SESSION ONCOLOGIE UROLOGIQUE DU REIN

Mercredi 11 Décembre 2024

Hôtel Mercure. Niort

Patrick BOUCHAERT – Oncologue Médical (CHU, Poitiers)

Rétrospective et Perspectives en Oncologie Urologique 2024

Liens d’intérêts

- Dr Bouchaert : ASTELLAS, BMS, DAIICHI SANKYO, GSK, IPSEN, JANSSEN, PFIZER

CANCER DU REIN AVANCE

- Stratégie thérapeutique
  - Rechallenge de l'immunothérapie
  - Que faire en cas de récidive post-adjuvant?
- Le sous-groupe favorable
- Données de survie globale avec le BELZUTIFAN
- Transplantation de microbiote fécal
- NIVOLUMAB IPILIMUMAB dans le non à cellules claires

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Essais de rechallenge d'immunothérapie en métastatique

Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial

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- *CONTACT-03*
- **ASCO 2023**
- Phase 3 randomisée en ouvert
- Rand° 1:1 (stratification sur IMDC, ligne immunothérapie antérieure, histologie) : CABOZANTINIB 60mg/j PO

  ± ATEZOLIZUMAB 1200 mg IV /3 semaines
- **522 patients** entre juillet 2020 et décembre 2021
- Suivi médian 15,2 mois
- 2 objectifs principaux : PFS selon revue indépendante et OS

Pal et al. Lancet 2023

Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 Study

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- *TiNivo-2*
- **ESMO 2024**
- Phase 3 randomisée en ouvert
- Rand° 1:1 (stratification sur IMDC et dernière ligne (contenant ou non ICI)) : TIVOZANIB 0,89 mg/j PO 21j/28 + NIVOLUMAB 480 mg IV/28j

  vs TIVOZANIB 1,34 mg/j 21j/28
- **343 patients** entre novembre 2021 et juin 2023
- Suivi médian 12,0 mois
- Obj principal : PFS selon revue indépendante

Choueiri et al. Lancet 2024

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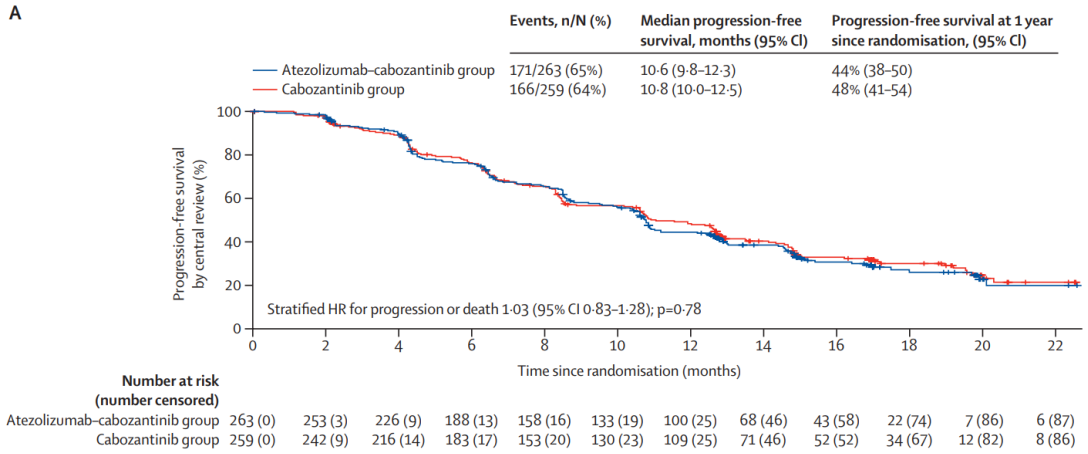
- Suivi médian 15,2 mois
- 2 objectifs principaux : PFS selon revue indépendante et OS
- PFS médiane 10,6 mois vs 10,8 mois (HR 1,03)



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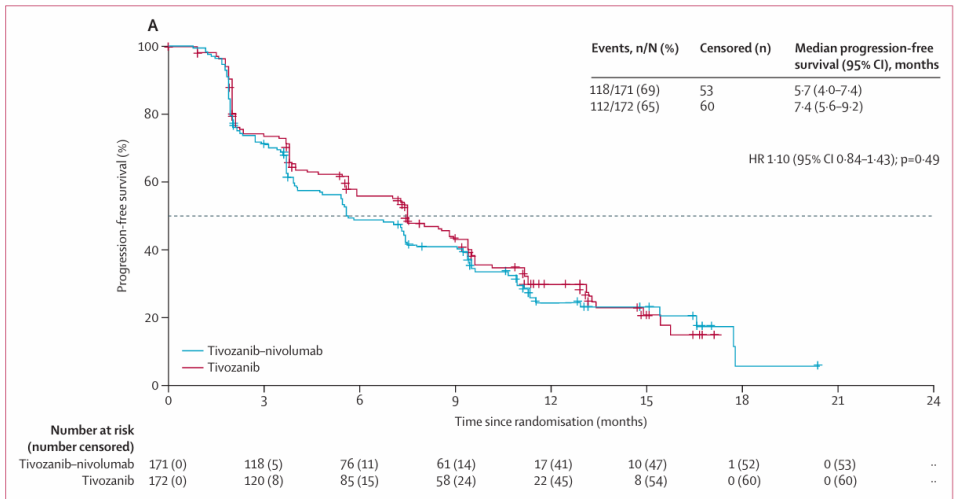
- Suivi médian 12,0 mois
- Objectif principal : PFS selon revue indépendante
- PFS médiane 5,7 vs 7,4 mois (HR 1,10)



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- Carcinome à cellules rénales avancé
- **Cellules claires ou non à cellules claires** (papillaire, chromophobe ou inclassable) avec ou sans composante sarcomatoïde
- Progression pendant ou après inhibiteur de checkpoint immunitaire en 1ère ou 2ème ligne avancée ou dans les 6 mois de la dernière dose d'immunothérapie en adjuvant (Ac anti-PD-1 ou anti-PD-L1). ITK anti-VEGF autorisé

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- Carcinome à cellules rénales avancé,
- **Composante à cellules claires**
- Progression pendant ou après une ou deux lignes thérapeutiques, dont l'une incluait un inhibiteur de checkpoint immunitaire

Choueiri et al. Lancet 2024

Essais de rechallenge d'immunothérapie en métastatique

	Atezolizumab plus cabozantinib group (n=263)	Cabozantinib group (n=259)
Age, years		
Median (range)	62 (20–85)	63 (18–89)
≥65	110 (42%)	115 (44%)
Sex		
Female	59 (22%)	62 (24%)
Male	204 (78%)	197 (76%)
Race		
White	219 (83%)	213 (82%)
Asian	33 (13%)	23 (9%)
Black or African American	2 (1%)	6 (2%)
Other	9 (3%)	17 (7%)
Most recent immune checkpoint inhibitor therapy		
Adjuvant	1 (<1%)	1 (<1%)
Locally advanced or metastatic; first line	144 (55%)	132 (51%)
Locally advanced or metastatic; second line	118 (45%)	124 (48%)
None	0	2 (1%)
Histology		
Dominant clear-cell without sarcomatoid	207 (79%)	200 (77%)
Dominant non-clear-cell without sarcomatoid	30 (11%)	31 (12%)
Any sarcomatoid	25 (10%)	28 (11%)
Missing data	1 (<1%)	0
IMDC score		
0	49 (19%)	69 (27%)
1–2	172 (65%)	153 (59%)
≥3	41 (16%)	36 (14%)
Missing data	1 (<1%)	1 (<1%)
PD-L1 immune cell expression		
<1%	149 (57%)	161 (62%)
≥1% and <5%	66 (25%)	60 (23%)
≥5%	19 (7%)	10 (4%)
Missing data	29 (11%)	28 (11%)
Previous VEGF-TKI use		
None	93 (35%)	95 (37%)
One	166 (63%)	159 (61%)
Two	4 (2%)	5 (2%)
Previous first-line treatment*†		
Ipilimumab plus nivolumab	80 (31%)	70 (27%)
Sunitinib	77 (29%)	72 (28%)
Pazopanib	36 (14%)	43 (17%)
Axitinib plus pembrolizumab	36 (14%)	28 (11%)
Previous second-line treatment*‡		
Nivolumab	104 (87%)	116 (93%)

Data are median (range) or n (%). IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. TKI=tyrosine-kinase inhibitor. *Treatments were mutually exclusive within each line of therapy, and patients could have received agents for more than one line of treatment; treatments included were those in ≥10% of patients in either treatment group. †Atezolizumab plus cabozantinib group n=262; cabozantinib group n=258. ‡Atezolizumab plus cabozantinib group n=119; cabozantinib group n=125.

Table 1: Characteristics of patients at baseline (intention-to-treat population)

antinib versus cabozantinib
s with renal cell carcinoma after
s immune checkpoint inhibitor
): a multicentre, randomised,

na Suárez, Martin H Voss, Guillermo de Velasco, Jad Chahoud, Anastasia Mochalova, ling, Chan Kim, Takahiro Osawa, Martín Angel, Suyasha Gupta, Omara Khan, Huseni, Christian Scheffold, Thomas Powles, Toni K Choueiri

- 522 patients
- 62 ans, 77% hommes
- Moins de 1% ont eu immunothérapie en adjuvant
- 30% NIVO IPI, 13% AXI PEMBRO en 1ère ligne,
- Le reste SUNITINIB ou PAZOPANIB. Ils ont alors eu le Nivo en seconde ligne
- **36% n'ont reçu aucun ITK anti VEGF**

Pal et al. Lancet 2023

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- 343 patients
- 64 ans, 76% hommes
- 14% ont eu traitement adjuvant
- **Précédente ligne thérapeutique contenant un ICI chez 71%**
- 63% en deuxième ligne
- **31% n'ont pas reçu d'ITK anti-angiogénique**

Choueiri e

	Tivozanib 0·89 mg plus nivolumab (n=171)	Tivozanib 1·34 mg (n=172)
Age, years	64·0 (37–87)	63·0 (33–82)
Sex		
Male	125 (73%)	134 (78%)
Female	46 (27%)	38 (22%)
Race		
White	112 (65%)	107 (62%)
Asian	1 (1%)	0
Black or African American	2 (1%)	8 (5%)
Not reported, other, or missing	56 (33%)	57 (33%)
Region		
North America	60 (35%)	52 (30%)
Europe	93 (54%)	102 (59%)
Rest of the world	18 (11%)	18 (10%)
Eastern Cooperative Oncology Group performance status		
0	76 (44%)	85 (49%)
1	94 (55%)	87 (51%)
Missing	1 (1%)	0
International Metastatic Renal Cell Carcinoma Database Consortium risk category		
Favourable	30 (18%)	31 (18%)
Intermediate	114 (67%)	113 (66%)
Poor	27 (16%)	28 (16%)
Histology		
Clear cell	157 (92%)	157 (91%)
Clear cell component	13 (8%)	14 (8%)
Missing data	1 (1%)	0
Had previous nephrectomy	108 (63%)	121 (70%)
Had adjuvant therapy	25 (15%)	22 (13%)
Previous lines of therapy		
One	111 (65%)	105 (61%)
Two	60 (35%)	67 (39%)
Previous immune checkpoint inhibitor		
Immune checkpoint inhibitor in the most recent line of therapy	122 (71%)	122 (71%)
Non-immune checkpoint inhibitor in the most recent line of therapy*	49 (29%)	50 (29%)
Previous vascular endothelial growth factor receptor tyrosine kinase inhibitor use		
None	53 (31%)	53 (31%)
One	96 (56%)	101 (59%)
Two	22 (13%)	18 (10%)

Data are n (%) or median (range). *The median time that patients from this group had been off immunotherapy was 10·4 months (IQR 7·4–17·7).

Table 1: Baseline patient characteristics

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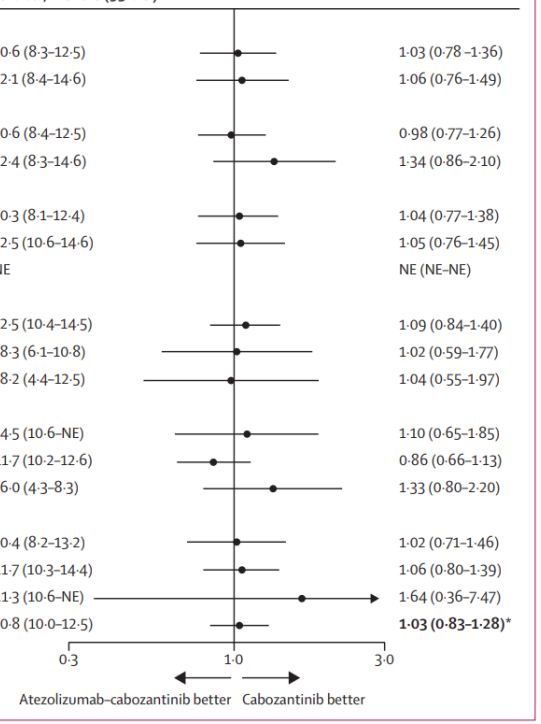
B

	Atezolizumab–cabozantinib (events/N)	Atezolizumab–cabozantinib median progression-free survival, months (95% CI)	Cabozantinib (events/N)	Cabozantinib median progression-free survival, months (95% CI)	HR for progression or death (95% CI)
Age, years					
<65	104/153	10·4 (8·5–12·4)	96/144	10·6 (8·3–12·5)	1·03 (0·78 –1·36)
≥65	67/110	10·6 (10·3–14·6)	70/115	12·1 (8·4–14·6)	1·06 (0·76–1·49)
Sex					
Male	130/204	10·6 (10·2–12·6)	128/197	10·6 (8·4–12·5)	0·98 (0·77–1·26)
Female	41/59	10·1 (8·3–12·7)	38/62	12·4 (8·3–14·6)	1·34 (0·86–2·10)
Most recent ICI therapy					
First line	98/144	9·9 (8·3–10·6)	87/132	10·3 (8·1–12·4)	1·04 (0·77–1·38)
Second line	72/118	12·4 (10·5–14·6)	77/124	12·5 (10·6–14·6)	1·05 (0·76–1·45)
Adjuvant	1/1	4·5 (NE–NE)	0/1	NE	NE (NE–NE)
Histology					
Dominant clear cell	128/ 207	10·7 (10·4–12·7)	117/200	12·5 (10·4–14·5)	1·09 (0·84–1·40)
Dominant non-clear cell	25/30	6·3 (4·4–10·5)	27/31	8·3 (6·1–10·8)	1·02 (0·59–1·77)
Any sarcomatoid component	18/25	8·3 (6·3–NE)	22/28	8·2 (4·4–12·5)	1·04 (0·55–1·97)
IMDC score					
0	25/ 49	14·3 (10·2–NE)	34/69	14·5 (10·6–NE)	1·10 (0·65–1·85)
1–2	109/172	10·8 (10·4–14·2)	104/153	11·7 (10·2–12·6)	0·86 (0·66–1·13)
3–6	36/41	4·9 (4·1–8·3)	28/36	6·0 (4·3–8·3)	1·33 (0·80–2·20)
Previous lines of VEGR-TKI					
0	61/93	9·7 (8·3–12·7)	60/95	10·4 (8·2–13·2)	1·02 (0·71–1·46)
1	107/166	10·6 (10·4–12·6)	102/159	11·7 (10·3–14·4)	1·06 (0·80–1·39)
2	3/4	6·7 (2·9–NE)	4/5	11·3 (10·6–NE)	1·64 (0·36–7·47)
All patients	171/263	10·5 (9·7–12·3)	166/259	10·8 (10·0–12·5)	**1·03 (0·83–1·28)***



