)	64 pts UCSF September 1, 2025
Nivo/Ipi or TKI/IO + Deferred CN vs no surgery + Maintenance Nivo or TKI/IO NORDIC-SUN	NTC03977571 RCT	Overall survival	400 pts Denmark September 1, 2026
(CYTO Reductive Surgery in Kidney Cancer Plus Immunotherapy (Nivo) and TKI(Cabo) (Cyto-KIK)	NCT04322955	Percentage of Participants with a Complete Response	48 pts Mark Stein, Columbia University February 2027
Immunotherapy (Nivo or Nivox2 or Pembro or Ave)-Based Combination Therapy With or Without CN for mRCC (PROBE Trial)	NTC04510597 Phase 3	Overall survival	364 pts SWOG July 2033

Nivo:Nivolumab, Beva:Bevacizumab, Ipi;ipilimumab, Pembro:Pembrolizumab, Axi:Axitinib, Cabo;Cabozantinib, CN:Cytoreductive nephrectomy, mRCC:metastatic Renal Cell Carcinoma, MET:Metastasectomy, IO:Immunotherapy Oncology, TKI:Tyrosine Kinase Inhibitor

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Données initiales contradictoires sur la difficulté et les risques de la néphrectomie après ICI

Cytoreductive Nephrectomy Following Immune Checkpoint Inhibitor Therapy Is Safe and Facilitates Treatment-free Intervals

Daniel D. Shapiro[a,b,*], Jose A. Karam[c], Logan Zemp[d], Viraj A. Master[e], Wade J. Sexton[d], Ali Ghasemzadeh[a], Benjamin N. Schmeusser[e], Facundo Davaro[d], Taylor Peak[d], Dattatraya Patil[e], Surena Matin[c], Philippe E. Spiess[d], E. Jason Abel[a]

EUROPEAN UROLOGY OPEN SCIENCE 50 (2023) 43–46

- 75 patients, upfront ICI, (MDA, MSKCC, Virginia, Elmhurst)
- 2017 – 2022
- Open nephrectomy : 72%
- Intraoperative complications : 4%
- 90-d postop complications : 25% (3 pts with Clavien ≥ III)
- 90-d death =0

Perioperative Complications and Oncologic Outcomes of Nephrectomy Following Immune Checkpoint Inhibitor Therapy: A Multicenter Collaborative Study

Wesley Yip[a,†], Alireza Ghoreifi[a,†], Thomas Gerald[b], Randall Lee[c], Jeffrey Howard[b], Aeen Asghar[a,c], Abhinav Khanna[d], Jie Cai[a], Manju Aron[a], Inderbir Gill[a], R. Houston Thompson[d], Robert Uzzo[c], Vitaly Margulis[b], Nirmish Singla[e], Hooman Djaladat[a,*]

EUROPEAN UROLOGY ONCOLOGY ARTICLE IN PRESS

- 113 patients, upfront ICI, (UCLA, Dallas, Fox Chase, Mayo, Johns Hopkins)
- 2011 – 2021
- Open nephrectomy : 53%
- Intraoperative complications : 2%
- 90-d postop complications : 24% (12 pts with Clavien ≥ III)

Conclusion : le CN post ICI est sans difficulté et sans complication majeure

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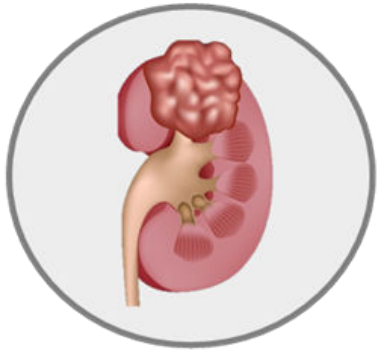
What have we learned with Carmena ? [1,2]

Oligometastatic



Upfront Cytoreductive Nephrectomy
+/- local treatment of metastases
+/- delayed systemic therapy

Non oligometastatic

IMDC Intermediate		IMDC Poor
1 risk factor AND 1 met site	2 risk factors OR >1 met site	
Upfront Cytoreductive Nephrectomy	1L Systemic therapy (sunitinib)	

CR or PR	SD or PD
Deferred Cytoreductive Nephrectomy*	2L Systemic therapy

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium
met, metastatic
CR, complete response; PR, partial response
SD, stable disease; PD, progression disease
1L, first line
2L, second line
*, to be discussed with multidisciplinary team (MDT)

1. *A. Méjean et al. N Engl J Med 2018;379:417-27*
2. *A. Méjean et al. Eur Urol 2021 Jun 26:S0302-2838(21)01815-7*

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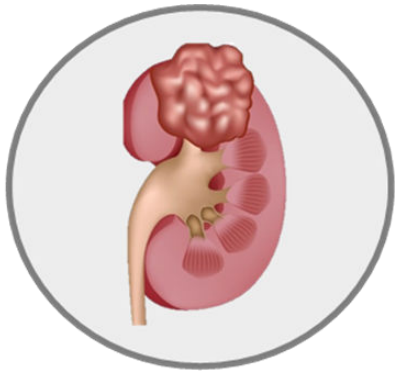
Oligometastatic



Non oligometastatic

- IMDC Intermediate
  - 1 risk factor AND 1 met site
  - 2 risk factors OR >1 met sites
- IMDC Poor

