SESSION CHIRURGIE ONCOLOGIE UROLOGIQUE DU REIN

06 décembre 2023

Niort

Aurélien FORGUES – Urologue (CH Saintes)

Patrick BOUCHAERT – Oncologue Médical (CHU, Poitiers)

Liens d’intérêts

- Patrick BOUCHAERT
  - ASTELLAS, BAYER, BMS, DAIICHI SANKYO, IPSEN, JANSSEN

CANCER DU REIN AVANCE

- Traitements systémiques de première ligne validés
  - Mise à jour des données de suivi
  - La question du sous-groupe de pronostic favorable
  - La question du « plateau »

- Intérêt de la poursuite de l'immunothérapie à la progression/rechallenge

- Données avec le BELZUTIFAN

CANCER DU REIN AVANCE

- **Traitements systémiques de première ligne validés**
  - Mise à jour des données de suivi
  - La question du sous-groupe de pronostic favorable
  - La question du « plateau »

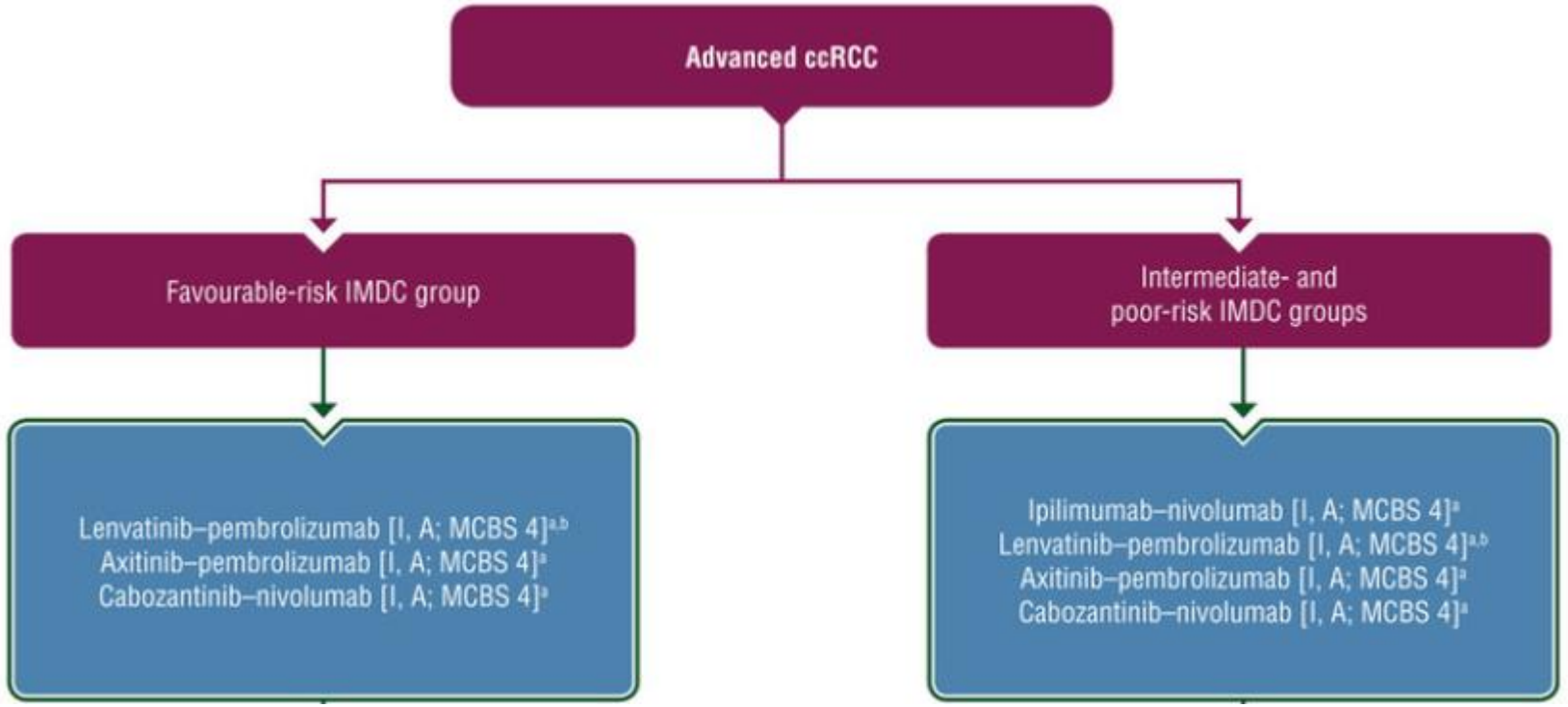
- Intérêt de la poursuite de l'immunothérapie à la progression/rechallenge

- Données avec le BELZUTIFAN

CANCER DU REIN METASTATIQUE

Cellules claires : Standards en première ligne

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

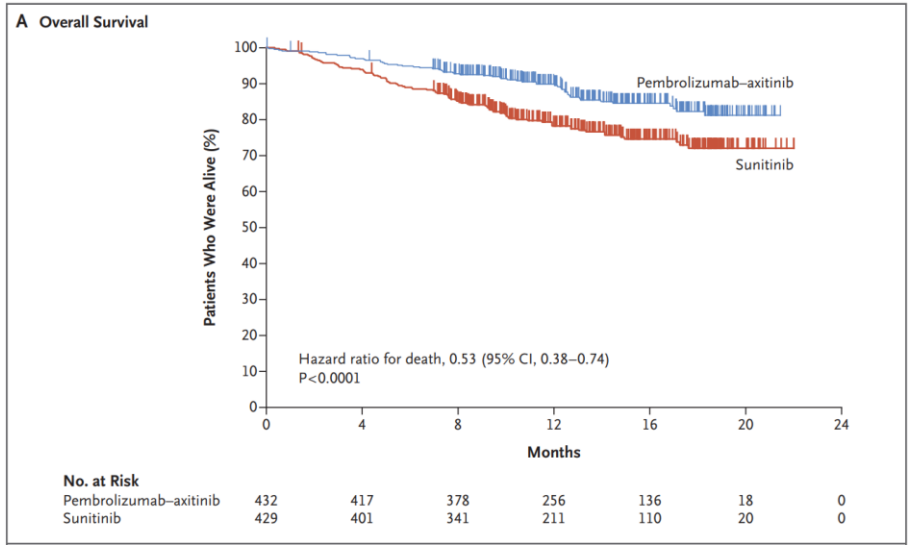


CANCER DU REIN METASTATIQUE

Données de suivi : KEYNOTE-426

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

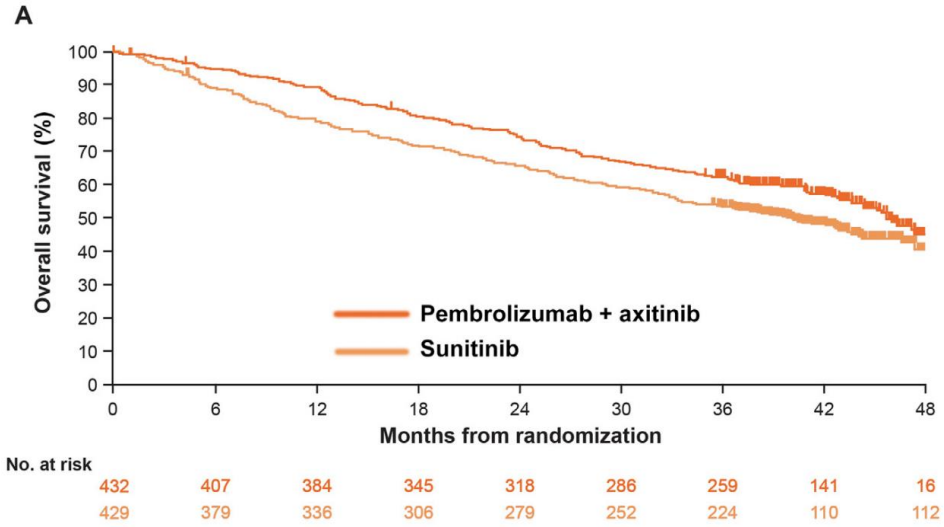
B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*