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	Tivozanib–nivolumab event/N	Tivozanib event/N	Tivozanib–nivolumab median progression-free survival, months (95% CI)	Tivozanib median progression-free survival, months (95% CI)	Hazard ratio for progression or death (95% CI)
Age (years)					
<65	68/89	65/97	4·8 (3·4–7·3)	7·4 (5·5–9·2)	1·25 (0·89–1·76)
≥65	50/82	47/75	9·2 (5·5–9·6)	7·6 (5·2–10·0)	0·92 (0·61–1·37)
Sex					
Male	86/125	88/134	5·6 (3·9–7·5)	7·4 (5·5–9·2)	1·01 (0·75–1·36)
Female	32/46	24/38	6·7 (3·7–10·9)	7·4 (5·6–12·9)	1·27 (0·75–2·16)
ECOG					
0	52/76	53/85	7·3 (4·0–9·4)	8·8 (7·2–11·1)	1·15 (0·78–1·69)
1	66/94	59/87	5·5 (3·7–9·0)	6·0 (3·7–8·6)	0·95 (0·67–1·36)
IMDC risk category					
Favourable	18/30	15/31	9·3 (4·0–11·4)	11·2 (9·3–13·1)	1·37 (0·69–2·73)
Intermediate	78/114	75/115	5·7 (4·0–9·4)	7·4 (4·5–8·4)	0·99 (0·72–1·36)
Poor	22/27	22/26	3·7 (2·7–7·4)	5·7 (2·3–9·2)	1·35 (0·73–2·50)
Previous nephrectomy status					
Complete	45/70	59/85	9·0 (5·5–9·6)	9·3 (5·5–11·1)	0·99 (0·65–1·49)
Partial	21/32	15/22	4·8 (2·2–10·9)	7·5 (2·1–15·2)	1·17 (0·60–2·27)
Other	4/6	11/14	5·8 (1·9–NE)	5·2 (1·5–9·2)	0·60 (0·19–1·97)
Previous systemic anticancer therapies (line of therapy)					
Second line	71/111	64/105	7·3 (5·4–9·3)	9·2 (7·4–10·0)	1·15 (0·82–1·62)
Third line	47/60	48/67	4·8 (3·2–7·5)	5·5 (2·9–7·4)	0·97 (0·65–1·45)
Use of immune checkpoint inhibitor in most recent line					
Yes	78/122	75/122	7·4 (5·6–9·6)	9·2 (7·4–10·0)	1·10 (0·80–1·52)
No	40/49	37/50	3·7 (2·7–5·4)	3·7 (1·9–7·2)	0·95 (0·61–1·50)
Use of VEGFR TKI in most recent line*					
Yes	37/45	37/50	3·4 (2·2–4·8)	3·7 (1·9–7·2)	0·96 (0·61–1·52)
No	37/66	36/65	9·6 (7·5–11·2)	9·3 (7·4–14·7)	0·95 (0·60–1·51)
Previous use of VEGFR TKI (any previous line)					
0 VEGFR TKI	29/53	28/53	9·6 (7·4–15·3)	9·4 (7·4–15·5)	1·03 (0·61–1·74)
1 VEGFR TKI	69/96	70/101	5·4 (3·7–6·7)	7·4 (5·5–8·8)	1·04 (0·74–1·45)
2 VEGFR TKI	20/22	14/18	3·1 (2·1–4·0)	3·8 (1·9–7·2)	1·33 (0·67–2·65)

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Adjuvant	1/1	4·5 (NE–NE)	0/1	NE	NE (NE–NE)
Histology					
Dominant clear cell	128/ 207	10·7 (10·4–12·7)	117/200	12·5 (10·4–14·5)	1·09 (0·84–1·40)
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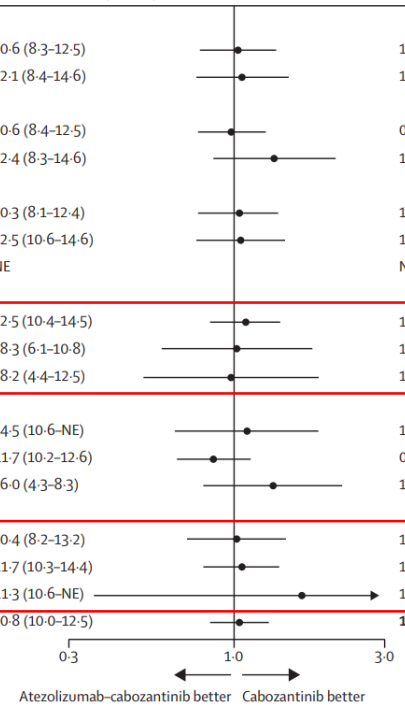
2	3/4	6·7 (2·9–NE)	4/5	11·3 (10·6–NE)	1·64 (0·36–7·47)
All patients	171/263	10·5 (9·7–12·3)	166/259	10·8 (10·0–12·5)	**1·03 (0·83–1·28)***



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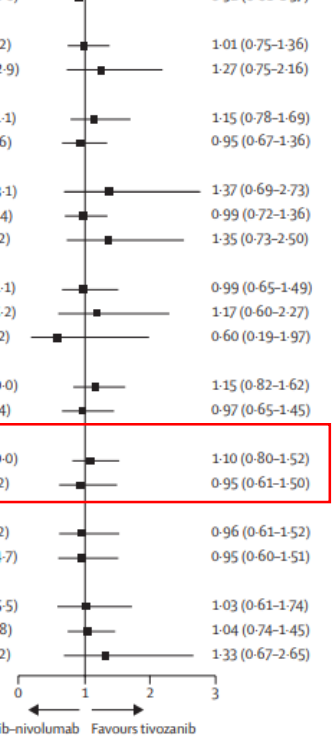
B

	Tivozanib–nivolumab event/N	Tivozanib event/N	Tivozanib–nivolumab median progression-free survival, months (95% CI)	Tivozanib median progression-free survival, months (95% CI)	Hazard ratio for progression or death (95% CI)
Age (years)					
<65	68/89	65/97	4·8 (3·4–7·3)	7·4 (5·5–9·2)	1·25 (0·89–1·76)
≥65	50/82	47/75	9·2 (5·5–9·6)	7·6 (5·2–10·0)	0·92 (0·61–1·37)
Sex					
Male	86/125	88/134	5·6 (3·9–7·5)	7·4 (5·5–9·2)	1·01 (0·75–1·36)
Female	32/46	24/38	6·7 (3·7–10·9)	7·4 (5·6–12·9)	1·27 (0·75–2·16)
ECOG					
0	52/76	53/85	7·3 (4·0–9·4)	8·8 (7·2–11·1)	1·15 (0·78–1·69)
1	66/94	59/87	5·5 (3·7–9·0)	6·0 (3·7–8·6)	0·95 (0·67–1·36)
IMDC risk category					
Favourable	18/30	15/31	9·3 (4·0–11·4)	11·2 (9·3–13·1)	1·37 (0·69–2·73)
Intermediate	78/114	75/115	5·7 (4·0–9·4)	7·4 (4·5–8·4)	0·99 (0·72–1·36)
Poor	22/27	22/26	3·7 (2·7–7·4)	5·7 (2·3–9·2)	1·35 (0·73–2·50)
Previous nephrectomy status					
Complete	45/70	59/85	9·0 (5·5–9·6)	9·3 (5·5–11·1)	0·99 (0·65–1·49)
Partial	21/32	15/22	4·8 (2·2–10·9)	7·5 (2·1–15·2)	1·17 (0·60–2·27)
Other	4/6	11/14	5·8 (1·9–NE)	5·2 (1·5–9·2)	0·60 (0·19–1·97)
Previous systemic anticancer therapies (line of therapy)					
Second line	71/111	64/105	7·3 (5·4–9·3)	9·2 (7·4–10·0)	1·15 (0·82–1·62)
Third line	47/60	48/67	4·8 (3·2–7·5)	5·5 (2·9–7·4)	0·97 (0·65–1·45)
Use of immune checkpoint inhibitor in most recent line					
Yes	78/122	75/122	7·4 (5·6–9·6)	9·2 (7·4–10·0)	1·10 (0·80–1·52)
No	40/49	37/50	3·7 (2·7–5·4)	3·7 (1·9–7·2)	0·95 (0·61–1·50)
Use of VEGFR TKI in most recent line*					
Yes	37/45	37/50	3·4 (2·2–4·8)	3·7 (1·9–7·2)	0·96 (0·61–1·52)
No	37/66	36/65	9·6 (7·5–11·2)	9·3 (7·4–14·7)	0·95 (0·60–1·51)
Previous use of VEGFR TKI (any previous line)					
0 VEGFR TKI	29/53	28/53	9·6 (7·4–15·3)	9·4 (7·4–15·5)	1·03 (0·61–1·74)
1 VEGFR TKI	69/96	70/101	5·4 (3·7–6·7)	7·4 (5·5–8·8)	1·04 (0·74–1·45)
2 VEGFR TKI	20/22	14/18	3·1 (2·1–4·0)	3·8 (1·9–7·2)	1·33 (0·67–2·65)



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Essais de rechallenge d'immunothérapie en métastatique

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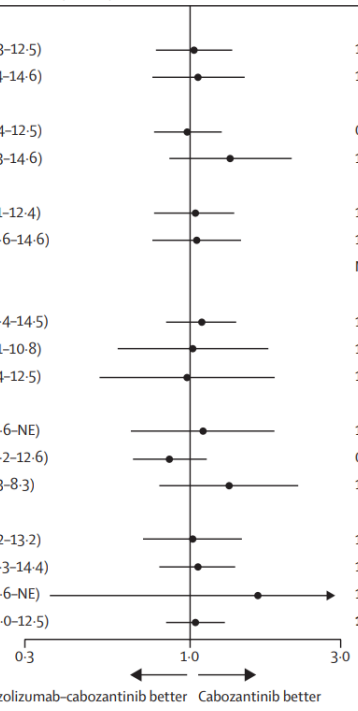
B

	Atezolizumab–cabozantinib (events/N)	Atezolizumab–cabozantinib median progression-free survival, months (95% CI)	Cabozantinib (events/N)	Cabozantinib median progression-free survival, months (95% CI)	HR for progression or death (95% CI)
Age, years					
<65	104/153	10·4 (8·5–12·4)	96/144	10·6 (8·3–12·5)	1·03 (0·78 –1·36)
≥65	67/110	10·6 (10·3–14·6)	70/115	12·1 (8·4–14·6)	1·06 (0·76–1·49)
Sex					
Male	130/204	10·6 (10·2–12·6)	128/197	10·6 (8·4–12·5)	0·98 (0·77–1·26)
Female	41/59	10·1 (8·3–12·7)	38/62	12·4 (8·3–14·6)	1·34 (0·86–2·10)
Most recent ICI therapy					
First line	98/144	9·9 (8·3–10·6)	87/132	10·3 (8·1–12·4)	1·04 (0·77–1·38)
Second line	72/118	12·4 (10·5–14·6)	77/124	12·5 (10·6–14·6)	1·05 (0·76–1·45)
Adjuvant	1/1	4·5 (NE–NE)	0/1	NE	NE (NE–NE)
Histology					
Dominant clear cell	128/ 207	10·7 (10·4–12·7)	117/200	12·5 (10·4–14·5)	1·09 (0·84–1·40)
Dominant non-clear cell	25/30	6·3 (4·4–10·5)	27/31	8·3 (6·1–10·8)	1·02 (0·59–1·77)
Any sarcomatoid component	18/25	8·3 (6·3–NE)	22/28	8·2 (4·4–12·5)	1·04 (0·55–1·97)
IMDC score					
0	25/ 49	14·3 (10·2–NE)	34/69	14·5 (10·6–NE)	1·10 (0·65–1·85)
1–2	109/172	10·8 (10·4–14·2)	104/153	11·7 (10·2–12·6)	0·86 (0·66–1·13)
3–6	36/41	4·9 (4·1–8·3)	28/36	6·0 (4·3–8·3)	1·33 (0·80–2·20)
Previous lines of VEGR-TKI					
0	61/93	9·7 (8·3–12·7)	60/95	10·4 (8·2–13·2)	1·02 (0·71–1·46)
1	107/166	10·6 (10·4–12·6)	102/159	11·7 (10·3–14·4)	1·06 (0·80–1·39)
2	3/4	6·7 (2·9–NE)	4/5	11·3 (10·6–NE)	1·64 (0·36–7·47)
All patients	171/263	10·5 (9·7–12·3)	166/259	10·8 (10·0–12·5)	**1·03 (0·83–1·28)***



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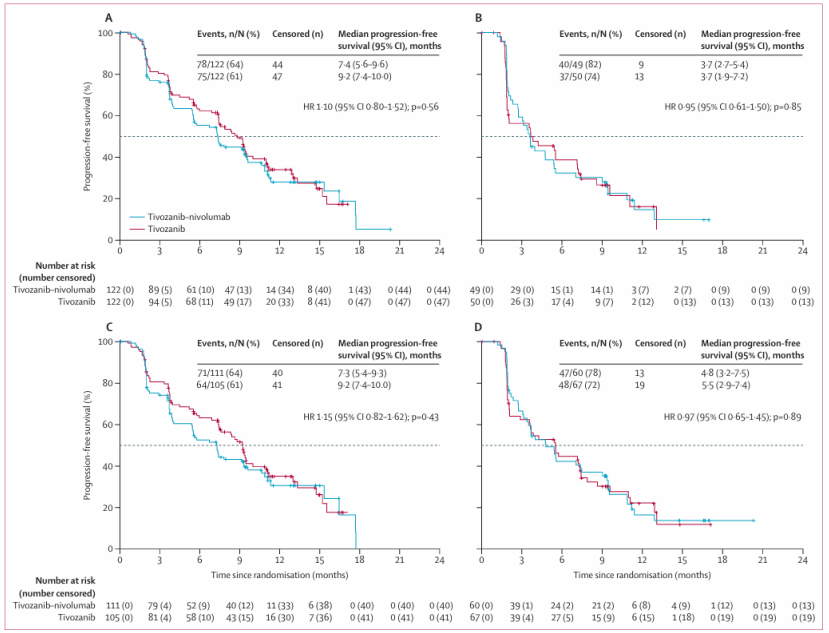

Figure 3: Kaplan–Meier estimate of (A) progression-free survival for patients with an immune checkpoint inhibitor as the most recent line of therapy, (B) those with a non-immune checkpoint inhibitor as the most recent line of therapy, (C) the study drug as second-line therapy, and (D) the study drug as third-line therapy
Dotted lines represent 50% marker. HR=hazard ratio.

A. ICI lors de la ligne la plus récente

B. Ligne la plus récente ne contenant pas d'ICI

C. Une seule ligne antérieure

B. Deux lignes antérieures

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	Atezolizumab plus cabozantinib group (n=262)	Cabozantinib group (n=256)
Any-cause adverse event	262 (100%)	254 (99%)
Any-cause adverse event related to treatment	252 (96%)	249 (97%)
Grade 3 or 4 adverse event	177 (68%)	158 (62%)
Grade 3 or 4 adverse event related to treatment	145 (55%)	121 (47%)
Death due to adverse event	17 (6%)	9 (4%)
Death due to adverse event related to treatment	3 (1%)	0
Serious adverse event	126 (48%)	84 (33%)
Serious adverse event related to treatment	63 (24%)	30 (12%)
Adverse event leading to withdrawal from a trial drug	41 (16%)	10 (4%)
Adverse event leading to withdrawal from atezolizumab	29 (11%)	0
Adverse event leading to withdrawal from cabozantinib	25 (10%)	10 (4%)
Adverse event leading to interruption or reduction of a trial drug	240 (92%)	223 (87%)
Adverse event leading to interruption of atezolizumab	159 (61%)	0
Adverse event leading to interruption or reduction of cabozantinib	234 (89%)*	223 (87%)†
Adverse events occurring in ≥20% patients in either group		
Diarrhoea	171 (65%)	181 (71%)
Palmar-plantar erythrodysesthesia syndrome	101 (39%)	105 (41%)
Decreased appetite	100 (38%)	97 (38%)
Hypothyroidism	95 (36%)	97 (38%)
Nausea	77 (29%)	92 (36%)
Asthenia	77 (29%)	75 (29%)
Hypertension	72 (27%)	87 (34%)
Fatigue	72 (27%)	61 (24%)
Increased alanine aminotransferase	62 (24%)	57 (22%)
Increased aspartate aminotransferase	60 (23%)	61 (24%)
Anaemia	53 (20%)	48 (19%)
Decreased weight	46 (18%)	64 (25%)

Data are n (%). *Due to an adverse event, 103 (39%) patients had dose reductions to a lowest dose of cabozantinib 40 mg, and 98 (37%) had a lowest dose of 20 mg. †Due to an adverse event, 104 (41%) patients had dose reductions to a lowest dose of cabozantinib 40 mg, and 77 (30%) had a lowest dose of 20 mg.

Table 3: Adverse events

- AE liés au traitement G3-4 : 55% vs 47%
- SAE liés au traitement : 24% vs 12%

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	Tivozanib 0·89 mg plus nivolumab (n=168)	Tivozanib 1·34 mg (n=171)
Any-cause TEAE	163 (97%)	167 (98%)
Treatment related	137 (82%)	144 (84%)
Tivozanib related	135 (80%)	144 (84%)
Nivolumab related	119 (71%)	0
Grade ≥3 adverse event*	102 (61%)	103 (60%)
Related	54 (32%)	60 (35%)
Serious adverse event*	54 (32%)	64 (37%)
Related	14 (8%)	15 (9%)
Death due to adverse event	7 (4%)	5 (3%)
Deemed related to study drug	0	1 (1%)
TEAE leading to withdrawal	27 (16%)	33 (19%)
Of tivozanib	19 (11%)	33 (19%)
Of nivolumab	22 (13%)	0
TEAE leading to dose interruption	82 (49%)	93 (54%)
Of tivozanib	79 (47%)	93 (54%)
Of nivolumab	35 (21%)	0
TEAE leading to dose reduction of tivozanib	18 (11%)	38 (22%)
Any-grade TEAE occurring in ≥10% of patients in either group		
Hypertension	62 (37%)	69 (40%)
Fatigue	49 (29%)	68 (40%)
Diarrhoea	51 (30%)	62 (36%)
Nausea	26 (15%)	47 (27%)
Decreased appetite	37 (22%)	46 (27%)
Vomiting	20 (12%)	36 (21%)
Asthenia	39 (23%)	35 (20%)
Proteinuria	16 (10%)	30 (18%)
Constipation	17 (10%)	29 (17%)
Arthralgia	26 (15%)	27 (16%)
Cough	26 (15%)	26 (15%)
Hypothyroidism	15 (9%)	26 (15%)
Back pain	21 (13%)	23 (13%)
Dyspnoea	15 (9%)	22 (13%)
Dysphonia	15 (9%)	22 (13%)
Weight decreased	17 (10%)	21 (12%)
Palmar-plantar erythrodysesthesia	10 (6%)	21 (12%)
Abdominal pain	12 (7%)	20 (12%)
Blood creatinine increased	14 (8%)	19 (11%)
Anaemia	28 (17%)	16 (9%)
Pruritus	26 (15%)	11 (6%)
Headache	23 (14%)	10 (6%)

TEAE=treatment-emergent adverse event. *Grade ≥3 adverse event includes all serious adverse event.