Upfront Cytoreductive Nephrectomy
+/- local treatment of mets
+/- delayed systemic therapy

Systemic therapy (ICI, TT, Combo)

- CR or PR → **Deferred Cytoreductive Nephrectomy**
- SD or PD → **2L Systemic therapy**

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium
Met, metastatic; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ICI, Immune Chekpoint inhibitor; TT, Targeted Therapy

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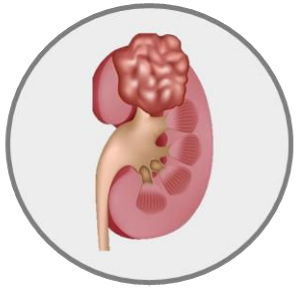
Conclusion

- Attendre les études de phase 3 pour répondre à la question
- Distinguer les mRCC synchrones et asynchrones
- La CN post-ICI est faisable et sans complication majeure
- Jusqu'à aujourd'hui (mai 2023) il semble qu'on puisse extrapoler les résultats de Carmena à l'aire des ICI

→ Le meilleur traitement du mRCC est de traiter la tumeur primaire ET les méta mais dans quel ordre : uCN or dCN ?

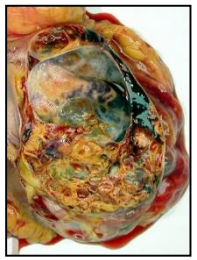
CN : Cytoreductive nephrectomy, mRCC:metastatic renal cell carcinoma, u/dCN : upfront/deferred CN, ICI:immune checkpoint inhibitor

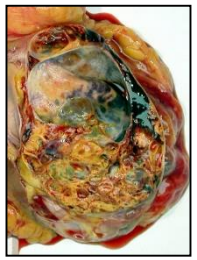


Historique de la néphrectomie en situation métastatique

2001	2007	2018	2020	2025
IL2/IFN	TKI	TKI	ICI/Combo	ICI/Combo/Autres

SWOG/EORTC → Extrapolation → CARMENA → Extrapolation → RCT





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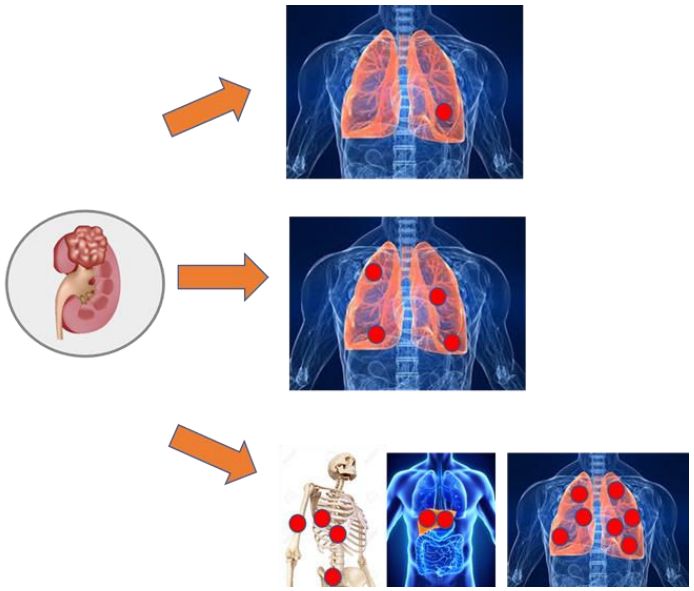
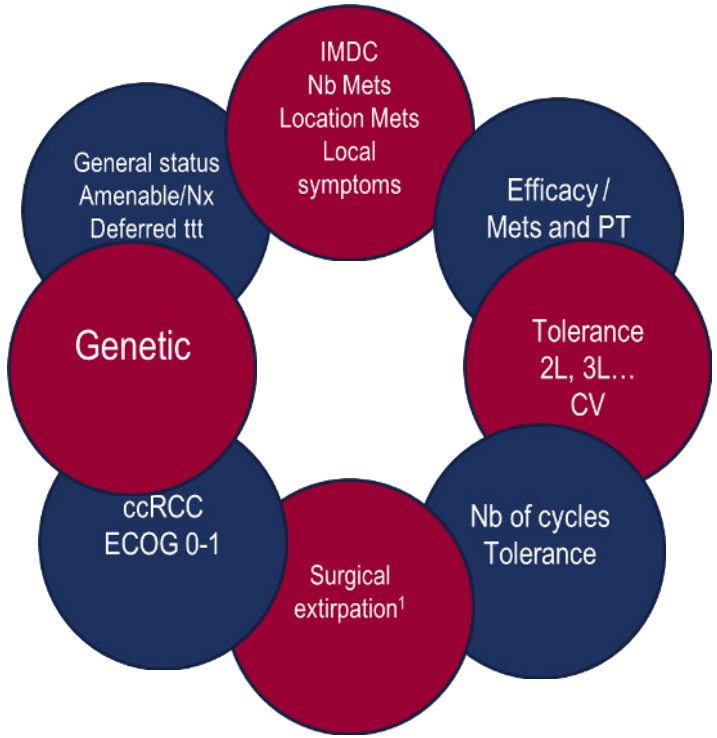
Le futur…





Algorithm / IA