- Suivi médian 12,8 mois
- HR 0,53

Pembrolizumab Plus Axitinib Versus Sunitinib as First-line Treatment of Advanced Renal Cell Carcinoma: 43-month Follow-up of the Phase 3 KEYNOTE-426 Study

Elizabeth R. Plimack[a,], Thomas Powles[b,c], Viktor Stus[d], Rustem Gafanov[e], Dmitry Nosov[f], Tom Waddell[g], Boris Alekseev[h], Frédéric Pouliot[i], Bohuslav Melichar[j], Denis Soulières[k], Delphine Borchiellini[l], Raymond S. McDermott[m], Ihor Vynnychenko[n], Yen-Hwa Chang[o], Satoshi Tamada[p], Michael B. Atkins[q], Chenxiang Li[r], Rodolfo Perini[r], L. Rhoda Molife[s], Jens Bedke[t], Brian I. Rini[u]*



- Suivi médian 43 mois
- HR 0,73

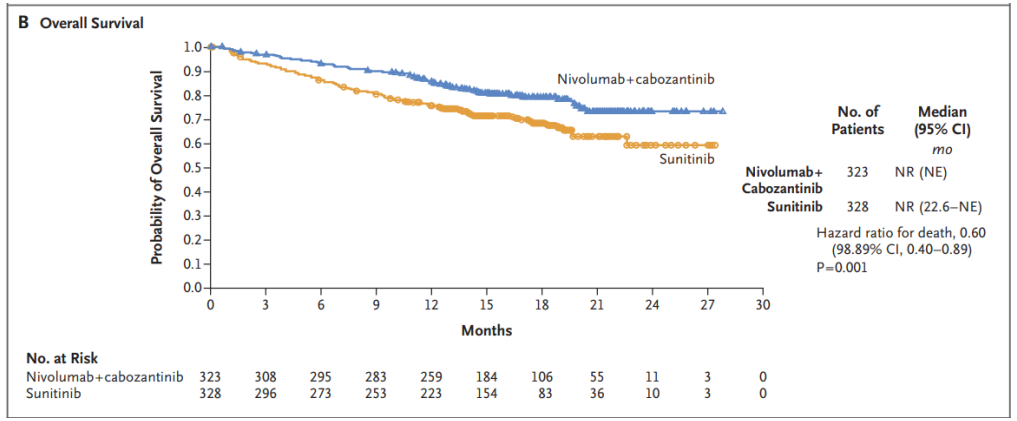
Rini et al. N Engl J Med 2019
Plimack et al. Eur Urol 2023

CANCER DU REIN METASTATIQUE

Données de suivi : CheckMate 9ER

Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

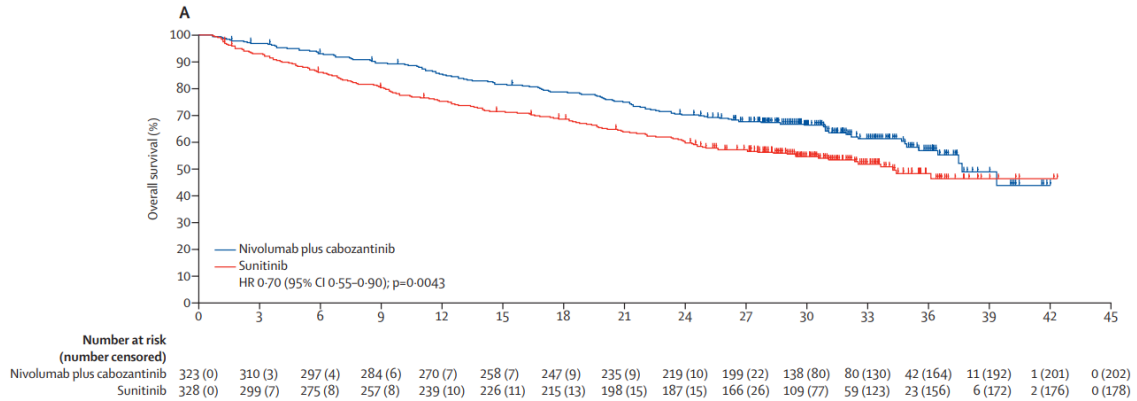
T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V.M. Oyervides Juárez, J.J. Hsieh, U. Basso, A.Y. Shah, C. Suárez, A. Hamzaj, J.C. Goh, C. Barrios, M. Richardet, C. Porta, R. Kowalyszyn, J.P. Feregrino, J. Żołnierek, D. Pook, E.R. Kessler, Y. Tomita, R. Mizuno, J. Bedke, J. Zhang, M.A. Maurer, B. Simsek, F. Ejzykowicz, G.M. Schwab, A.B. Apolo, and R.J. Motzer, for the CheckMate 9ER Investigators*



- Suivi médian 18,1 mois
- HR 0,60

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial

Robert J Motzer, Thomas Powles, Mauricio Burotto, Bernard Escudier, Maria T Bourlon, Amishi Y Shah, Cristina Suárez, Alketa Hamzaj, Camillo Porta, Christopher M Hocking, Elizabeth R Kessler, Howard Gurney, Yoshihiko Tomita, Jens Bedke, Joshua Zhang, Burcin Simsek, Christian Scheffold, Andrea B Apolo, Toni K Choueiri



- Suivi médian 32,9 mois
- HR 0,70

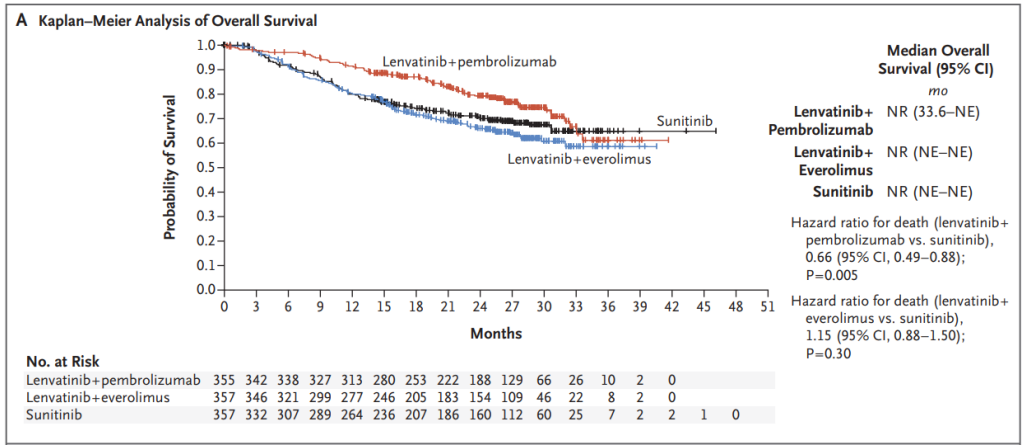
Choueiri et al. N Engl J Med 2021
Motzer et al. Lancet Oncol 2022