Table 2: Overview of adverse events

- AE G3+ liés au traitement 32% vs 35%
- SAE liés au traitement 8% vs 9%

Choue

CANCER DU REIN AVANCE

- **Stratégie thérapeutique**
  - Rechallenge de l'immunothérapie
  - **Que faire en cas de récidive post-adjuvant?**
- Le sous-groupe favorable
- Données de survie globale avec le BELZUTIFAN
- Transplantation de microbiote fécal
- NIVOLUMAB IPILIMUMAB dans le non à cellules claires

Données sur les traitements post-immunothérapie adjuvante

First-line Systemic Therapy Following Adjuvant Immunotherapy in Renal Cell Carcinoma: An International Multicenter Study

Talal El Zarif[a,b,†], Karl Semaan[b,†], Wanling Xie[c], Marc Eid[b], Martin Zarba[d], Wadih Issa[e], Tian Zhang[e], Charles B. Nguyen[f], Ajjai Alva[f], Catherine C. Fahey[g], Kathryn E. Beckermann[g], Jose A. Karam[h], Matthew T. Campbell[i], Giuseppe Procopio[j], Marco Stellato[j], Sebastiano Buti[k,l], Anezka Zemankova[m], Bohuslav Melichar[m], Francesco Massari[n,o], Veronica Mollica[n,o], Balaji Venugopal[p,q], Hedyeh Ebrahimi[r], Guillermo de Velasco[s], Howard Paul Gurney[t], Ugo De Giorgi[u], Omi Parikh[v], Eric Winquist[w], Viraj Master[x], Abraham Ruiz Garcia[y], Hernan Javier Cutuli[z], Thomas Robert Ferguson[aa], Marine Gross-Goupil[bb], Sylvan C. Baca[b], Sumanta K. Pal[r], David A. Braun[cc], Rana R. McKay[dd], Daniel Y.C. Heng[d,‡], Toni K. Choueiri[b,‡,]*

- **Etude rétrospective multi-centrique (29 centres)** incluant les patients ayant présenté une **récidive après traitement adjuvant par immunothérapie** (au moins une injection d'anti-PD-1/L1) entre septembre 2017 et juin 2023

- Objectif principal : PFS en première ligne métastatique

- Patients ayant récidivé sous immunothérapie ou dans les 3 mois suivant la complétion de l'immunothérapie considérés résistants à l'immunothérapie

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Table 1 – Baseline characteristics of overall recurrence cohort

	Total (*N* = 94)
Age at RCC diagnosis, median (Q1–Q3)	56 (48–65)
Sex, *N* (%)	
Male	71 (76)
Race, *N* (%)	
White	85 (90)
Asian	4 (4.3)
Other	5 (5.3)
Ethnicity	
Non-Hispanic/non-Latinx, *N* (%)	75 (89)
Not reported [a]	10
Region, *N* (%)	
North America	39 (46)
South America	2 (2.2)
Europe	41 (44)
Asia	1 (1.1)
Australia	7 (7.4)
Smoking	
Never, *N* (%)	49 (54)
Not reported [a]	3
Disease risk category, *N* (%)	
M0, intermediate to high risk	66 (70)
M0, high risk	15 (16)
M1, NED	13 (14)
Histology, *N* (%)	
Clear cell	83 (88)
Sarcomatoid features, *N* (%)	
Present	15 (16)
Adjuvant immunotherapy, *N* (%)	
Pembrolizumab	37 (39)
Atezolizumab	28 (30)
Nivolumab + ipilimumab	15 (16)
Nivolumab	10 (11)
Pembrolizumab + belzutifan	3 (3.2)
Durvalumab	1 (1.1)
Recurrence timing, *N* (%)	
<3 mo	49 (52)
Sites of recurrence [b], *N* (%)	
Lung	47 (50)
Lymph nodes	40 (43)
Bone	11 (12)
Adrenal	8 (8.5)
Liver	7 (7.4)
Brain	3 (3.2)
Others	42 (45)
Number of sites of recurrence, *N* (%)	
>1 site	47 (50)
Treatment received at recurrence, *N* (%)	
Systemic therapy	**76 (81)**
IO + IO	12 (13)
IO + VEGF-TT	26 (28)
VEGF-TT	37 (40)
VEGF-TT + mTORi	1 (1.1)
Surgery	**16 (17)**
Radiation	**2 (2.1)**

IO = immune oncology; mTORi = mammalian target of rapamycin inhibitor; NED = no evidence of disease; RCC = renal cell carcinoma; VEGF-TT = vascular endothelial growth factor–targeted therapy.

[a] Missing values were not included in the denominator for calculation of % in subgroups.

[b] Sum of sites of recurrence is >94 as a subset of patients have multiple sites of metastases.

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- **94 patients inclus**, âge médian 56 ans, 76% d'hommes, 88% à cellules claires. 16% de composante sarcomatoïde
- Traitement adjuvant : PEMBRO seul 39%, ATEZO seul 30%, NIVO-IPI 16%
- Durée médiane de traitement adjuvant 5,5 mois.
- Raisons d'arrêt : traitement terminé 38%, récidive 42%, toxicité 17%
- **76 (81%) ont reçu traitement systémique à la récidive** (le reste chirurgie ou radiothérapie ; 16 et 2 patients) :
- **37 anti-angiogénique, 26 immuno + anti-angiogénique, 12 double-immunothérapie**
- 52% ont récidivé dans les 3 mois. Plus de récidive osseuse chez les patients ayant récidivé dans les 3 mois vs après (20% vs 2,2%)

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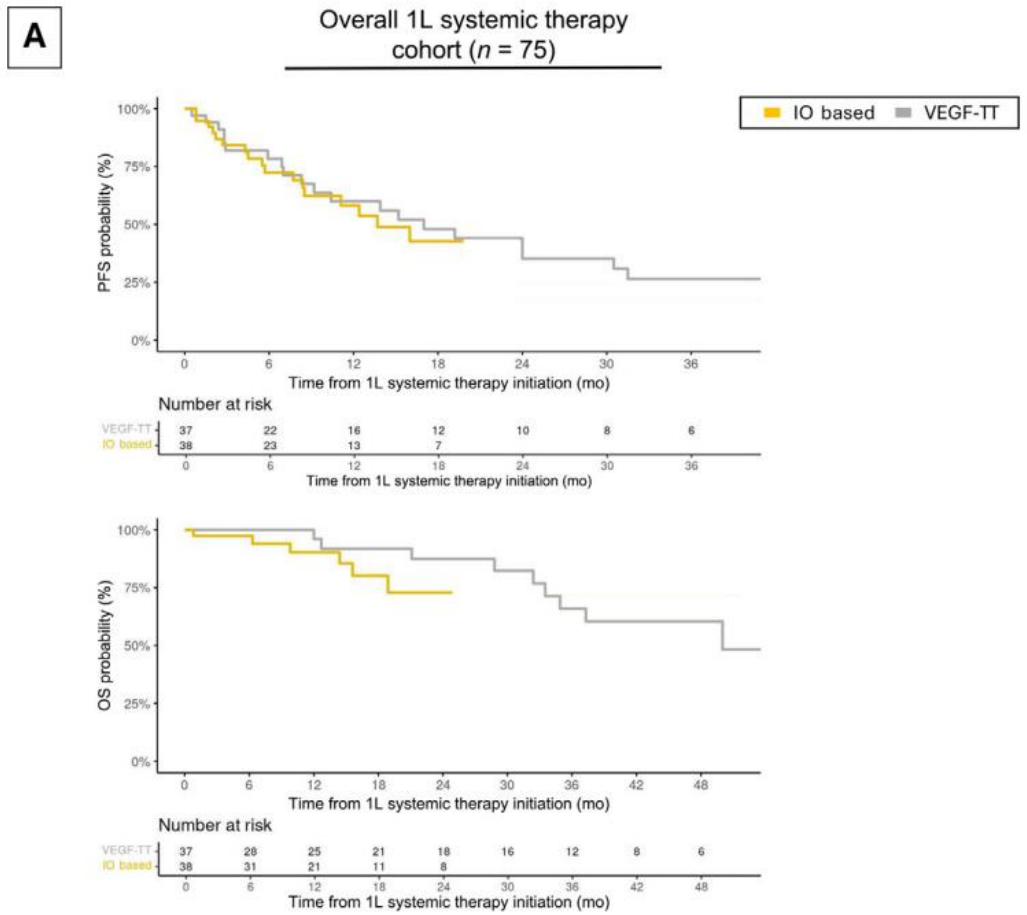

- Suivi médian 15 mois
- PFS médiane 15 mois
- PFS en haut, OS en bas
- Selon le type de traitement

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First-line Systemic Therapy Following Adjuvant Immunotherapy in Renal Cell Carcinoma: An International Multicenter Study

Talal El Zarif[a,b,†], Karl Semaan[b,†], Wanling Xie[c], Marc Eid[b], Martin Zarba[d], Wadih Issa[e], Tian Zhang[e], Charles B. Nguyen[f], Ajjai Alva[f], Catherine C. Fahey[g], Kathryn E. Beckermann[g], Jose A. Karam[h], Matthew T. Campbell[i], Giuseppe Procopio[j], Marco Stellato[j], Sebastiano Buti[k,l], Anezka Zemankova[m], Bohuslav Melichar[m], Francesco Massari[n,o], Veronica Mollica[n,o], Balaji Venugopal[p,q], Hedyeh Ebrahimi[r], Guillermo de Velasco[s], Howard Paul Gurney[t], Ugo De Giorgi[u], Omi Parikh[v], Eric Winquist[w], Viraj Master[x], Abraham Ruiz Garcia[y], Hernan Javier Cutuli[z], Thomas Robert Ferguson[aa], Marine Gross-Goupil[bb], Sylvan C. Baca[b], Sumanta K. Pal[r], David A. Braun[cc], Rana R. McKay[dd], Daniel Y.C. Heng[d,‡], Toni K. Choueiri[b,‡,]*

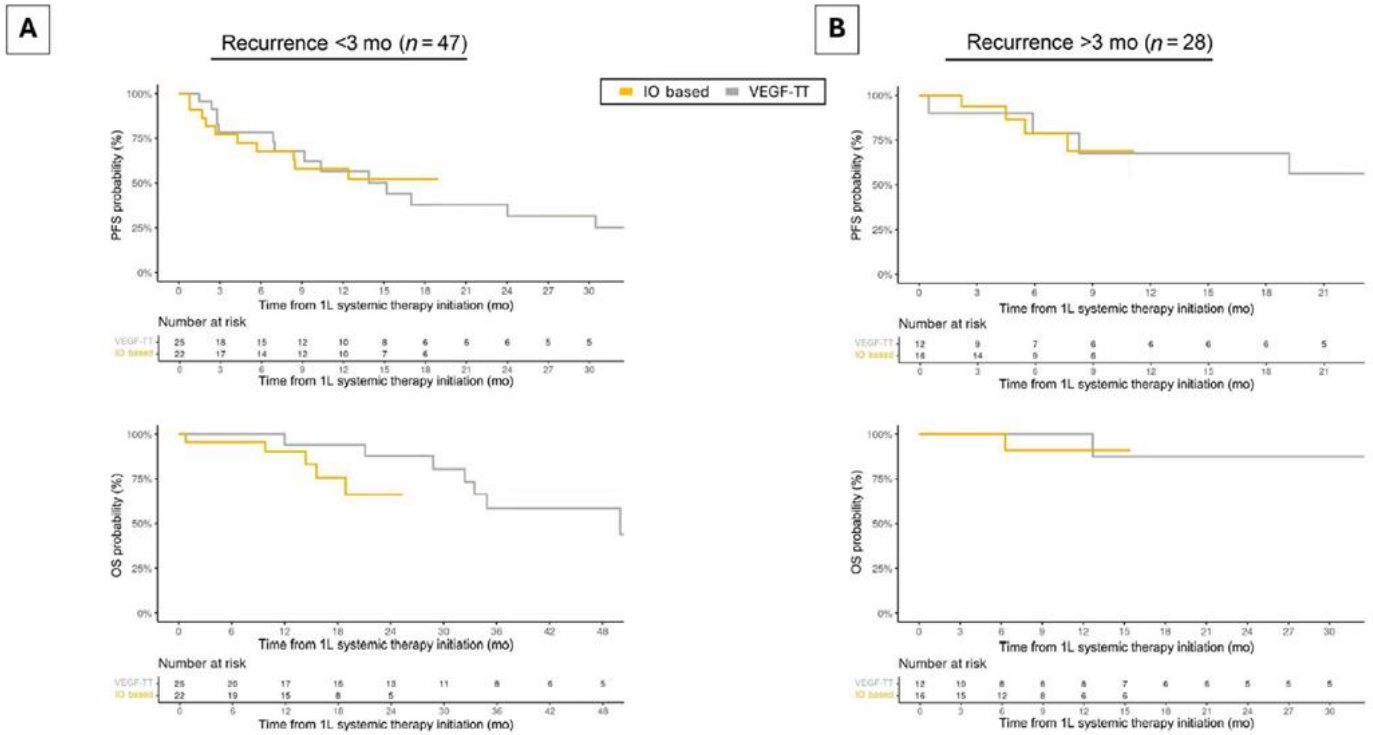

Fig. 2 – Progression-free and overall survival across 1L systemic therapy regimens among patients recurring in (A) <3 mo or (B) >3 mo following adjuvant IO. IO = immune oncology; 1L = first line; OS = overall survival; PFS = progression-free survival; VEGF-TT = vascular endothelial growth factor–targeted therapy.

- Suivi médian 15 mois
- PFS en haut, OS en bas
- Selon type de traitement

A. Récidive<3 mois

B. Récidive>3 mois

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Avis d'expert

ASCO Daily News®
Clinical News From the American Society of Clinical Oncology

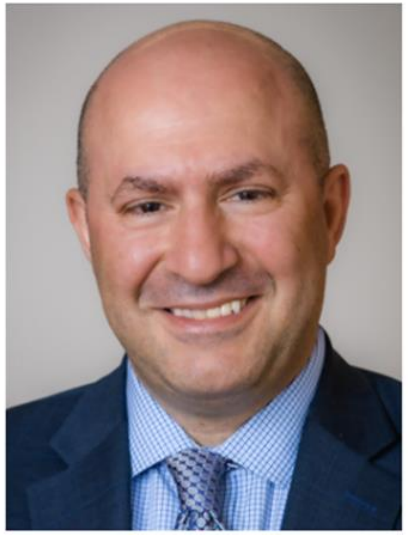
Using Clinical Characteristics to Guide Treatment of Recurrent RCC After Adjuvant Pembrolizumab

January 10, 2024

Maria T. Bourlon, MD, MS; Paola Valdez, MD; Toni Choueiri, MD, FASCO; and Elaine Lam, MD

Patients with progression during adjuvant therapy or shortly after discontinuation (≤ 3 months) can be considered to have refractory disease. Those developing metastatic disease between 3 to 12 months can be considered to have early recurrence. In both scenarios, primary or constitutive resistance is the underlying physiopathology, associated to the inability of the tumor cells to mount an antitumor response, and the most convenient strategy seems to be to treat with a drug targeting a different mechanism of action, such as VEGF receptor tyrosine kinase inhibitor (TKI).[11]

In contrast, late recurrences are defined as those that occur after at least 12 months of completing adjuvant pembrolizumab and are believed to be a consequence of secondary or acquired resistance associated with epigenetic, transcriptomic, and/or proteomic changes that facilitate immune evasion.[11] In this scenario, patients might respond again to ICI rechallenge and have multiple options, including treatment with a TKI alone or an ICI-based combination. Data for these approaches are not available, and their use is extrapolated from studies of similar scenarios in the metastatic subsequent-line setting.



Dr. Toni Choueiri

CANCER DU REIN AVANCE

- Stratégie thérapeutique
  - Rechallenge de l'immunothérapie
  - Que faire en cas de récidive post-adjuvant?
- **Le sous-groupe favorable**
- Données de survie globale avec le BELZUTIFAN
- Transplantation de microbiote fécal
- NIVOLUMAB IPILIMUMAB dans le non à cellules claires

CANCER DU REIN AVANCE

Intérêt des combinaisons ITK + immuno dans population de pronostic favorable

A U.S. Food and Drug Administration–pooled Analysis of Frontline Combination Treatment Survival Benefits by Risk Groups in Metastatic Renal Cell Carcinoma

Daniel Lee [†,], Haley Gittleman [†], Chana Weinstock, Daniel Suzman, Erik Bloomquist, Sundeep Agrawal, Michael Brave, Jamie Brewer, Jaleh Fallah, Harpreet Singh, Shenghui Tang, Amna Ibrahim, Richard Pazdur, Julia A. Beaver, Laleh Amiri-Kordestani*

- Analyse exploratoire poolée incluant les données individuelles des patients inclus dans les 4 essais randomisés de phases 3 ayant permis la validation des combinaisons ITK + immunothérapie en 1ère ligne du carcinome à cellules rénales avancé

Lee et al. Eur Urol 2023

CANCER DU REIN AVANCE

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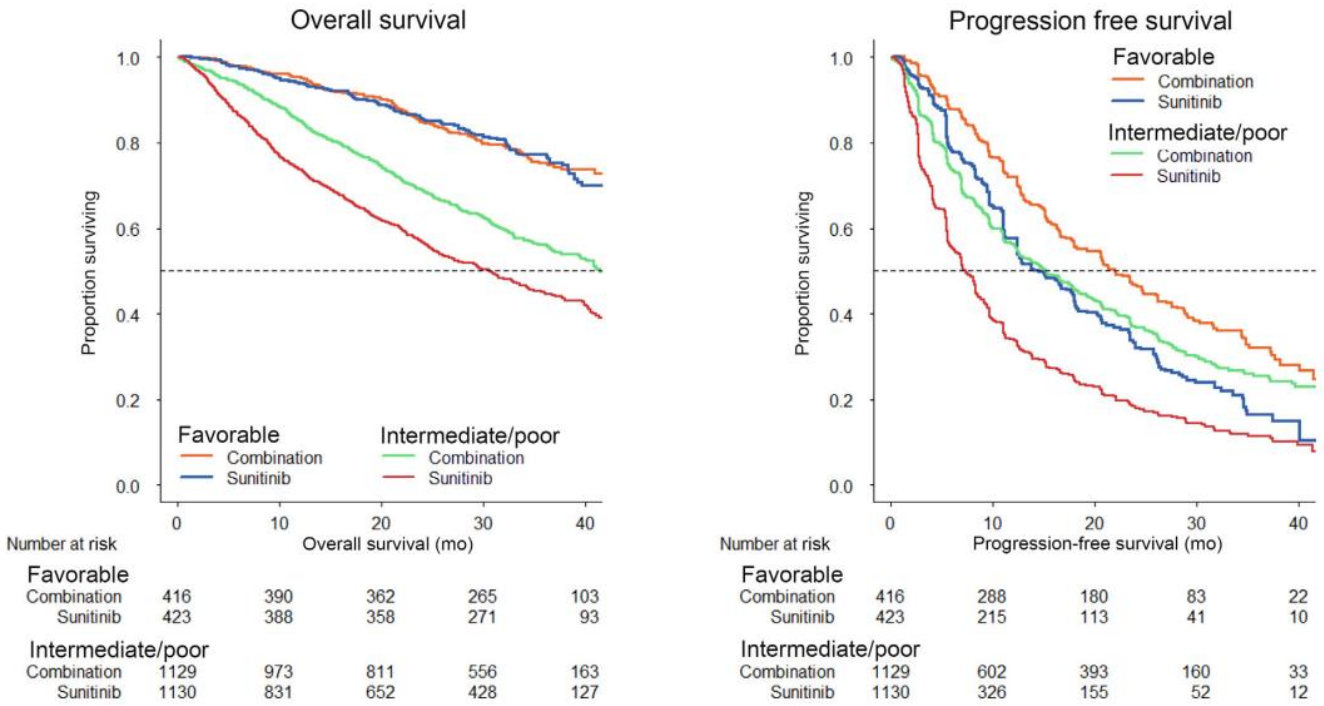

Fig. 2 – (A) OS and (B) PFS from the trials by risk group and treatment. OS = overall survival; PFS = progression-free survival.

Table 3 – Multivariable analyses of selected demographic parameters by risk groups for OS and PFS

Arm	*N*	Deaths	Median[a] (95% CI)	Adjusted[b] HR (95% CI)
OS				
Favorable				
Combination	416	106	NR (46.4, NR)	1.24 (0.86, 1.78)
Sunitinib	423	102	NR (NR, NR)	
Intermediate/poor				
Combination	1,129	483	41.5 (39.5, 45.8)	0.64 (0.55, 0.75)
Sunitinib	1,130	591	30.6 (27.1, 33.6)	
PFS				
Favorable				
Combination	416	235	22.0 (19.3, 26.0)	0.63 (0.50, 0.79)
Sunitinib	423	257	14.5 (12.5, 18.0)	
Intermediate/poor				
Combination	1,129	709	15.2 (13.2, 17.7)	0.52 (0.45, 0.60)
Sunitinib	1,130	785	7.3 (6.9, 8.3)	

CI = confidence interval; HR = hazard ratio; NR = not reported; OS = overall survival; PFS = progression-free survival.
[a] Months.
[b] Adjusted for sex, prior nephrectomy, sarcomatoid component, and stage at diagnosis.

- Il faut noter que le suivi médian dans les essais poolés était de 28 à 34 mois alors que la survie médiane dans la pop° de pronostic favorable dépasse probablement 4 ans

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CANCER DU REIN AVANCE

Question de l'intérêt de la combinaison NIVOLUMAB IPILIMUMAB dans la population favorable

Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 8-year follow-up results of efficacy and safety from the phase III CheckMate 214 trial

N. M. Tannir[1*], L. Albigès[2], D. F. McDermott[3], M. Burotto[4], T. K. Choueiri[5,6], H. J. Hammers[7], P. Barthélémy[8], E. R. Plimack[9], C. Porta[10†], S. George[11], F. Donskov[12,13], M. B. Atkins[14], H. Gurney[15], C. K. Kollmannsberger[16], M.-O. Grimm[17], C. Barrios[18], Y. Tomita[19], D. Castellano[20], V. Grünwald[21], B. I. Rini[22], R. Jiang[23], H. Desilva[24], V. Fedorov[25], C.-W. Lee[26] & R. J. Motzer[27]

- **1096 patients inclus entre octobre 2014 et février 2016.**
- **847 de risque interm/mauvais et 249 de risque favorable**
- Pour cette analyse : base gelée en octobre 2023 : suivi médian de 99,1 mois
- Rappel : **objectifs principaux : OS, PFS et RR (selon revue radiologique indépendante) dans pop° de pronostic intermédiaire ou mauvais**
- Objectifs secondaires : OS, PFS et ORR (selon revue radiologique indépendante) dans population ITT et tolérance
- Objectifs exploratoires : OS, PFS et ORR dans population de risque favorable

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Question de l'intérêt de la combinaison NIVOLUMAB IPILIMUMAB dans la population favorable

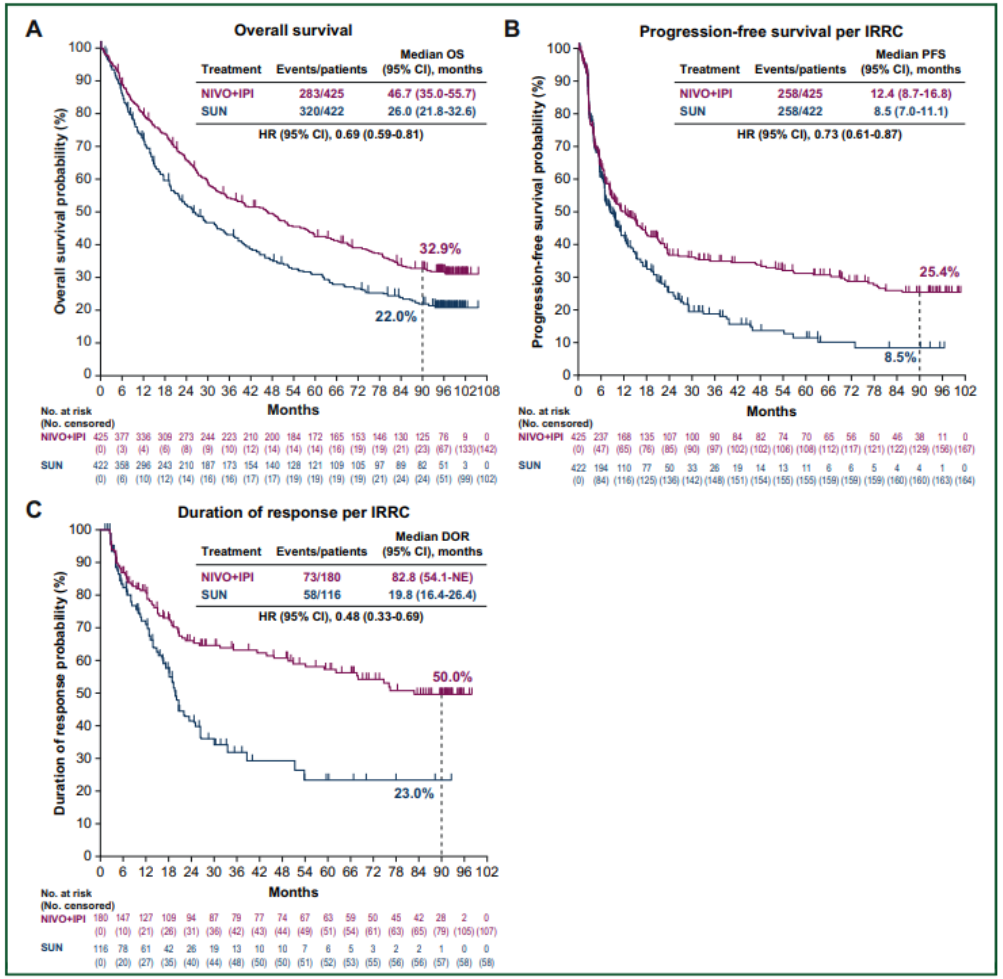

Figure 2. Kaplan–Meier estimates of overall survival (OS), progression-free survival (PFS), and duration of response (DOR) in patients with intermediate/poor risk. NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib. Symbols represent censored observations. Stratified Cox proportional hazards model. The hazard ratio (HR) is NIVO+IPI over SUN. Stratified by the International Metastatic Renal Cell Carcinoma Database Consortium prognostic risk score (0, 1-2, and 3-6) and region (United States, Canada/Western Europe/Northern Europe, rest of world) as entered into the interactive voice-response system. Response was assessed by an independent radiology review committee (IRRC) according to RECIST version 1.1. Two-sided 95% confidence interval (CI) for the median DOR computed by the Brookmeyer and Crowley method (log–log transformation).

- 1096 patients inclus entre octobre 2014 et février 2016.
- 847 de risque interm/mauvais et 249 de risque favorable
- Pour cette analyse : base gelée en octobre 2023 : **suivi médian de 99,1 mois**

- **Population de pronostic intermédiaire/mauvais**
- HR OS 0,69
- HR PFS 0,73
- Durée médiane de réponse 82,8 mois vs 19,8 mois

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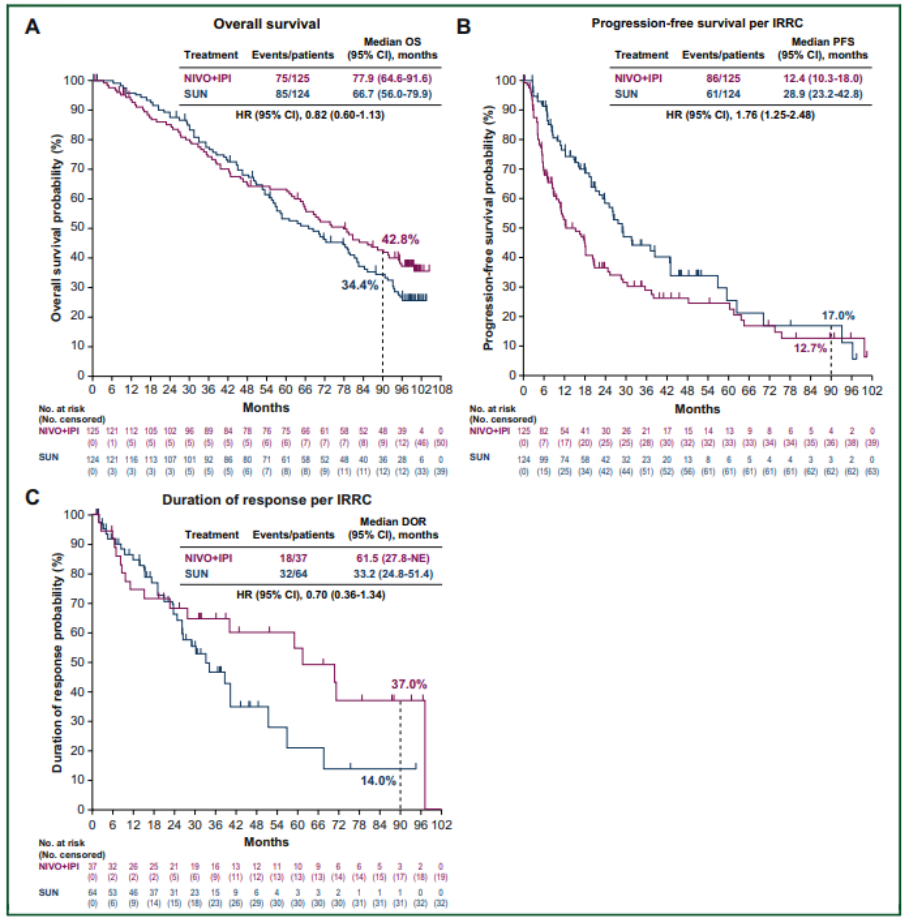
Question de l'intérêt de la combinaison NIVOLUMAB IPILIMUMAB dans la population favorable



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NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib. Symbols represent censored observations. Stratified Cox proportional hazards model. The hazard ratio (HR) is NIVO+IPI over SUN. Stratified by the International Metastatic Renal Cell Carcinoma Database Consortium prognostic risk score (0, 1-2, 3-6) and region (United States, Canada/Western Europe/Northern Europe, rest of world) as entered into the interactive voice-response system. Response was assessed by an independent radiology review committee (IRRC) according to RECIST version 1.1. Two-sided 95% confidence interval (CI) for the median DOR computed by the Brookmeyer and Crowley method (log−log transformation).

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- 847 de risque interm/mauvais et 249 de risque favorable
- Pour cette analyse : base gelée en octobre 2023 : **suivi médian de 99,1 mois**

- **Population de pronostic favorable**
- HR OS 0,82 (HR de 1,45 lors de l'analyse initiale avec suivi médian de 25,2 mois)
- HR PFS 1,76
- Durée médiane de réponse 61,5 mois vs 33,2 mois
- 31 des 75 décès (41,3%) sous IPI NIVO sont survenues dans les 3 premières années, dont 44% n'ont pas reçu de seconde ligne

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Question de l'intérêt de la combinaison NIVOLUMAB IPILIMUMAB dans la population favorable

Table S3. Summary of overall survival (OS) over time in patients with favorable risk

Median follow-up	Median OS (95% CI), months	
	NIVO+IPI (*N* = 125)	SUN (*N* = 124)
25.2 months[1]	NR (NE)	32.9 (NE)
	HR (99.8% CI), 1.45 (0.51-4.12)	
32.4 months[2]	NR (NE)	NR (NE)
	HR (95% CI), 1.22 (0.73-2.04)	
39.3 months[3]	NR (NE)	NR (NE)
	HR (95% CI), 1.19 (0.77-1.85)	
55 months[4]	NR (NE)	NR (56.0-NE)
	HR (95% CI), 0.93 (0.62-1.40)	
67.7 months[5]	74.1 (64.6-74.1)	68.4 (56.7-NE)
	HR (95% CI), 0.94 (0.65-1.37)	
99.1 months	77.9 (64.6-91.6)	66.7 (56.0-79.9)
	HR (95% CI), 0.82 (0.60-1.13)	

NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; NR, not reached; SUN, sunitinib.