CANCER DU REIN METASTATIQUE

Données de suivi : CLEAR

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

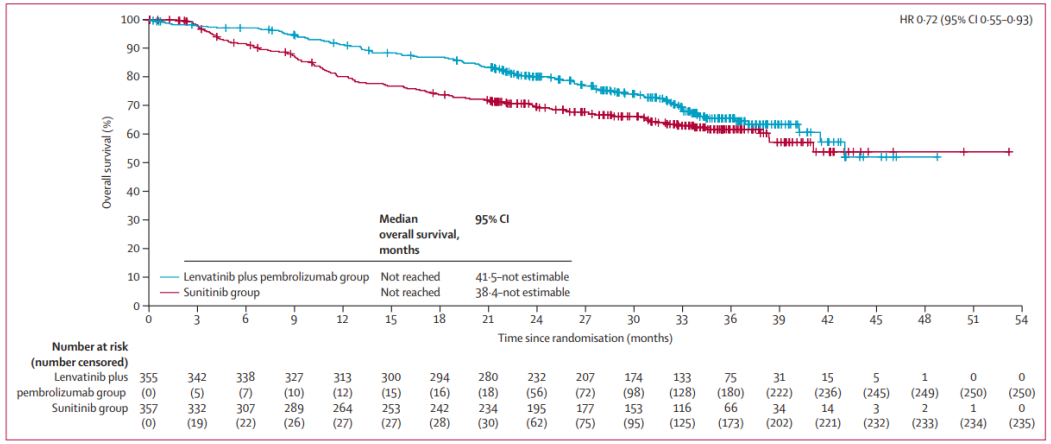
R. Motzer, B. Alekseev, S.-Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.-H. Hong, A. Kapoor, T. Alonso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A.D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*



- Suivi médian 26,6 mois
- HR (LENVA-PEMBRO vs SUNI) 0,66
- HR (LENVA-EVE vs SUNI) 1,15

Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study

Toni K Choueiri, Masatoshi Eto, Robert Motzer, Ugo De Giorgi, Tomas Buchler, Naveen S Basappa, María José Méndez-Vidal, Sergei Tjulandin, Se Hoon Park, Bohuslav Melichar, Thomas Hutson, Carlos Alemany, Bradley McGregor, Thomas Powles, Viktor Grünwald, Boris Alekseev, Sun Young Rha, Evgeny Kopyltsov, Anil Kapoor, Teresa Alonso Gordoa, Jeffrey C Goh, Michael Staehler, Jaime R Merchan, Ran Xie, Rodolfo F Perini, Kalgi Mody, Jodi McKenzie, Camillo G Porta



- Suivi médian 33,7 mois
- HR (LENVA-PEMBRO vs SUNI) 0,72

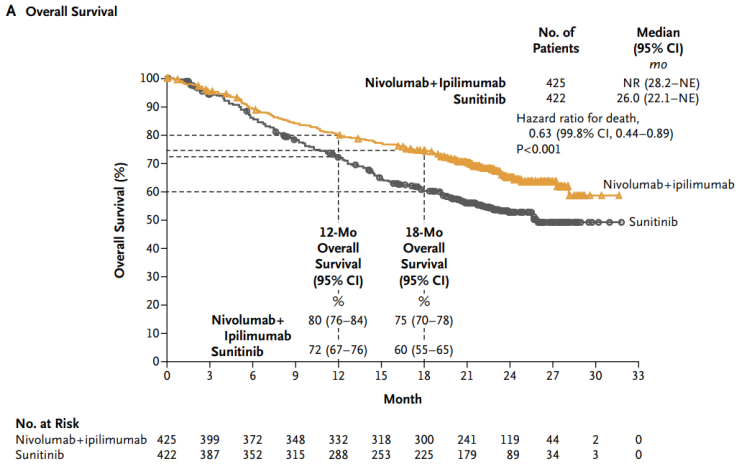
Motzer et al. N Engl J Med 2021
Choueiri et al. Lancet Oncol 2023

CANCER DU REIN METASTATIQUE

Données de suivi : CheckMate 214

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

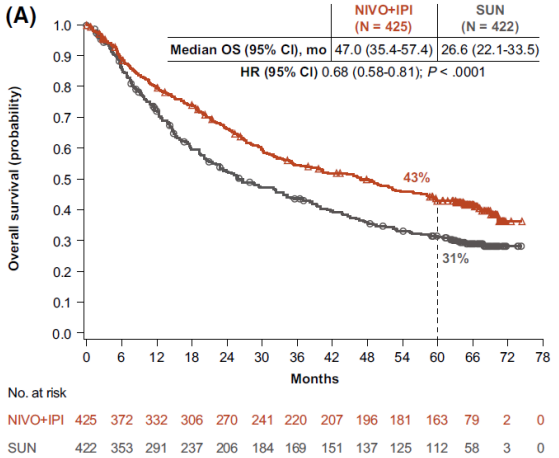
R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*



- Population de pronostic intermédiaire ou mauvais
- Suivi médian 25,2 mois
- HR 0,63

Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma

Robert J. Motzer, MD[1]; David F. McDermott, MD[2]; Bernard Escudier, MD[3]; Mauricio Burotto, MD[4]; Toni K. Choueiri, MD[5]; Hans J. Hammers, MD, PhD[6]; Philippe Barthélémy, MD, PhD[7]; Elizabeth R. Plimack, MD[8]; Camillo Porta, MD[9]; Saby George, MD[10]; Thomas Powles, MD[11]; Frede Donskov, MD, PhD[12]; Howard Gurney, MD[13]; Christian K. Kollmannsberger, MD[14]; Marc-Oliver Grimm, MD[15]; Carlos Barrios, MD[16]; Yoshihiko Tomita, MD, PhD[17]; Daniel Castellano, MD[18]; Viktor Grünwald, MD, PhD[19]; Brian I. Rini, MD[20]; M. Brent McHenry, PhD[21]; Chung-Wei Lee, MD, PhD[22]; Jennifer McCarthy, MA[23]; Flavia Ejzykowicz, PhD[24]; and Nizar M. Tannir, MD[25]



- Pronostic intermédiaire ou mauvais
- Suivi médian 67,7 mois
- HR 0,68

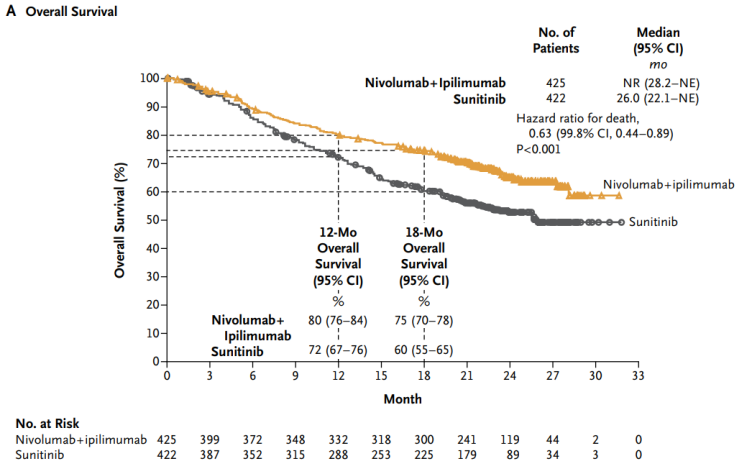
Motzer et al. N Engl J Med 2018
Motzer et al. Cancer 2022