- 1096 patients inclus entre octobre 2014 et février 2016.
- 847 de risque interm/mauvais et 249 de risque favorable
- Pour cette analyse : base gelée en octobre 2023 : **suivi médian de 99,1 mois**

- **Population de pronostic favorable**
- HR OS 0,82 (HR de 1,45 lors de l'analyse initiale avec suivi médian de 25,2 mois)

- **Evolution des données de survie globale dans le groupe favorable en fonction du délai de suivi médian**

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Question de l'intérêt de la combinaison NIVOLUMAB IPILIMUMAB dans la population favorable

Table 1. Response per independent radiology review committee (IRRC) using RECIST version 1.1 in the intent-to-treat (ITT) population and by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor and favorable risk

Response assessment	ITT		Intermediate/poor risk		Favorable risk	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (n = 425)	SUN (n = 422)	NIVO+IPI (n = 125)	SUN (n = 124)
Objective response rate, n (%) (95% CI)[a]	217 (39.5) (35.3-43.7)	180 (33.0) (29.0-37.1)	180 (42.4) (37.6-47.2)	116 (27.5) (23.3-32.0)	37 (29.6) (21.8-38.4)	64 (51.6) (42.5-60.7)
Best overall response, n (%)[a]						
Complete response	66 (12.0)	19 (3.5)	50 (11.8)	11 (2.6)	16 (12.8)	8 (6.5)
Partial response	151 (27.5)	161 (29.5)	130 (30.6)	105 (24.9)	21 (16.8)	56 (45.2)
Stable disease	197 (35.8)	230 (42.1)	130 (30.6)	186 (44.1)	67 (53.6)	44 (35.5)
Progressive disease	97 (17.6)	77 (14.1)	82 (19.3)	71 (16.8)	15 (12.0)	6 (4.8)
Unable to determine/not reported	39 (7.1)	59 (10.8)	33 (7.8)	49 (11.6)	6 (4.8)	10 (8.1)
Median time to response (Q1-Q3), months	n = 217 2.8 (2.7-4.0)	n = 180 4.0 (2.8-5.7)	n = 180 2.8 (2.6-3.9)	n = 116 3.1 (2.8-5.5)	n = 37 2.8 (2.7-4.2)	n = 64 4.2 (2.8-7.0)
Ongoing response	n = 217 126 (58.1)	n = 180 90 (50.0)	n = 180 107 (59.4)	n = 116 58 (50.0)	n = 37 19 (51.4)	n = 64 32 (50.0)
Ongoing complete response	n = 66 53 (80.3)	n = 19 17 (89.5)	n = 50 42 (84.0)	n = 11 10 (90.9)	n = 16 11 (68.8)	n = 8 7 (87.5)

Data are n (%) or n/N (%) unless otherwise specified.
CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IRRC, independent radiology review committee; ITT, intent to treat; NIVO+IPI, nivolumab plus ipilimumab; Q, quartile; SUN, sunitinib.
[a]Response assessed by an IRRC according to RECIST version 1.1.

- RR interm/mauvais : 42,4% vs 27,5% (CR 11,8 vs 2,6%)
- **RR favorable 29,6% vs 51,6% (CR 12,8 vs 6,5 %)**

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Question de l'intérêt de la combinaison NIVOLUMAB IPILIMUMAB dans la population favorable

Table 3. Comprehensive safety reporting of immune-mediated adverse events (IMAEs) in all treated patients

Non-endocrine IMAEs and management[a]	NIVO+IPI (n = 547)				
Category[b]	Reported AE	Patients with resolved events[c]	Resolution of the event after IMM[c]	Median time to onset[d]	Median time to resolution[e-g]
	Patients, n	n (%)	No. of patients/total n (%)	Weeks (range)	Weeks (95% CI)
Pneumonitis					
Any grade	28	26/28 (92.9)	24/28 (85.7)	12.7 (1.1-210.3)	4.9 (4.0-6.4)
Grade 3-4	9	8/9 (88.9)	6/9 (66.7)	15.9 (4.9-46.4)	1.3 (0.7-4.4)
Diarrhea/colitis					
Any grade	57	53/57 (93.0)	52/57 (91.2)	7.4 (0.3-274.3)	4.6 (2.7-6.0)
Grade 3-4	27	26/29 (89.7)	25/29 (86.2)	7.7 (0.3-274.3)	2.1 (1.1-5.4)
Hepatitis					
Any grade	42	38/42 (90.5)	38/42 (90.5)	9.9 (2.1-347.3)	6.0 (3.0-7.0)
Grade 3-4	36	33/37 (89.2)	33/37 (89.2)	9.5 (2.1-347.3)	6.1 (4.1-8.0)
Nephritis/renal dysfunction[h]					
Any grade	28	20/28 (71.4)	19/28 (67.9)	13.4 (0.1-147.7)	13.0 (5.3-28.4)
Grade 3-4	10	9/11 (81.8)	7/11 (63.6)	25.3 (5.1-147.7)	4.9 (1.6-15.1)
Rash					
Any grade	104	80/103 (77.7)	74/103 (71.8)	9.1 (0.1-188.9)	13.1 (7.9-24.1)
Grade 3-4	19	18/21 (85.7)	16/21 (76.2)	10.7 (0.1-284.3)	6.0 (2.6-10.1)

Endocrine IMAEs and management[a,i]	NIVO+IPI (n = 547)			
Category[b]	Reported AE	Patients with resolved events[c]	Median time to onset[d]	Median time to resolution[e-g]
	Patients, n	n (%)	Weeks (range)	Weeks (95% CI)
Adrenal insufficiency				
Any grade	40	8/40 (20.0)	15.6 (8.9-157.3)	NR (NE)
Grade 3-4	18	5/18 (27.8)	18.6 (9.0-215.3)	NR (3.4-NE)
Hypothyroidism/thyroiditis				
Any grade	125	46/125 (36.8)	9.6 (0.1-331.3)	NR (NE)
Grade 3-4	4	4/4 (100)	8.8 (4.1-12.0)	4.6 (2.0-NE)
Hypothyroidism				
Any grade	111	36/111 (32.4)	11.9 (0.1-331.3)	NR (NE)
Grade 3-4	3	3/3 (100)	9.3 (8.3-12.0)	3.3 (2.0-NE)
Thyroiditis				
Any grade	18	12/18 (66.7)	4.1 (2.0-20.1)	20.1 (3.1-72.1)
Grade 3-4	1	1/1 (100)	4.1 (4.1-4.1)	12.1 (NE)
Diabetes mellitus				
Any grade	14	2/14 (14.3)	21.7 (2.7-230.0)	NR (NE)
Grade 3-4	6	2/6 (33.3)	17.4 (2.7-45.7)	NR (0.4-NE)
Hyperthyroidism				
Any grade	66	60/66 (90.9)	6.0 (0.9-61.9)	6.6 (5.9-8.0)
Grade 3-4	4	4/4 (100)	3.1 (2.0-11.4)	5.6 (0.9-NE)
Hypophysitis				
Any grade	26	19/26 (73.1)	11.8 (5.6-31.9)	2.7 (0.7-111.3)
Grade 3-4	15	12/15 (80.0)	11.4 (6.7-22.6)	1.3 (0.6-10.1)

- Effets secondaires immunologiques
- Délai médian d'apparition et de résolution (si résolution)

- **Délai médian de résolution non atteint pour insuffisance surrénalienne, hypothyroïdie et diabète**

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY
driving innovation in oncology

SPECIAL ARTICLE

Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

T. Powles[1], L. Albiges[2], A. Bex[3,4,5], E. Comperat[6], V. Grünwald[7], R. Kanesvaran[8], H. Kitamura[9], R. McKay[10], C. Porta[11,12], G. Procopio[13], M. Schmidinger[14], C. Suarez[15], J. Teoh[16], G. de Velasco[17], M. Young[1,18] & S. Gillessen[19,20], on behalf of the ESMO Guidelines Committee*

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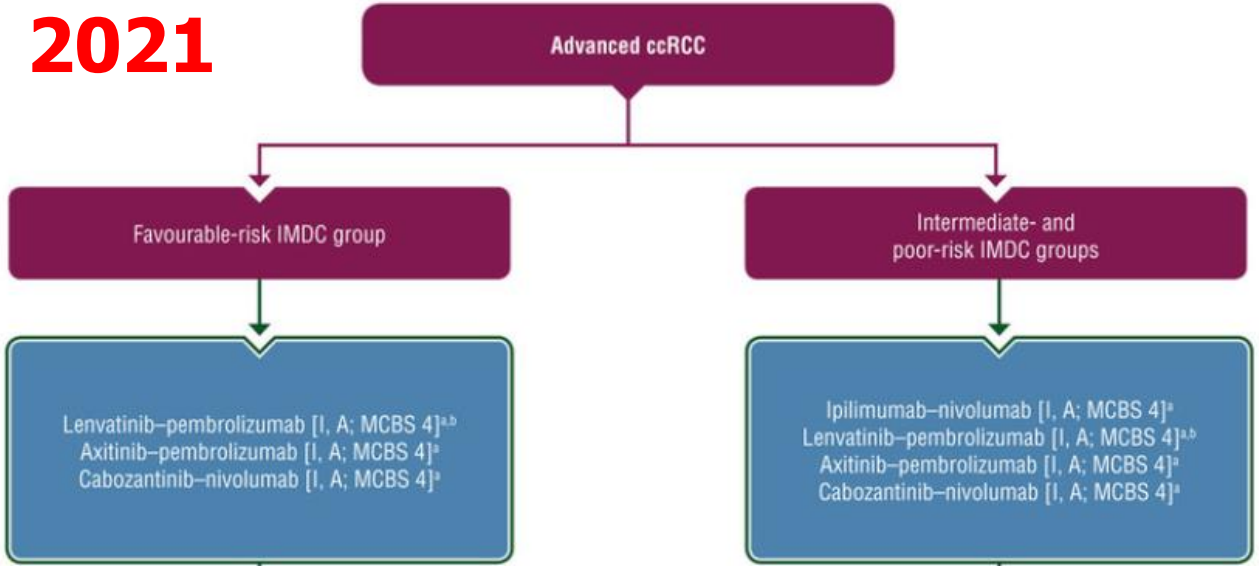
2021



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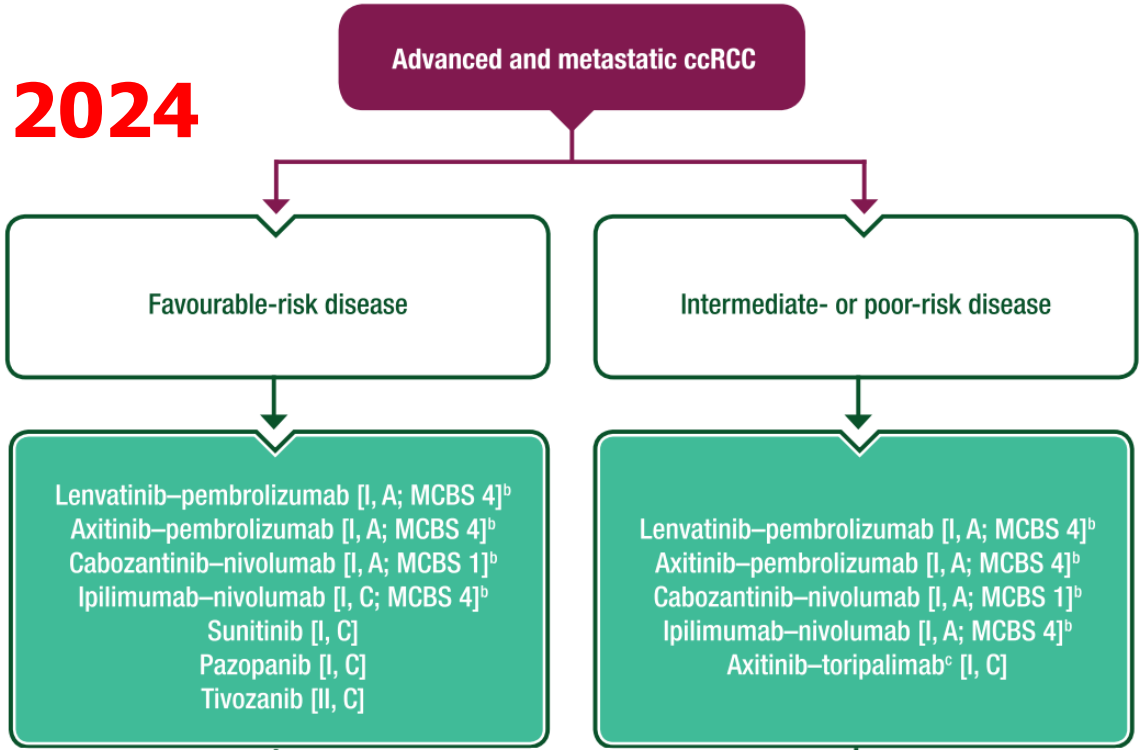

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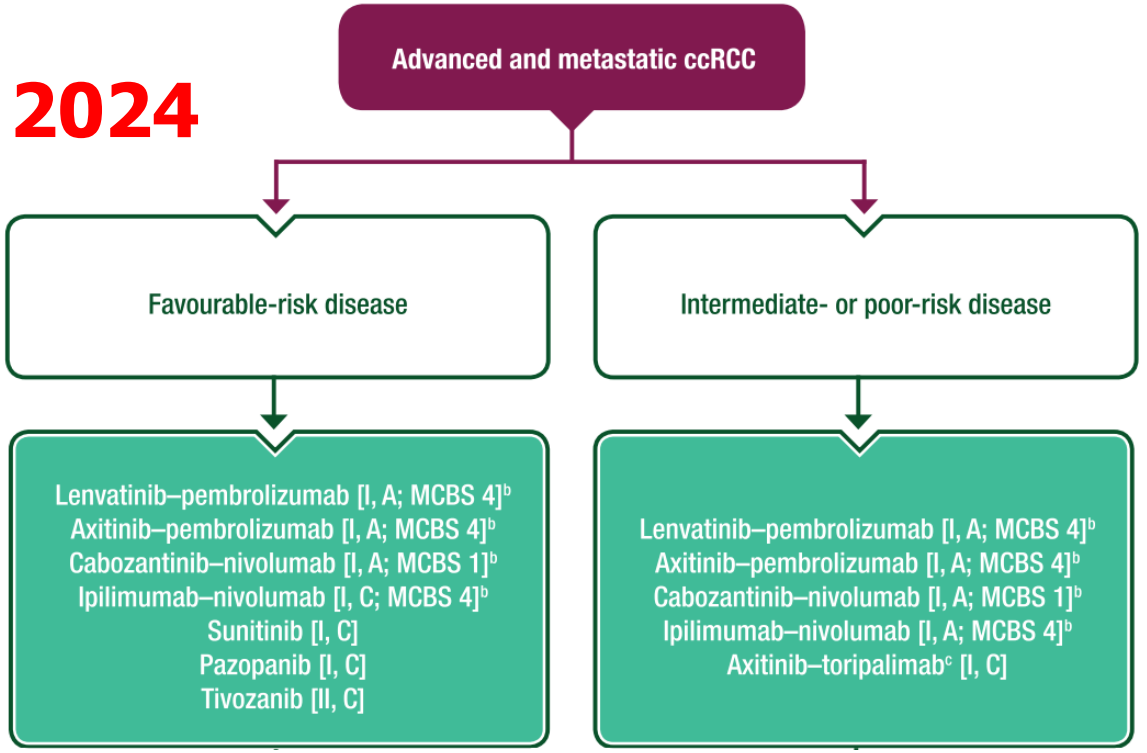
- Pas de position unanime des auteurs pour l'intégration de la combinaison NIVOLUMAB IPILIMUMAB dans les maladies de risque favorable
- En faveur : bénéfice en OS dans la population ITT incluant des patients de risque favorable et les potentielles réponses complètes durables, très rarement observées sous SUNITINIB
- En défaveur : l'absence de bénéfice en survie globale dans ce sous-groupe et des survie sans progression et taux de réponse moins bons que sous SUNITINIB, ainsi que le risque de toxicité sévère ou définitive



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CANCER DU REIN AVANCE

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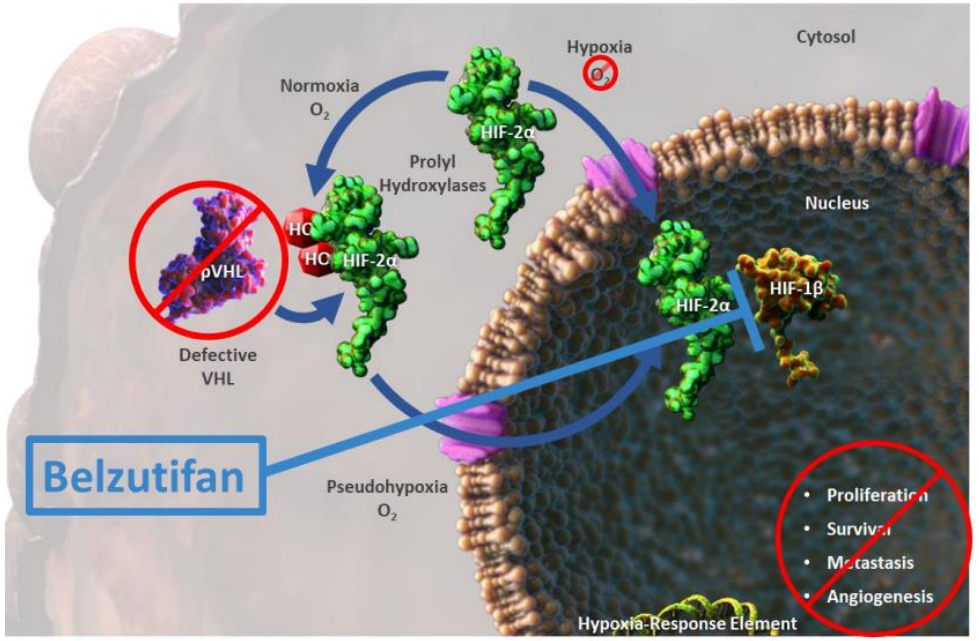
CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN

- Gène VHL perdu dans 90% des carcinomes rénaux à cellules claires
- En condition hypoxique, HIF-2α (Hypoxia-inductible Factor) hétérodimérise pour former un facteur de transcription actif (HIF1) uprégulant des gènes impliqués dans la croissance tumorale dont VEGF et EPO
- Développement de petite molécules empéchant la dimérisation
- Belzutifan (MK-6482) : inhibiteur sélectif de HIF-2α oral



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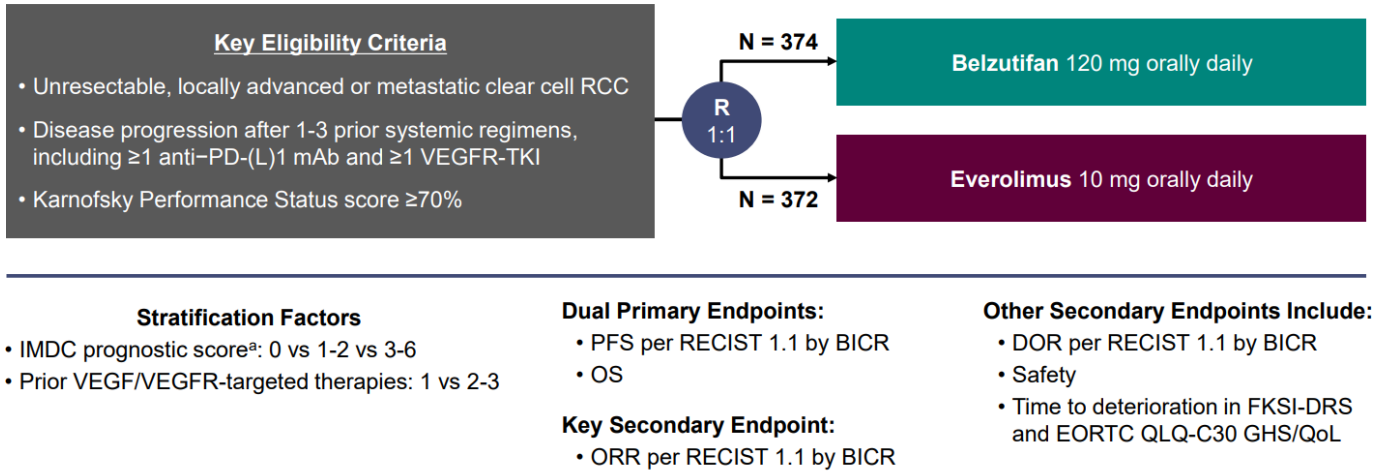
CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3 en monothérapie

Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma

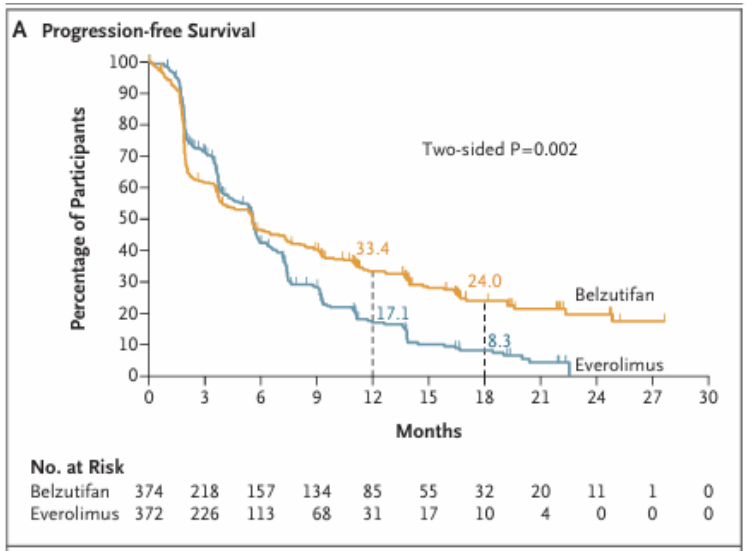
T.K. Choueiri, T. Powles, K. Peltola, G. de Velasco, M. Burotto, C. Suarez, P. Ghatalia, R. Iacovelli, E.T. Lam, E. Verzoni, M. Gümüş, W.M. Stadler, C. Kollmannsberger, B. Melichar, B. Venugopal, M. Gross-Goupil, A. Poprach, M. De Santis, F.A. Schutz, S.H. Park, D.A. Nosov, C. Porta, J.L. Lee, X. Garcia-del-Muro, E. Biscaldi, R. Manneh Kopp, M. Oya, L. He, A. Wang, R.F. Perini, D. Vickery, L. Albiges, and B. Rini, for the LITESPARK-005 Investigators*

LITESPARK-005 Study (NCT04195750)



- 2 objectifs principaux :
  - PFS selon relecture centralisée
  - OS

Choueiri et al. N Engl J Med 2024



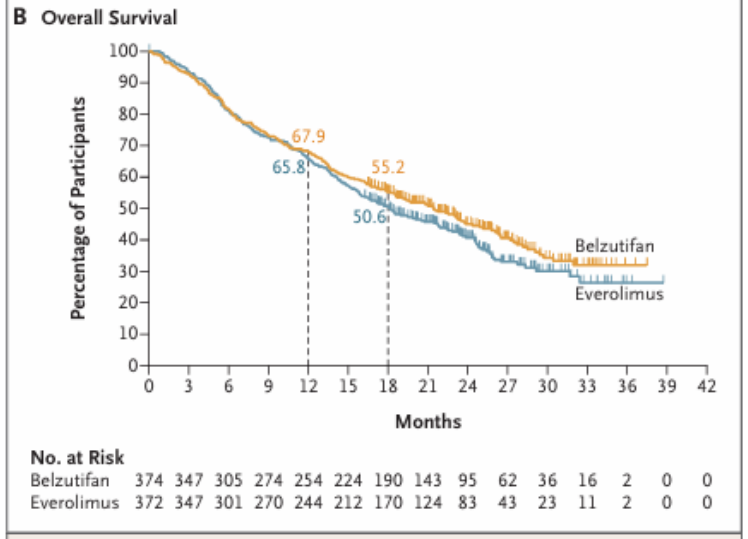


Figure 1. Progression-free Survival and Overall Survival in the Intention-to-Treat Population.

Panel A shows the nonparametric Kaplan–Meier estimates of progression-free survival as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors, version 1.1, at the first interim analysis (the final analysis for this end point). Tick marks indicate data censored at the last time point the participant was known to be alive and without disease progression. Panel B shows the nonparametric Kaplan–Meier estimates of overall survival at the second interim analysis. Tick marks indicate data censored at the last time point the participant was known to be alive.

CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3 en monothérapie

- **746 patients randomisés** entre mars 2020 et janvier 2022
- 43,3% deux lignes antérieures, 42,8% 3 lignes
- Délai médian entre randomisation et seconde analyse intermédiaire **25,7 mois**
- 22,6% toujours sous BELZUTIFAN et 5,0% sous EVEROLIMUS.
- 47,3% et 64,5% de chaque bras ont reçu une autre ligne
- **PFS médiane 5,6 vs 5,6 mois**
- **PFS** 6 mois 46,6% vs 42,5% ; 12 mois 33,4% vs 17,1% ; **18 mois 24,0% vs 8,3%.** P=0,002

- 441 décès lors de la seconde analyse intermédiaire
- **OS médiane 21,4 vs 18,1 mois (HR 0,88 ; p=0,20)**

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3 en monothérapie

Table 2. Best Response in the Intention-to-Treat Population.*

Response	First Interim Analysis			Second Interim Analysis		
	Belzutifan (N=374)	Everolimus (N=372)	Estimated Difference	Belzutifan (N=374)	Everolimus (N=372)	Estimated Difference
Objective response — % (95% CI)	21.9 (17.8–26.5)	3.5 (1.9–5.9)	18.4 (14.0–23.2)†	22.7 (18.6–27.3)	3.5 (1.9–5.9)	19.2 (14.8–24.0)
Confirmed best overall response — no. (%)						
Complete response	10 (2.7)	0		13 (3.5)	0	
Partial response	72 (19.3)	13 (3.5)		72 (19.3)	13 (3.5)	
Stable disease‡	147 (39.3)	245 (65.9)		143 (38.2)	245 (65.9)	
Progressive disease	126 (33.7)	80 (21.5)		127 (34.0)	80 (21.5)	
Not evaluable§	5 (1.3)	8 (2.2)		5 (1.3)	8 (2.2)	
No assessment¶	14 (3.7)	26 (7.0)		14 (3.7)	26 (7.0)	

* The best response was assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1
† P<0.001 for the between-group difference in objective response.
‡ This category includes participants who initiated new anticancer therapy without a documented partial or complete response or disease progression.
§ A response was considered to be not evaluable if the participant had insufficient data for assessment of response according to RECIST, version 1.1.
¶ This category includes participants who did not have a postbaseline assessment at the data cutoff date.

ORR 22,7% vs 3,5%

Durée réponse médiane 19,5 mois vs 13,7 mois

Délai médian réponse 3,8 vs 3,7 mois

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3 en monothérapie

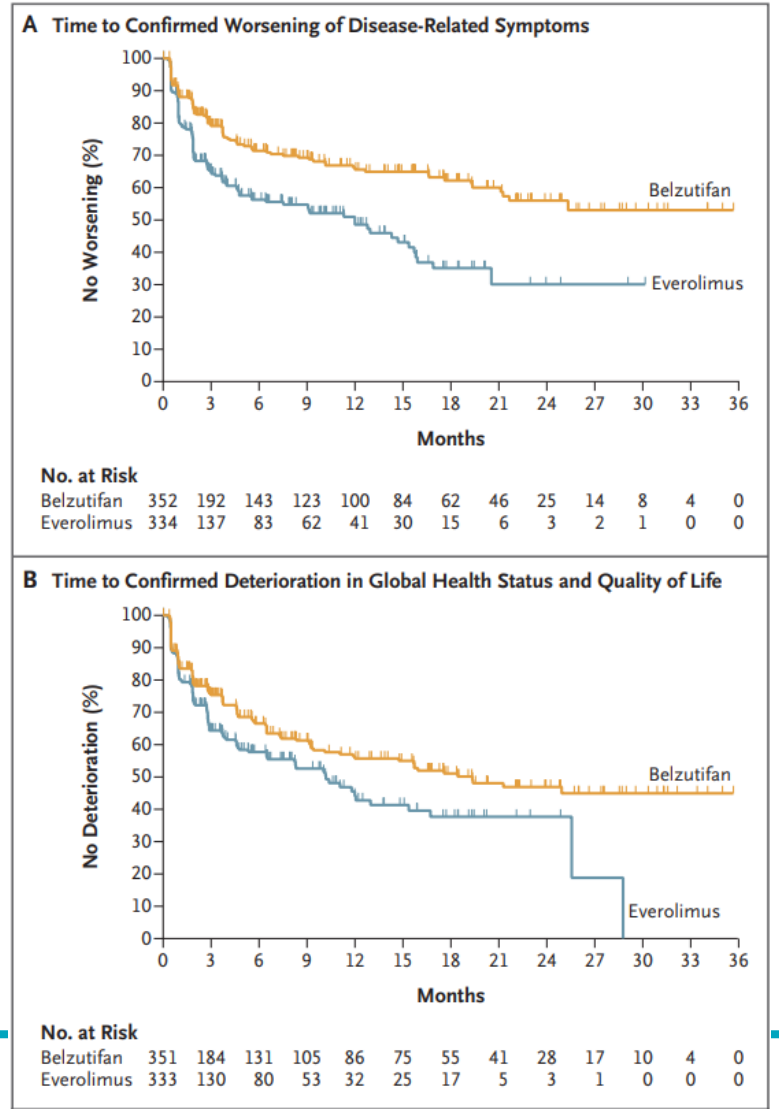

Figure 2. Time to Confirmed Worsening of Symptoms and Deterioration in Global Health Status and Quality of Life.

Panel A shows the nonparametric Kaplan–Meier estimates of the time to confirmed worsening of disease-related symptoms as assessed by Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) score in the participant-reported outcomes full-analysis population at the second interim analysis. The participant-reported outcomes full-analysis population included all participants who underwent randomization and who received at least one dose of trial treatment and completed at least one assessment. Tick marks indicate data censored at the last available FKSI-DRS assessment if the participant was still receiving treatment or if the participant withdrew from the trial without deterioration in symptoms according to FKSI-DRS score. Panel B shows the nonparametric Kaplan–Meier estimates of the time to confirmed deterioration in global health status and quality of life as assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (QLQ-C30) scores in the participant-reported outcomes full-analysis population at the second interim analysis. Tick marks indicate data censored at the last available QLQ-C30 global health status and quality-of-life assessment if the participant was still receiving treatment or withdrew from the trial without deterioration in quality of life according to QLQ-C30 global health status and quality-of-life scores.

- Participant-Reported Outcomes

Délai médian dégradation FKSI-DRS :

NR vs 11,99 mois (HR 0,53)

Délai médian dégradation EORTC QLQ-C30

19,35 vs 10,19 mois (HR 0,75)

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CANCER DU REIN AVANCE

- Stratégie thérapeutique
  - Rechallenge de l'immunothérapie
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- Le sous-groupe favorable
- Données de survie globale avec le BELZUTIFAN
- **Transplantation de microbiote fécal**
- NIVOLUMAB IPILIMUMAB dans le non à cellules claires

CANCER DU REIN AVANCE

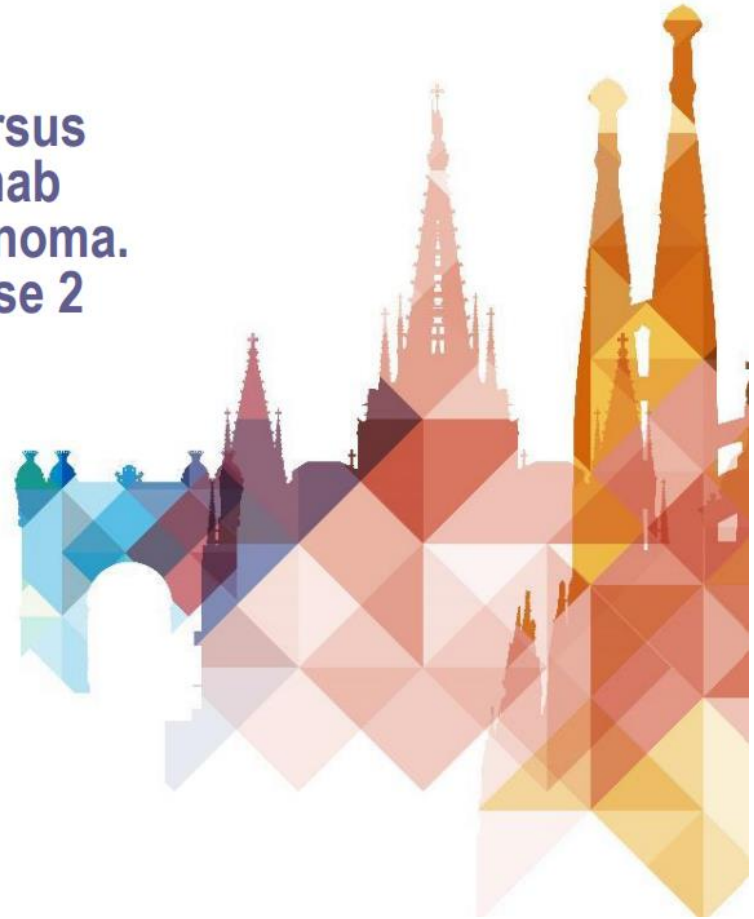
Transplantation de microbiote fécal

BARCELONA 2024 ESMO congress

Fecal microbiota transplantation (FMT) versus placebo in patients receiving pembrolizumab plus axitinib for metastatic renal cell carcinoma. Preliminary results of the randomized phase 2 TACITO trial.

Chiara Ciccarese[1], Serena Porcari[2], Sebastiano Buti[3], Giuseppe Fornarini[4], Giulia Claire Giudice[3], Alessandra Damassi[4], Francesca Primi[5], Julio Rodrigo Giròn Berrios[5], Luciano Stumbo[6], Daniela Arduini[1], Andrea Severino[2], Debora Rondinella[2], Luca Masucci[7], Maurizio Sanguinetti[7], Antonio Gasbarrini[2], Giovanni Cammarota[2], Nicola Segata[8], Giampaolo Tortora[1], Gianluca Ianiro[2], Roberto Iacovelli[1]

1. Department of Medical and Surgical Sciences, Medical Oncology, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 2. Department of Medical and Surgical Sciences, Gastroenterology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; 3. Department of Medicine and Surgery, University of Parma, Parma, Italy; 4. UO Oncologia Medica 1, IRCCS Ospedale Policlinico San Martino, Genova, Italy; 5. Medical Oncology, Central Hospital of Belcolle, Viterbo, Italy; 6. Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy; 7. Microbiology Unit, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 8. Department of Computational, Cellular and Integrative Biology, University of Trento, Trento, Italy.



CANCER DU REIN AVANCE

Transplantation de microbiote fécal

TACITO Study design:

50 Patients
- RCC of any histology
- Measurable disease
- ECOG PS 0-1
- Eligible to axitinib + pembrolizumab

R — 1:1

- **Fecal Microbiota Transplantation (FMT)**
- **Placebo (Pbo)**

Axitinib + pembrolizumab (AxiP) per SOC

FMT/Pbo-1
Within 8 wks from the start of AxiP

Fecal/Pbo transplantation by **colonoscopy.**

FMT/Pbo-2
12 wks after FMT/pbo-1

FMT/Pbo-3
24 wks after FMT/pbo-1

Fecal/Pbo transplantation by frozen **oral capsules.**

Primary endpoint:
The rate of patients free of progression after 1 year from randomization (1y-PFS rate).