CANCER DU REIN METASTATIQUE

Données de suivi : CheckMate 214

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*



- Population de pronostic intermédiaire ou mauvais
- Suivi médian 25,2 mois
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Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma

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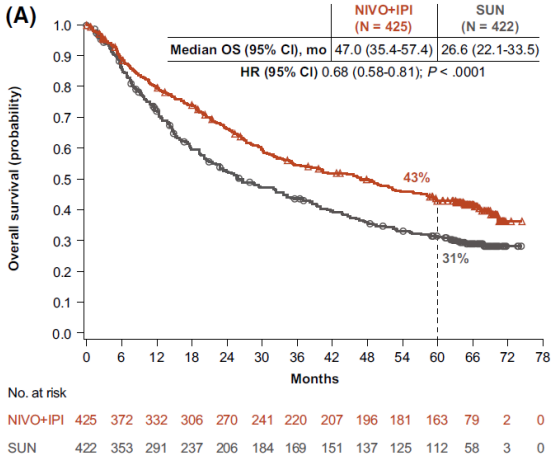
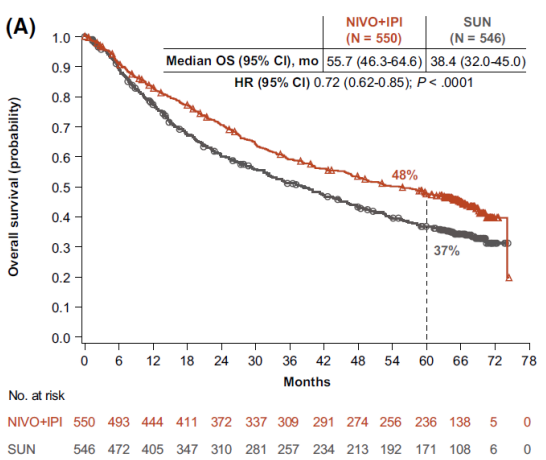


- Pronostic intermédiaire ou mauvais
- Suivi médian 67,7 mois
- HR 0,68



- Population ITT
- Suivi médian 67,7 mois
- HR 0,72

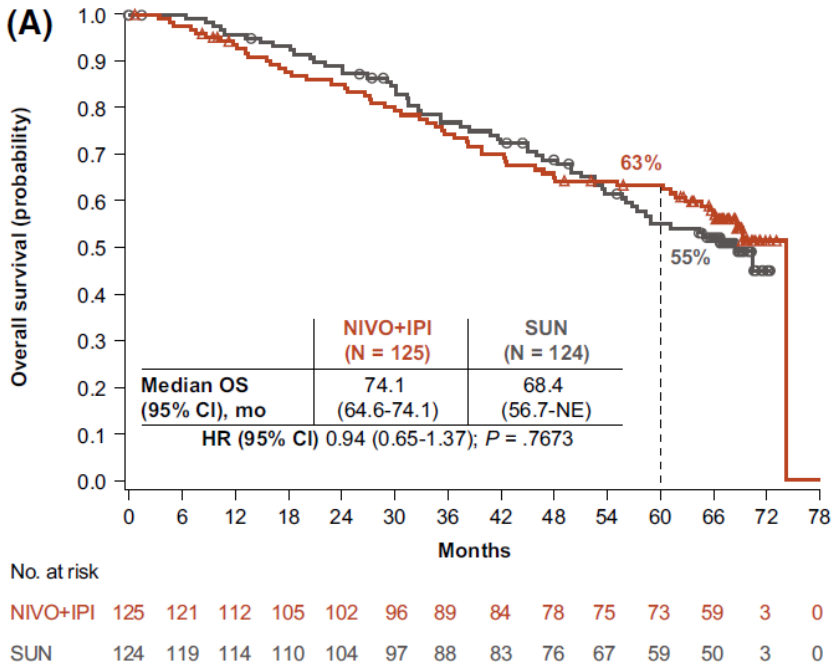
Motzer et al. N Engl J Med 2018
Motzer et al. Cancer 2022

CANCER DU REIN METASTATIQUE

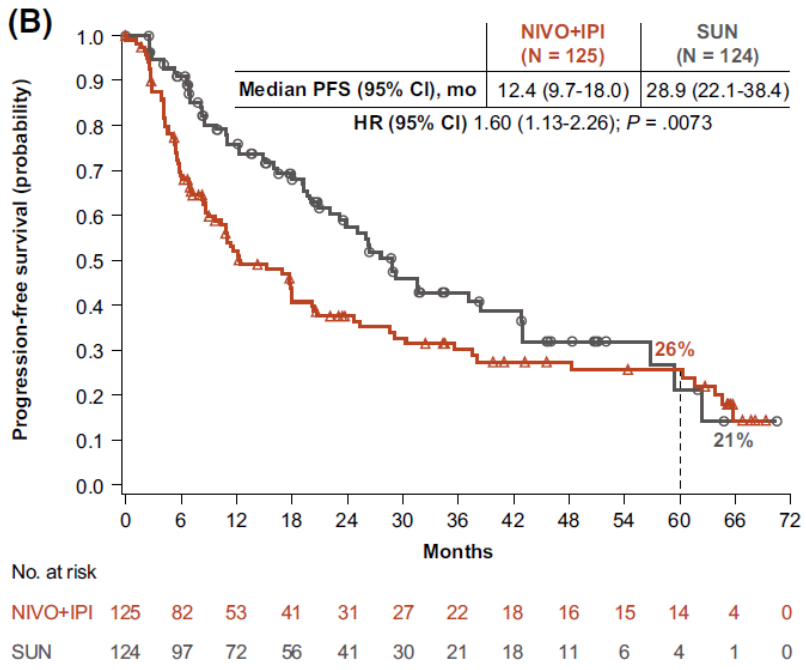
CheckMate 214 : données du sous-groupe de pronostic favorable

Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma

Robert J. Motzer, MD[1]; David F. McDermott, MD[2]; Bernard Escudier, MD[3]; Mauricio Burotto, MD[4]; Toni K. Choueiri, MD[5]; Hans J. Hammers, MD, PhD[6]; Philippe Barthélémy, MD, PhD[7]; Elizabeth R. Plimack, MD[8]; Camillo Porta, MD[9]; Saby George, MD[10]; Thomas Powles, MD[11]; Frede Donskov, MD, PhD[12]; Howard Gurney, MD[13]; Christian K. Kollmannsberger, MD[14]; Marc-Oliver Grimm, MD[15]; Carlos Barrios, MD[16]; Yoshihiko Tomita, MD, PhD[17]; Daniel Castellano, MD[18]; Viktor Grünwald, MD, PhD[19]; Brian I. Rini, MD[20]; M. Brent McHenry, PhD[21]; Chung-Wei Lee, MD, PhD[22]; Jennifer McCarthy, MA[23]; Flavia Ejzykowicz, PhD[24]; and Nizar M. Tannir, MD[25]



- OS
- Suivi médian 67,7 mois
- HR 0,94



- PFS
- HR 1,60

Motzer et al. Cancer 2022

CANCER DU REIN METASTATIQUE

CheckMate 214 : données du sous-groupe de pronostic favorable

Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma

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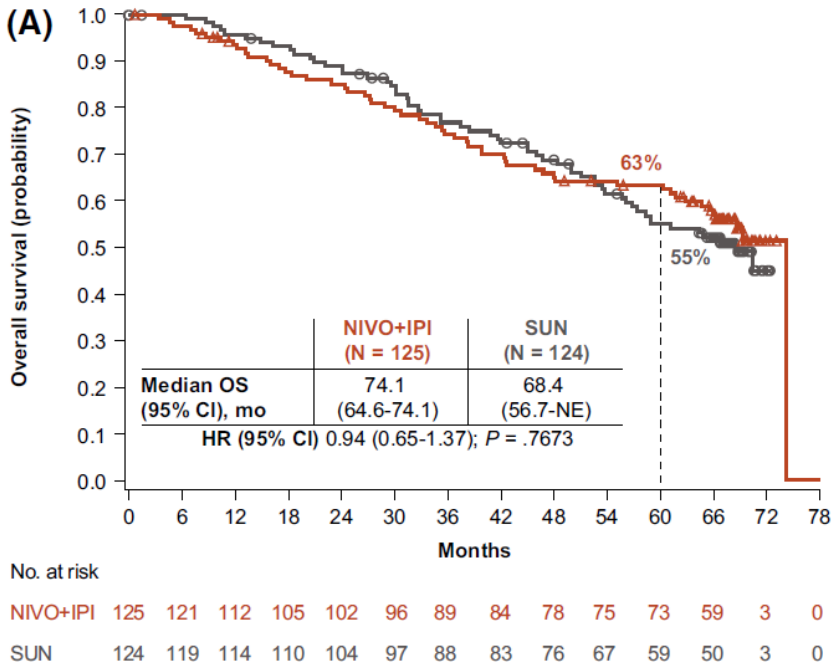
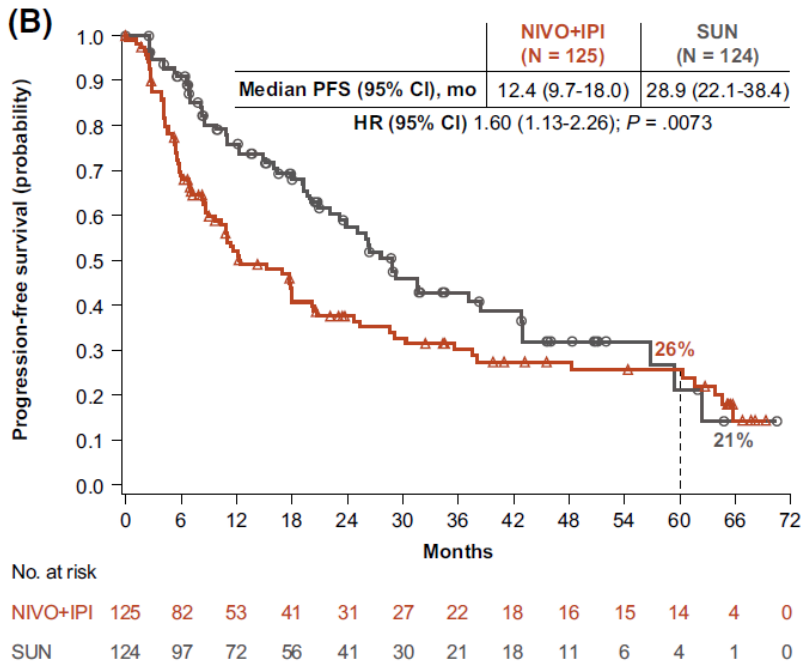


- OS
- Suivi médian 67,7 mois
- HR 0,94



- PFS
- HR 1,60

Faut-il faire de l'immunothérapie au sous-groupe favorable?

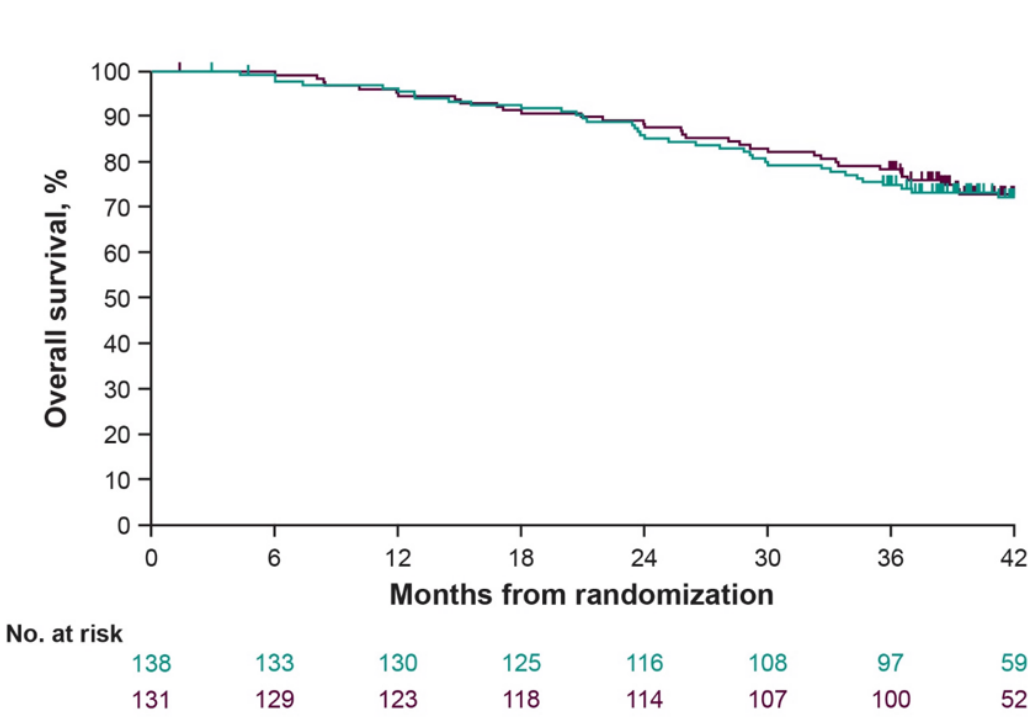
Motzer et al. Cancer 2022

CANCER DU REIN METASTATIQUE

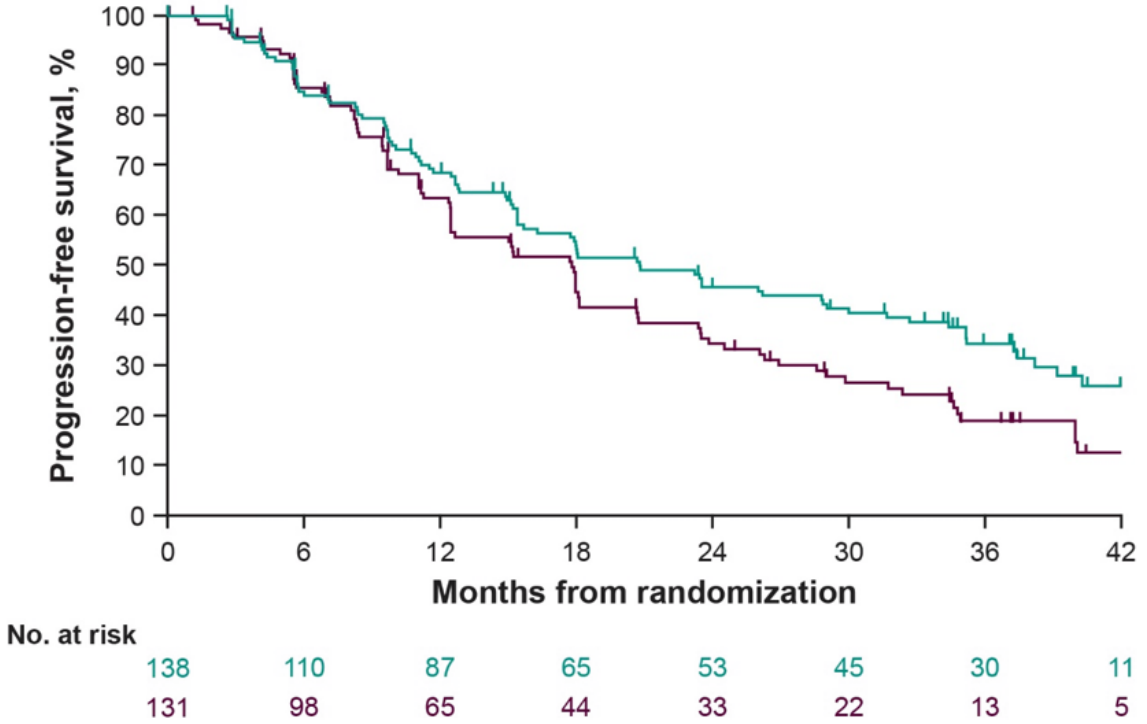
KEYNOTE-426 : données de sous-groupe de pronostic favorable