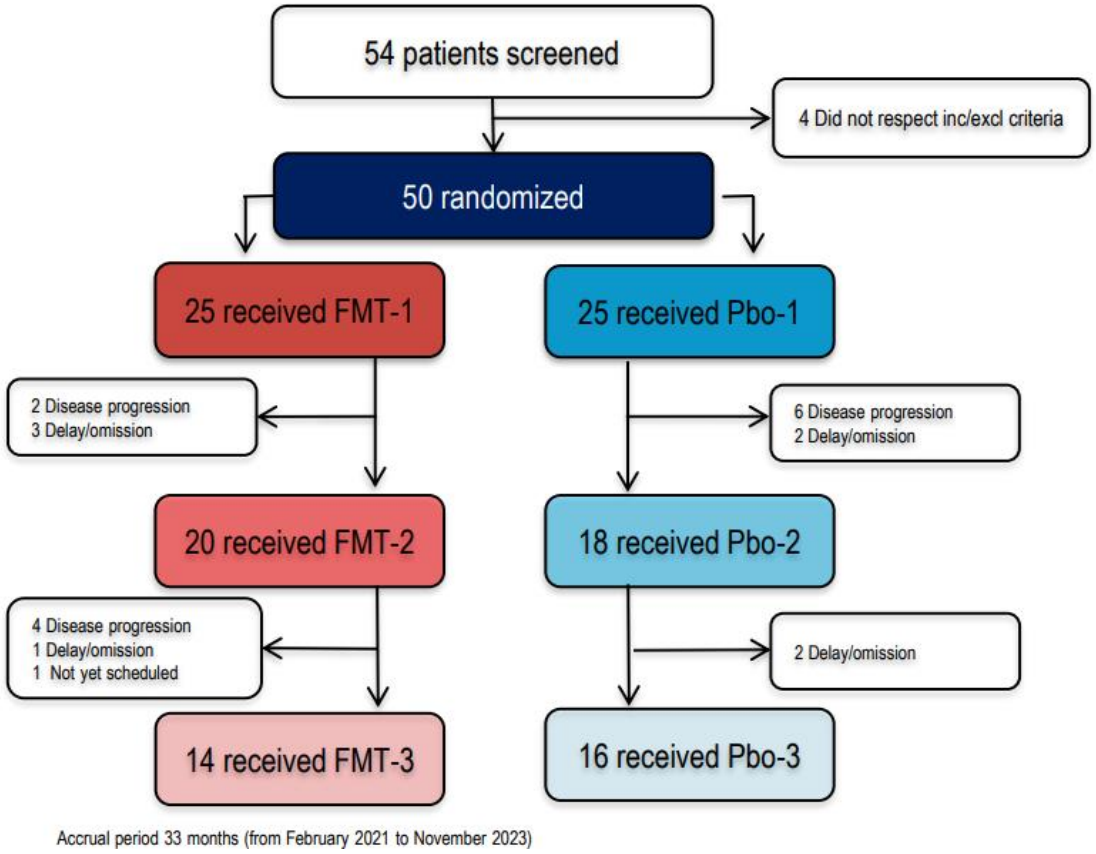
Secondary endpoints:
mPFS, mOS, ORR, safety, microbiota characterization.

FMT/Pbo-1 fecal administration was performed via colonoscopy, by infusing at least 50 g of fresh feces from the donor, within 6 hours of thawing, previously filtered and manually homogenized in 100/200 ml of saline solution, according to international guidelines for frozen stool[1]

CANCER DU REIN AVANCE

Transplantation de microbiote fécal

TACITO patient's flow and baseline characteristics:



Accrual period 33 months (from February 2021 to November 2023)

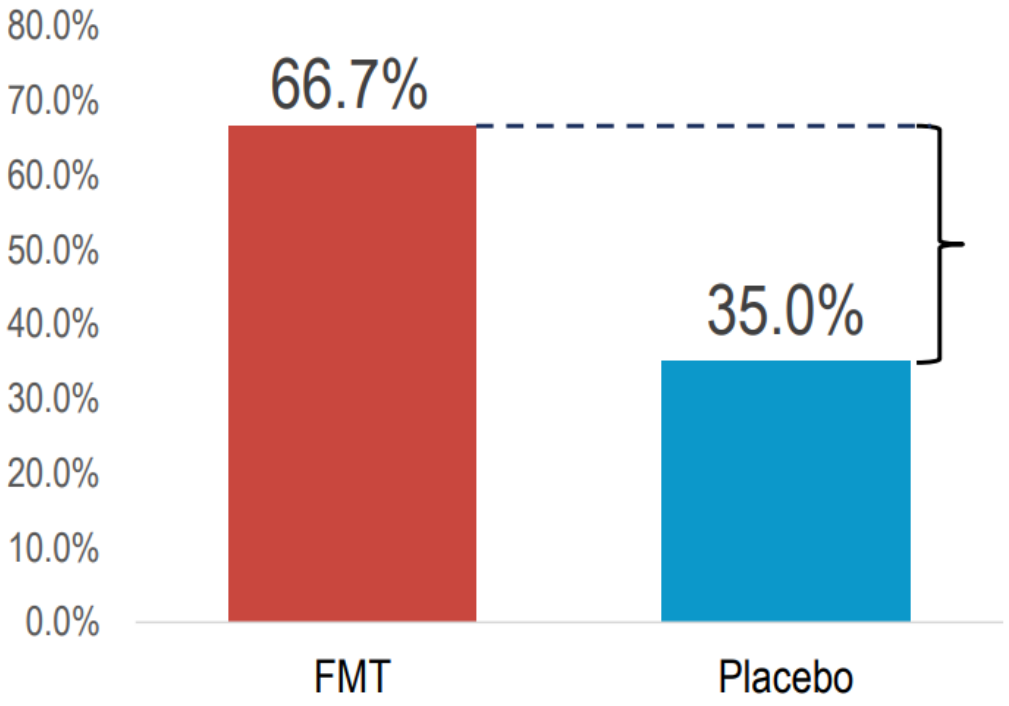
Baseline characteristics	FMT N=25 (%)	Placebo N=25 (%)
Median age (years) (min-max)	61 (47 - 78)	61 (42 - 80)
Male sex	19 (76.0%)	19 (76.0%)
Nephrectomy	14 (56.0%)	16 (64.0%)
Tumor histology		
Clear cell	23 (92.0%)	21 (84%)
Papillary	1 (4%)	3 (12%)
Chromophobe	1 (4%)	1 (4%)
Sites of metastases		
Lung	19 (76.0%)	16 (64.0%)
Lymph node	9 (36.0%)	15 (60.0%)
Bone	7 (28.0%)	6 (24.0%)
Pancreas	6 (24.0%)	2 (8.0%)
Liver	3 (12.0%)	6 (24.0%)
IMDC prognostic class		
Favorable	7 (28.0%)	8 (32.0%)
Intermediate	14 (56.0%)	12 (48.0%)
Poor	4 (16.0%)	5 (20.0%)

CANCER DU REIN AVANCE

Transplantation de microbiote fécal

Primary endpoint

Rate of patients free of progression after 1 year from randomization:



FMT increased the 1-y PFS rate of 31.7% compared to Pbo (p = 0.036)

The primary endpoint was met.

44 patients had ≥12 months of follow-up: 24 (96%) FMT *vs.* 20 (80%) Pbo

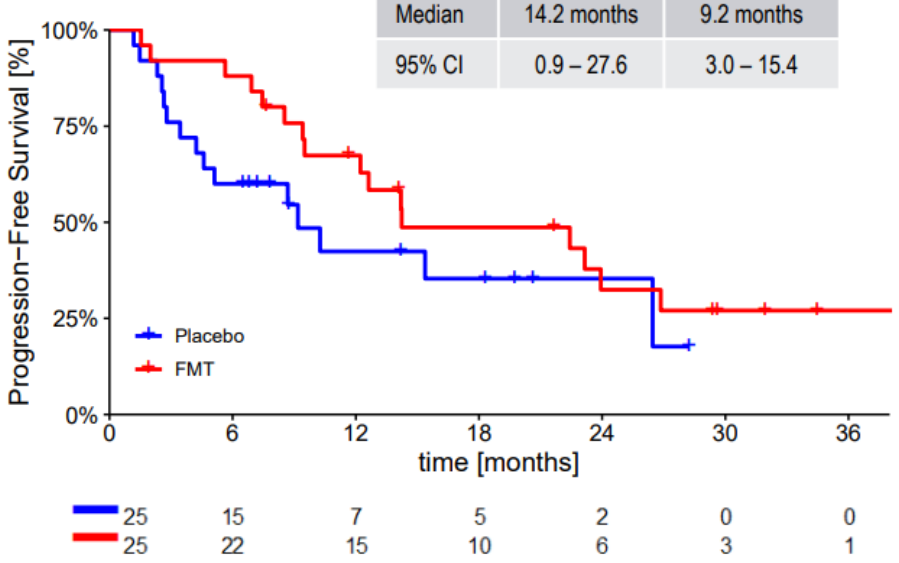
CANCER DU REIN AVANCE

Transplantation de microbiote fécal

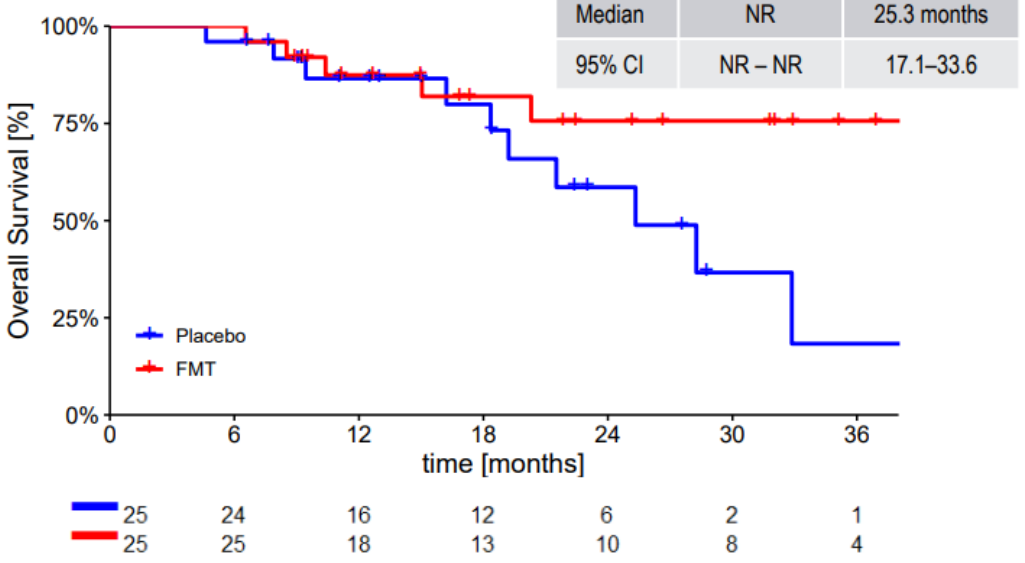
Secondary endpoints

PFS and OS in the overall population:

PFS	FMT N=25	Placebo N=25
Median	14.2 months	9.2 months
95% CI	0.9 – 27.6	3.0 – 15.4



OS	FMT N=25	Placebo N=25
Median	NR	25.3 months
95% CI	NR – NR	17.1–33.6



At cut-off date 16/25 pts progressed in the FMT group and 15/25 in the Pbo group. 5/25 pts in the FMT and 10/25 in the Pbo group died. The median FU value was 28.2 months for PFS and 18.9 months for OS.

CANCER DU REIN AVANCE

- Stratégie thérapeutique
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CANCER DU REIN AVANCE

NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires

BARCELONA 2024 ESMO congress

Prospective Randomised Phase-II Trial of

Ipilimumab/Nivolumab versus Standard of Care in

***non-clear* Renal Cell Cancer**

Results of the SUNNIFORECAST Trial

Lothar Bergmann, Frankfurt, Germany

Marit Ahrens, Laurence Albiges, Marine Gross-Goupil , Ektarini Boleti, Gwenaelle Gravis, Aude Flechon, Marc-Oliver Grimm, Jens Bedke, Philippe Barthelemy, Daniel Castellano, Begona Mellado, Philipp Ivanyi, Anne Flörcken, Cristina Suarez, Pablo Maroto, Viktor Grünwald, Iris Burkholder, Arndt Hartmann, John Haanen

CANCER DU REIN AVANCE

NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires

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SUNNIFORECAST – Study design

Key Inclusion Criteria (KIC)

- Metastatic or locally advanced nccRCC (>50% ncc component):

  nccRCC subtypes: papillary, chromophobe, collecting duct carcinoma (CDC), renal medullary carcinoma (RMC), unclassified, etc., or sarcomatoid*
- No prior systemic therapy for RCC
- Tumor material available
- Measurable disease as per RECIST v1.1
- Karnofski performance status ≥ 70%
- No active CNS metastases

**sarcomatoid is defined for lesions with at least 20% sarcomatoid component*

Follow-up (median, range):
22.3 mos (0.5 – 70.2)

Principal Investigator and Coordinator:
Prof. Dr. L. Bergmann, Med. Klin. II, Goethe University, Frankfurt, Germany

R
1:1

Arm A
Nivolumab 3 mg/kg IV
+ Ipilimumab 1 mg/kg IV q3w
4 times

Followed by
Nivolumab
240 mg flat IV q2w or 480 mg flat q4w

Arm B
Standard of Care agent(s)

- until progression, unacceptable toxicity, or withdrawal of consent
- pts. may be treated beyond progression under protocol-defined circumstances

Stratification

- Histology (papillary vs non-papillary)
- IMDC score

Central pathological review

N=306 pts. (planned)

Primary Endpoint: OS rate at 12 months

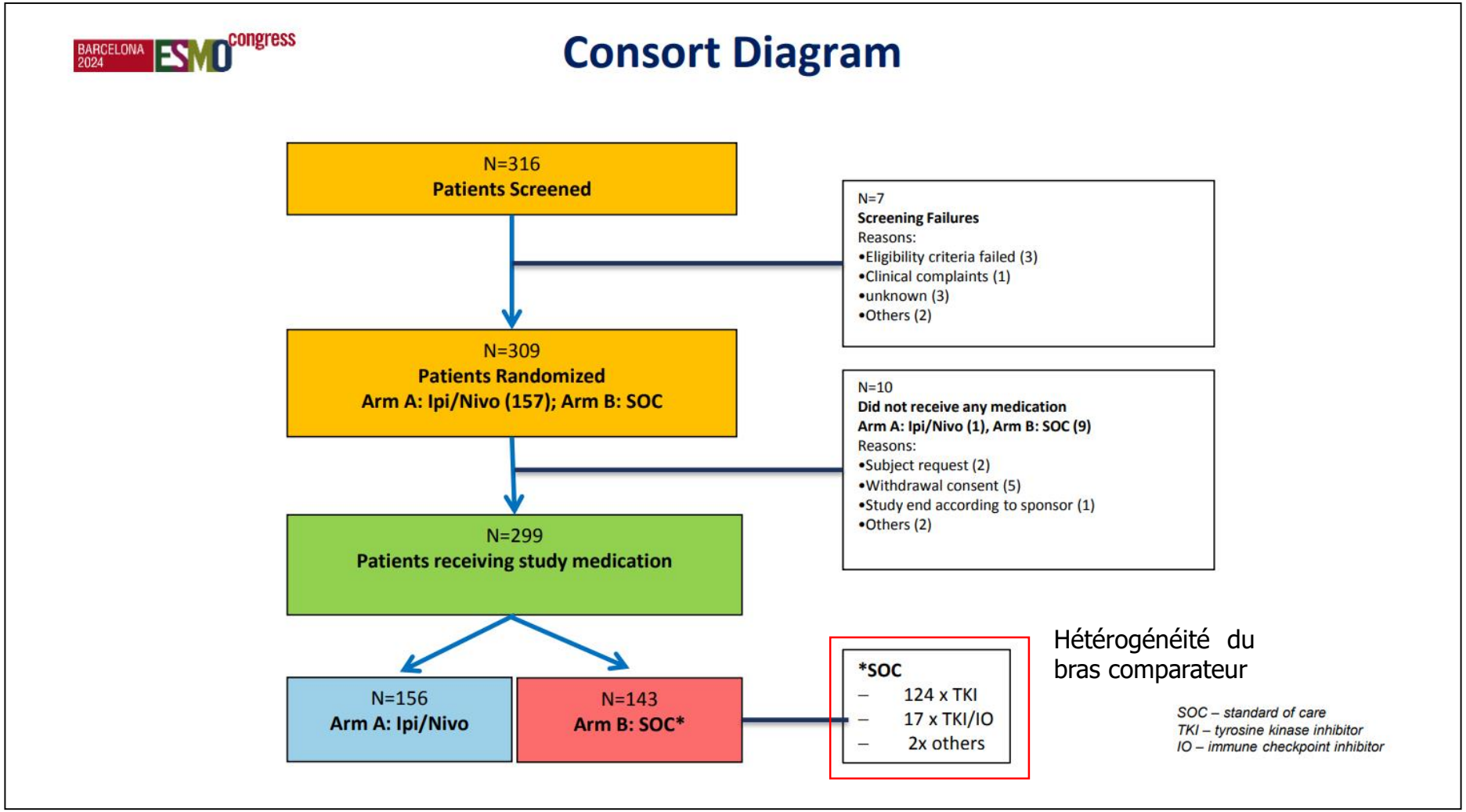
Key Secondary Endpoints: OS, OS-rate at 6 and 18 months; PFS, ORR, TTP, Safety, QoL

Exploratory Endpoints: predictive biomarkers (e.g.PD-L1 expression)

CNS, central nervous system; IV, intravenous; ORR, objective response rate; TTP time to progression; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PO, oral; PS, performance status; R, randomized; RCC, renal cell carcinoma.