Pembrolizumab Plus Axitinib Versus Sunitinib as First-line Treatment of Advanced Renal Cell Carcinoma: 43-month Follow-up of the Phase 3 KEYNOTE-426 Study

Elizabeth R. Plimack[a,], Thomas Powles[b,c], Viktor Stus[d], Rustem Gafanov[e], Dmitry Nosov[f], Tom Waddell[g], Boris Alekseev[h], Frédéric Pouliot[i], Bohuslav Melichar[j], Denis Soulières[k], Delphine Borchiellini[l], Raymond S. McDermott[m], Ihor Vynnychenko[n], Yen-Hwa Chang[o], Satoshi Tamada[p], Michael B. Atkins[q], Chenxiang Li[r], Rodolfo Perini[r], L. Rhoda Molife[s], Jens Bedke[t], Brian I. Rini[u]*



- OS
- Suivi médian 43 mois
- HR 1,2



- PFS
- HR 0,76

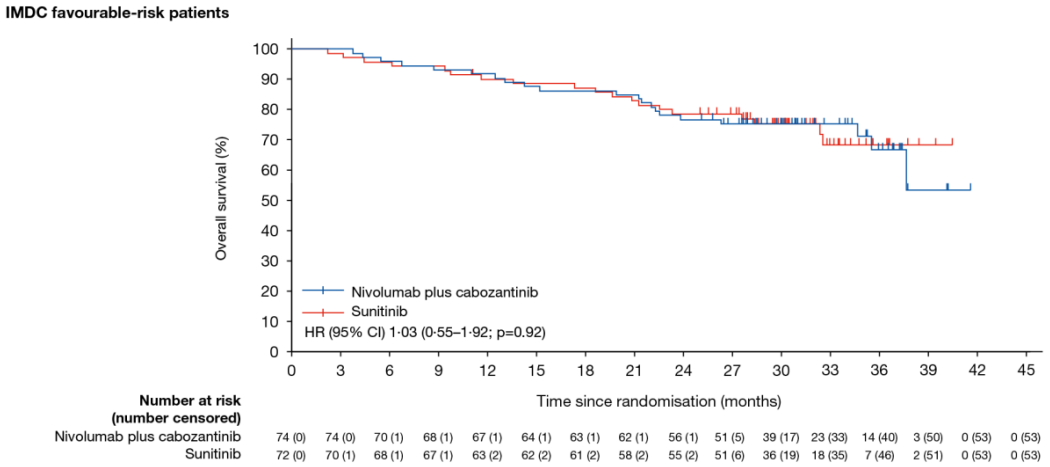
Plimack et al. Eur Urol 2023

CANCER DU REIN METASTATIQUE

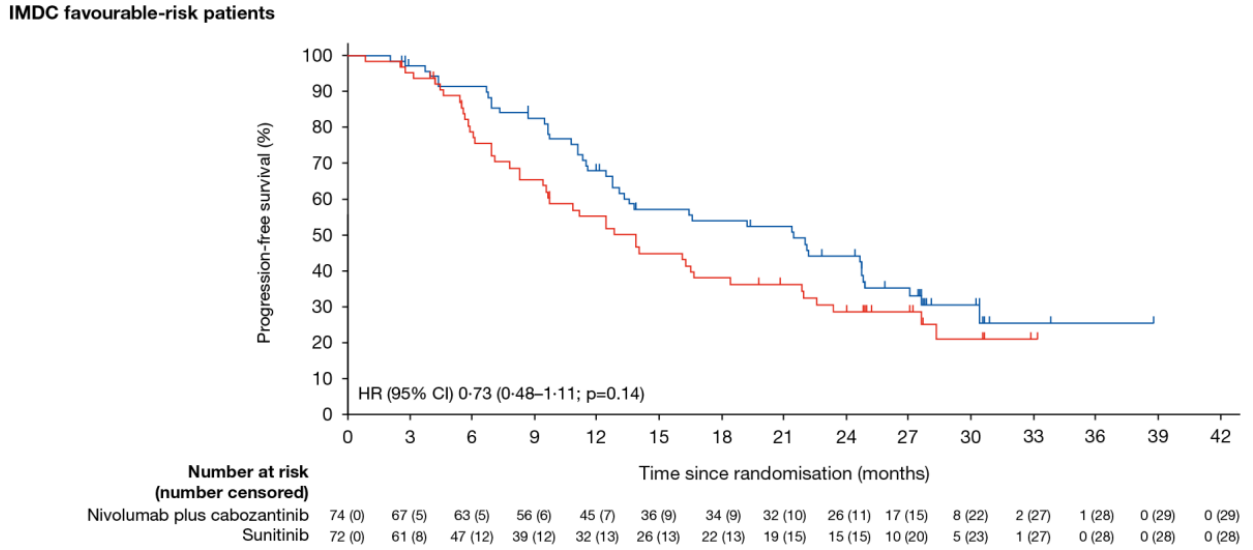
CheckMate 9ER : données du sous-groupe de pronostic favorable

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial

Robert J Motzer, Thomas Powles, Mauricio Burotto, Bernard Escudier, Maria T Bourlon, Amishi Y Shah, Cristina Suárez, Alketa Hamzaj, Camillo Porta, Christopher M Hocking, Elizabeth R Kessler, Howard Gurney, Yoshihiko Tomita, Jens Bedke, Joshua Zhang, Burcin Simsek, Christian Scheffold, Andrea B Apolo, Toni K Choueiri



- OS
- Suivi médian 32,9 mois
- HR 1,03



- PFS
- HR 0,73

Motzer et al. Lancet Oncol 2022

CANCER DU REIN METASTATIQUE

CLEAR : données du sous-groupe de pronostic favorable

Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study

Toni K Choueiri, Masatoshi Eto, Robert Motzer, Ugo De Giorgi, Tomas Buchler, Naveen S Basappa, María José Méndez-Vidal, Sergei Tjulandin, Se Hoon Park, Bohuslav Melichar, Thomas Hutson, Carlos Alemany, Bradley McGregor, Thomas Powles, Viktor Grünwald, Boris Alekseev, Sun Young Rha, Evgeny Kopyltsov, Anil Kapoor, Teresa Alonso Gordoa, Jeffrey C Goh, Michael Staehler, Jaime R Merchan, Ran Xie, Rodolfo F Perini, Kalgi Mody, Jodi McKenzie, Camillo G Porta

Figure S2. Updated OS of patients in MSKCC and IMDC risk groups (data cutoff date: March 31, 2021)[a]

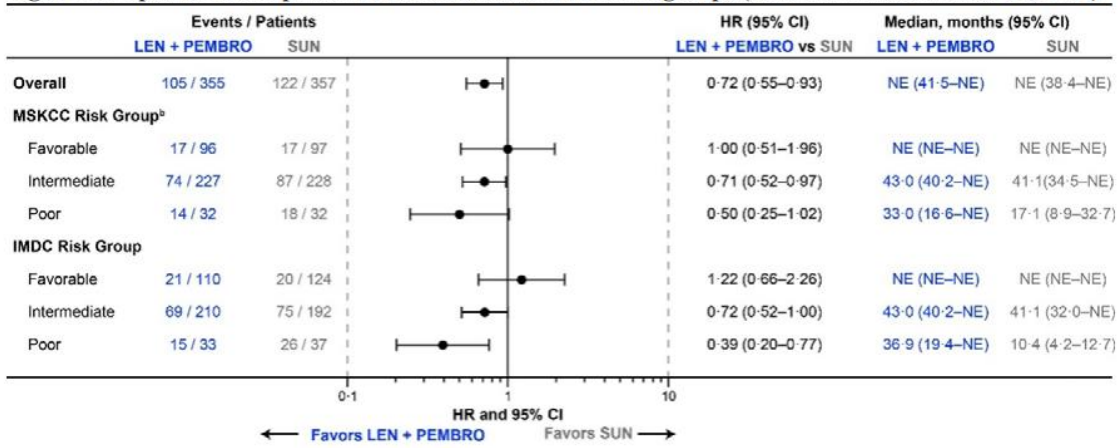
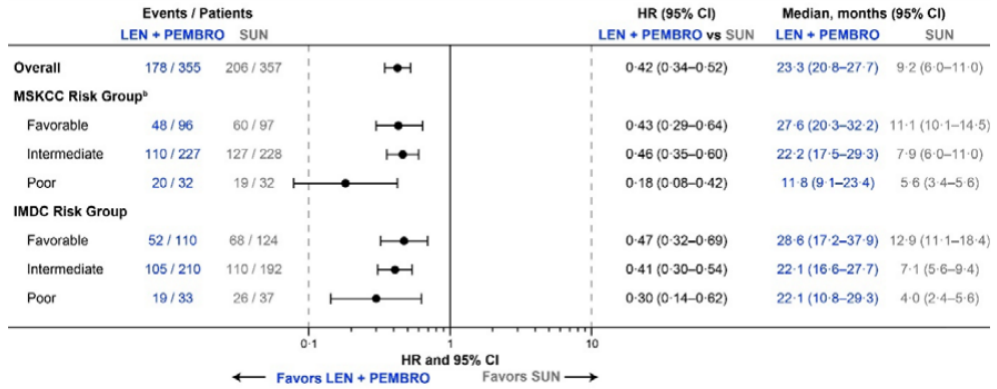


Figure S1. Forest plot of HR for lenvatinib plus pembrolizumab versus sunitinib in progression-free survival by independent review committee per RECIST version 1.1 with stratification factors[a]



- OS
- Suivi médian 26,6 mois
- HR (LENVA-PEMBRO vs SUNI) 1,22

- PFS
- HR (LENVA-PEMBRO vs SUNI) 0,47

Choueiri et al. Lancet Oncol 2023

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

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*

Table 1 – Summary of included IO/TKI trials

Study	Approval	Trial design	*N*	Primary endpoints	Secondary endpoints
KEYNOTE-426	Pembrolizumab + axitinib	Randomized, open label	861	OS and PFS	ORR
JAVELIN	Avelumab + axitinib	Randomized, open label	886	OS and PFS[a]	OS and PFS[b]
CheckMate-9ER	Nivolumab + cabozantinib	Randomized, open label	651	PFS	OS and ORR
CLEAR	Pembrolizumab + lenvatinib	Randomized, open label	712	PFS	OS and ORR

IO/TKI = immuno-oncology/tyrosine kinase inhibitor; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.
[a] In PD-L1+ population.
[b] In overall population.

- 4 essais randomisés en ouvert testant les combinaisons AVE-AXI, PEMBRO-AXI, NIVO-CABO, PEMBRO-LENVA et ayant randomisés les patients 1:1 vs bras contrôle SUNITINIB
- 839 pts risque de favorable, 2259 pts de risque interm/mauvais (1809 et 450)

Table 2 – Patient demographics and tumor characteristics (by risk score group)

	Favorable (*N* = 839)	Intermediate/poor (*N* = 2259)
Age (yr), median (IQR)	62 (55, 68)	61 (54, 68)
Male sex, *N* (%)	606 (72)	1,687 (75)
Race, *N* (%)		
White	656 (81)	1,753 (80)
Asian or Pacific Islander	130 (16)	339 (15)
Black	10 (1.2)	38 (1.7)
American Indian/Alaska Native	4 (0.5)	12 (0.5)
Multiple or Other	12 (1.5)	57 (2.6)
Missing	27	60
Combination treatment arm, *N* (%)	416 (50)	1,129 (50)
Prior nephrectomy, *N* (%)	771 (92)	1,637 (72)
Sarcomatoid component, *N* (%)		
Yes	32 (5.9)	197 (14)
No	514 (94)	1,173 (86)
Missing	293	889
Stage at diagnosis, *N* (%)		
Stage I, II, or III	625 (81)	749 (34)
Stage IV	148 (19)	1,435 (66)
Missing	66	75

IQR = interquartile range.

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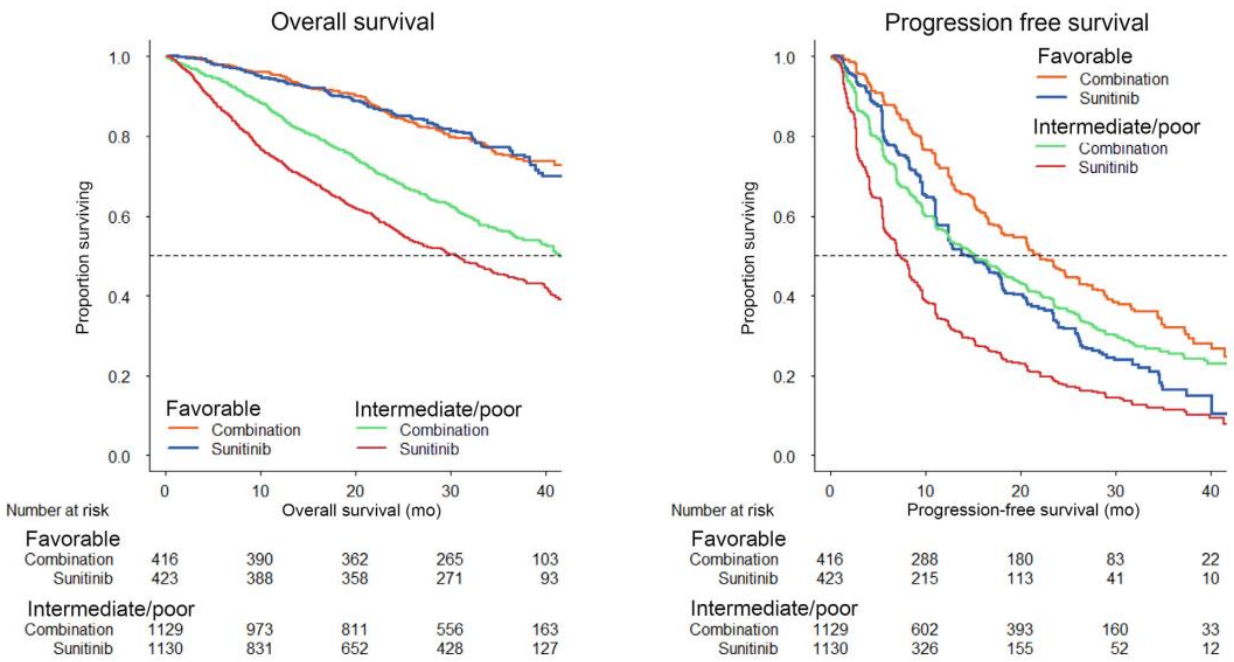

Fig. 2 – (A) OS and (B) PFS from the trials by risk group and treatment. OS = overall survival; PFS = progression-free survival.