CANCER DU REIN AVANCE

NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires



CANCER DU REIN AVANCE

NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires

BARCELONA 2024 ESMO congress

Histological subtypes

According to WHO classification 2022*

Subtypes of nccRCC (central pathological review)	Total N=309	Ipilimumab/Nivolumab N=157	Standard of Care (SOC) N=152	*p-value*
Papillary RCC	178 (57.6 %)	89 (56.7%)	89 (58.6%)	
Chromophobe RCC	60 (19.4 %)	28 (17.8%)	32 (21.2%)	
Renal medullary carcinoma	3 (1.0 %)	0 (0.0%)	3 (2.0%)	
Translocation RCC (TFE, TEFEB)	17 (5.5%)	12 (7.6%)	5 (3.3%)	
Tubulocystic RCC	3 (1.0 %)	3 (1.9%)	0 (0.0%)	
Mucinous tubular and spindle cell carcinoma	1 (0.3 %)	1 (0.6%)	0 (0.0%)	
Sarcomatoid	14 (4.5 %)	8 (5.1%)	6 (3.9%)	*p=0.17*
Ductus Bellini carcinoma	3 (1.0%)	0 (0.0%)	3 (2.0%)	
Others	21 (6.7 %)	11 (7.0%)	10 (6.6%)	

Population hétérogène

** Moch H, Amin MB, Berney DM, et al. The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2022 Nov;82(5):458-468.*

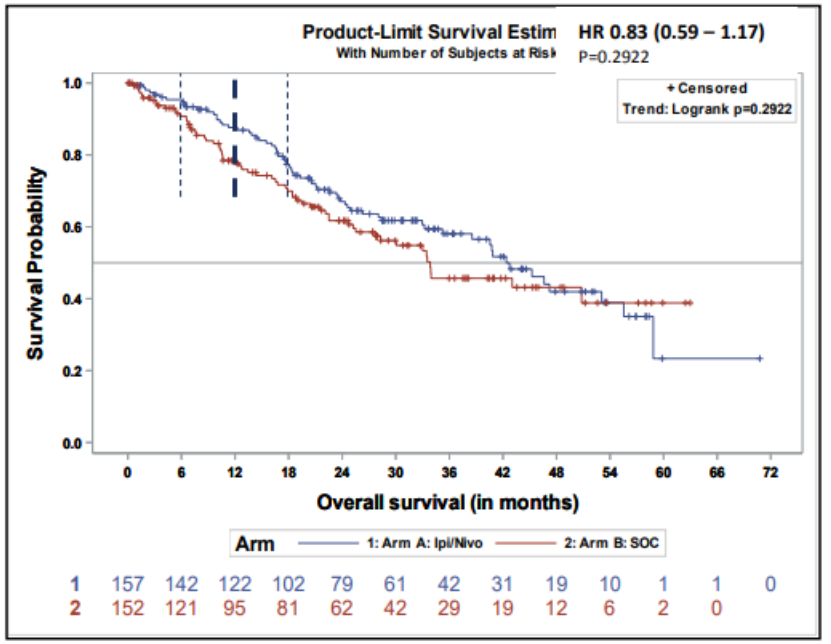
CANCER DU REIN AVANCE

NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires

BARCELONA 2024 ESMO congress

Overall survival rate and OS

	Total N=309	Ipilimumab/ Nivolumab N=157	Standard of Care (SOC) N=152	*p-value*
OS rate at 12 mos (95%-CI)	**82.5%** (77.46% - 86.46%)	**86.9%** (80.24% - 91.46%)	**76.8%** (68.62% - 83.09%)	***p=0.0141***
OS rate at 6 mos (95%-CI)	92.8% (95.27% - 2.83%)	94.7% (89.72% - 97.32%)	90.0% (83.75% - 93.98%)	*p=0.067*
OS rate at 18 mos (95%-CI)	73.4% (67.67% - 78.28%)	76.6% (68.69% - 82.79%)	69.1% (60.25% - 76.34%)	*p=0.084*
OS mos (median, 95%-CI)	40.8 (33.2 - 47.21)	42.4 (35.24 – 55.54)	33.9 (25.52 – *)	*p=0.292*

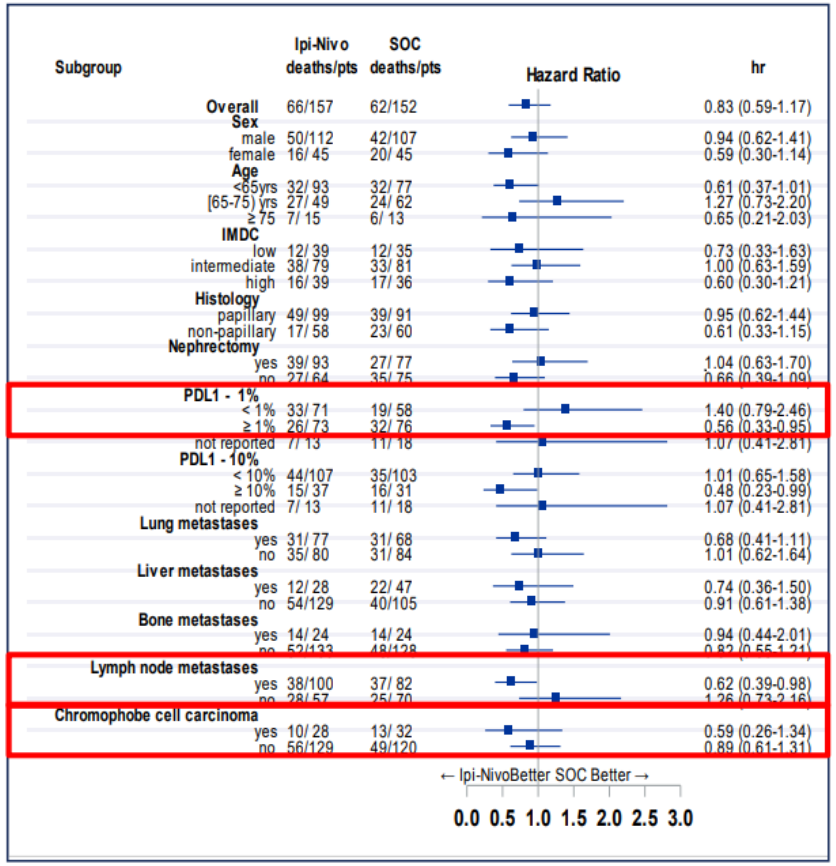


Median follow-up: 24.3 mos (0.5 -70.2)

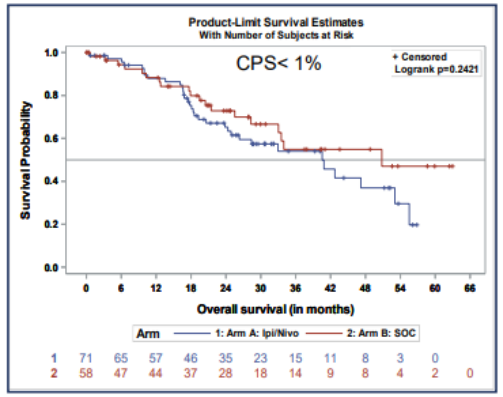
CANCER DU REIN AVANCE

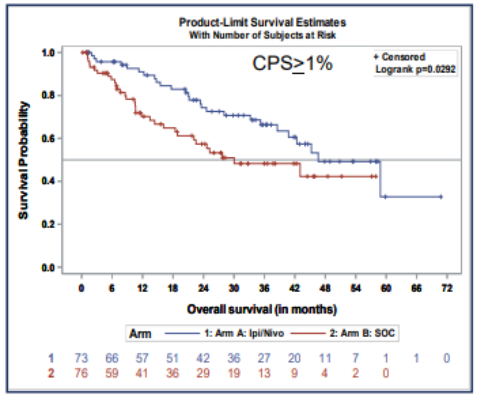
NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires

Forest Plot for OS



PDL1 and OS





Baseline PDL1 CPS (OS – Univariate Cox regression)	NIVO/IPI	SOC	HR	p-value
< 1%	33/71	19/58	1.40 (0.79-2.46)	*p=0.244*
≥ 1 %	26/73	32/76	0.56 (0.33-0.95)	*p=0.031*
not reported	7/13	11/18	1.07 (0.41-2.81)	*p=0.884*

CANCER DU REIN AVANCE

NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires

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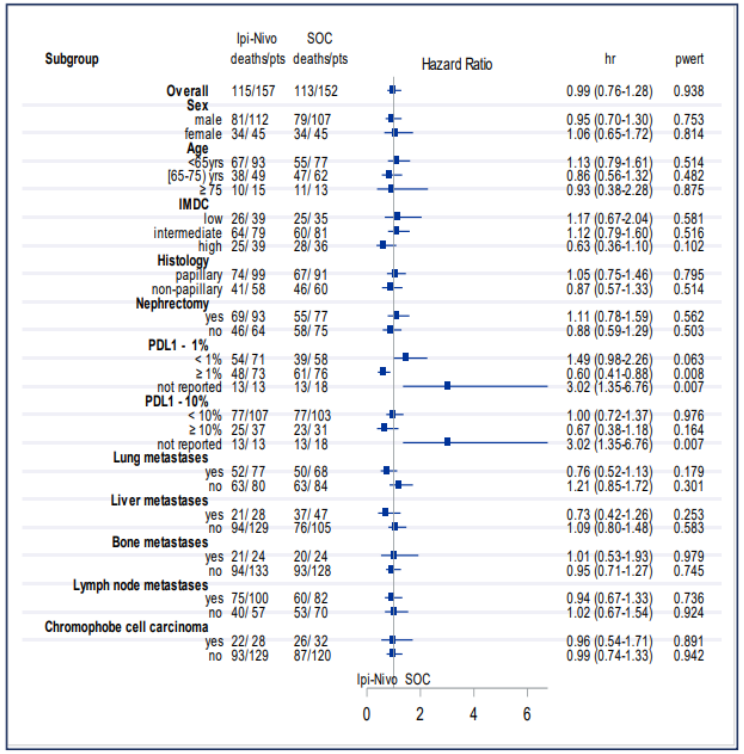
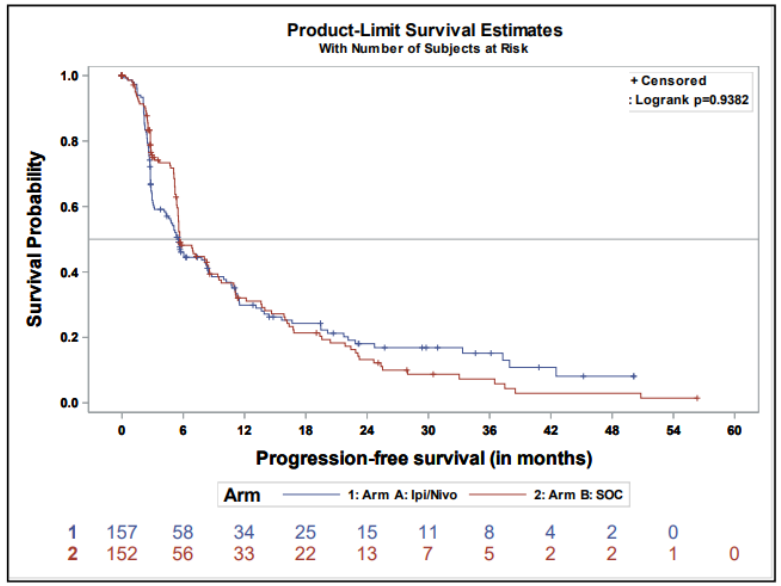
Progression-free survival

Forest Plot for PFS





	IPI/Nivo	SOC
PFS mos.	5.52	5.65
(median, range)	4.30 – 8.23	5.49 – 8.46
	HR 0.99 (0.76-1.18)	

CANCER DU REIN AVANCE

NIVOLUMAB IPILUMAB dans le carcinome rénal non à cellules claires

Overall Response

Histology	Treatment	CR	PR	ORR	SD	PD
all nccRCC (N=247*)	Nivo/Ipi	10 (8.0%)	31 (24.8%)	41 (32.8%)	41 (32.8%)	43 (34.4%)
	SOC	2 (1.6%)	22 (18.0%)	124 (19.6%)	75 (61.5%)	23 (18.9%)
	p=0.001					

CANCER DU REIN AVANCE

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CANCER DU REIN AVANCE

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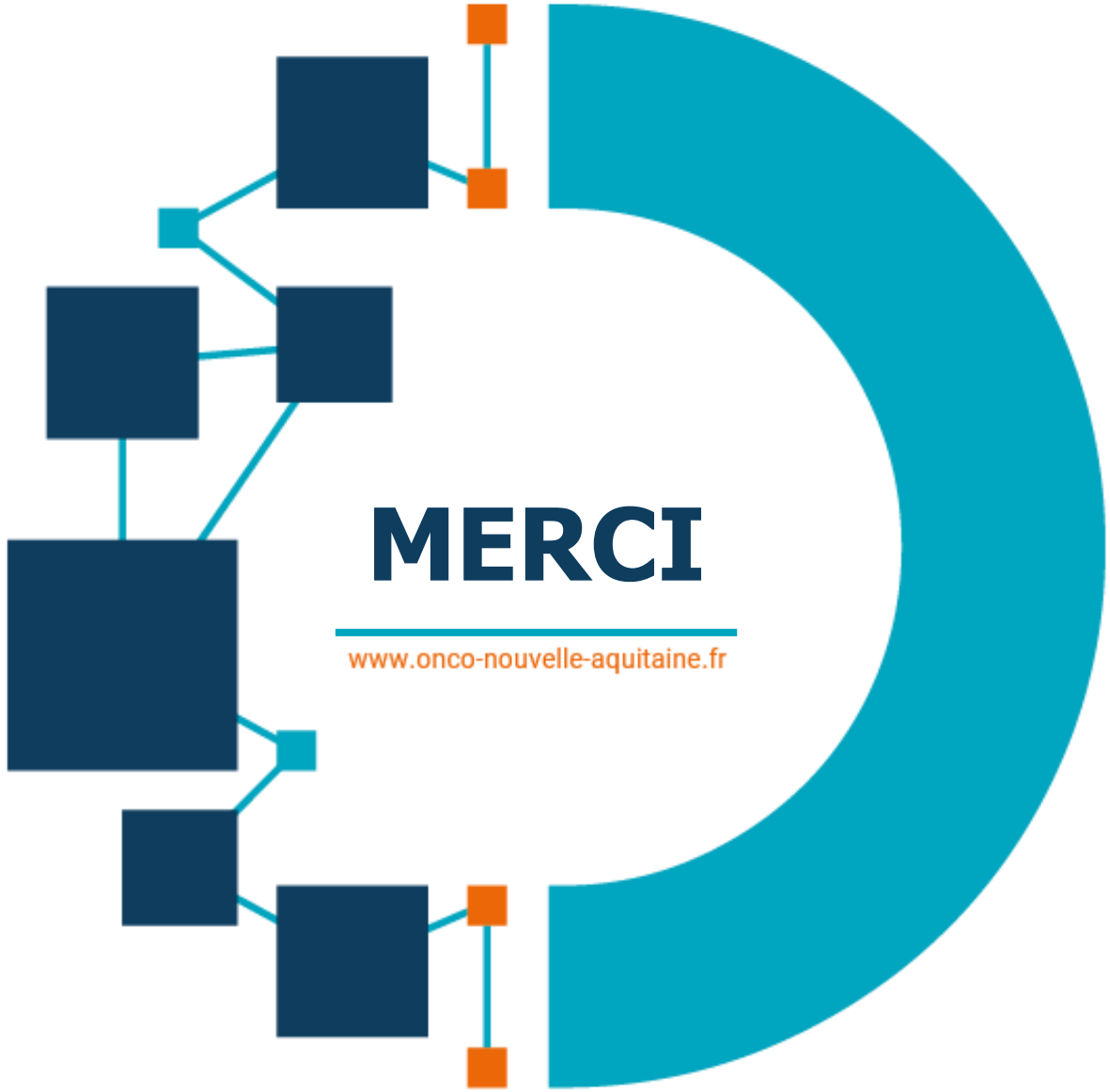
- NIVOLUMAB IPILIMUMAB dans le non à cellules claires

AVEZ-VOUS DES QUESTIONS ?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