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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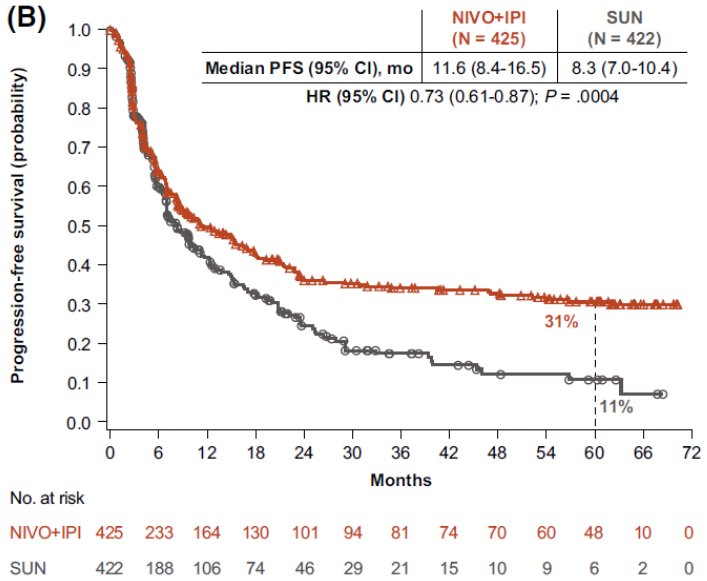
CANCER DU REIN METASTATIQUE

La question du « plateau » de survie sans progression

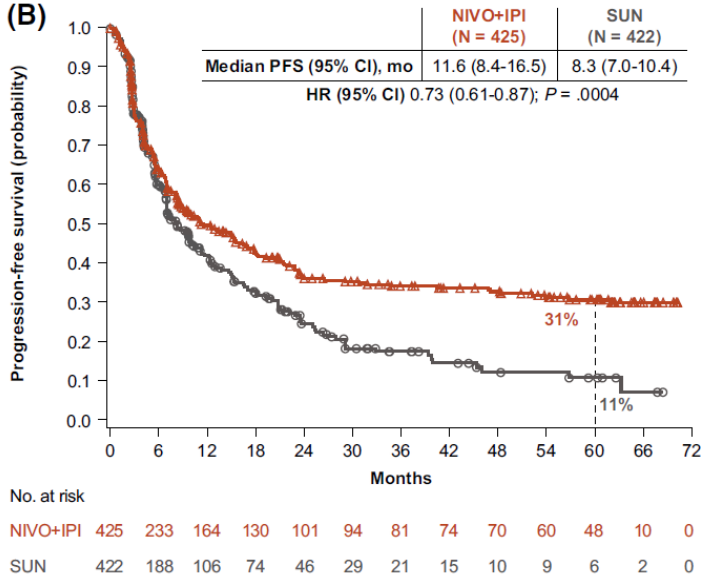


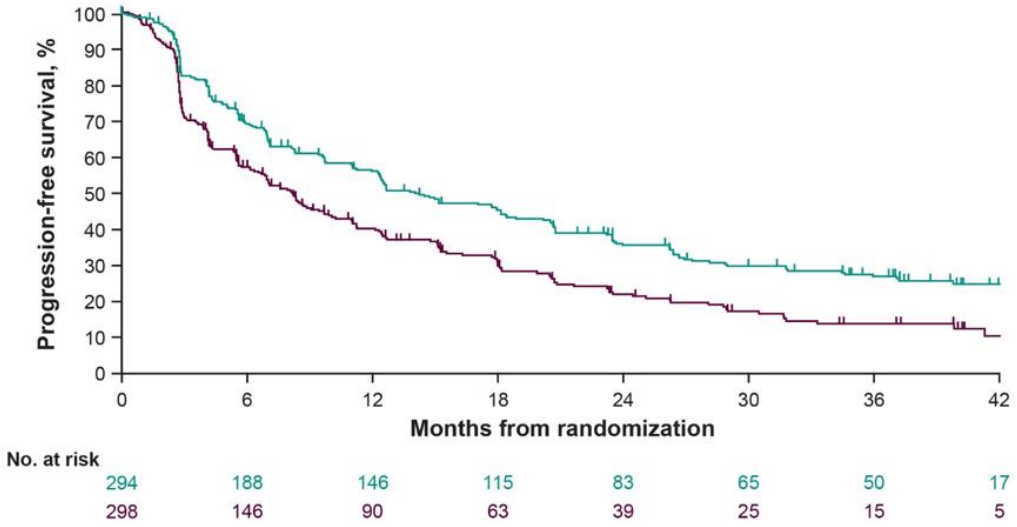
- CheckMate 214 (NIVO-IPI)
- PFS pop° pronostic intermédiaire ou mauvais
- Suivi médian 67,7 mois

Motzer et al. Cancer 2022

CANCER DU REIN METASTATIQUE

La question du « plateau » sans progression





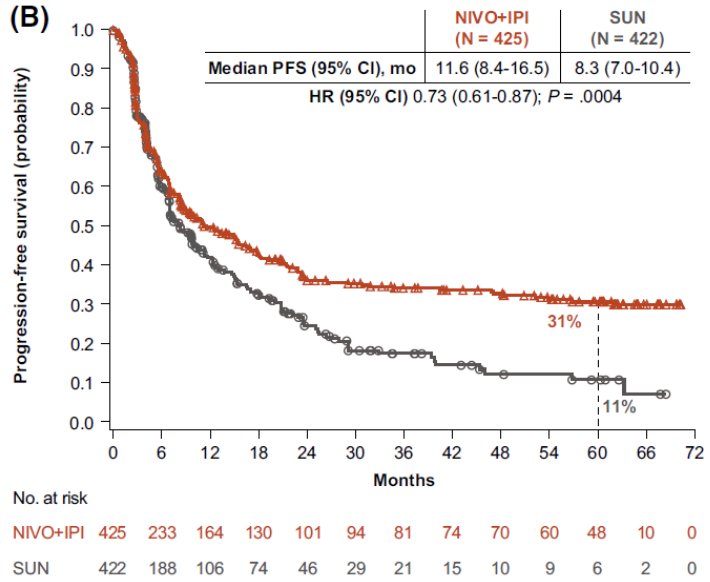
- CheckMate 214 (NIVO-IPI)
- PFS pop° pronostic intermédiaire ou mauvais
- Suivi médian 67,7 mois

- KEYNOTE-426 (AXI PEMBRO)
- PFS pop° pronostic intermédiaire ou mauvais
- Suivi médian 43 mois

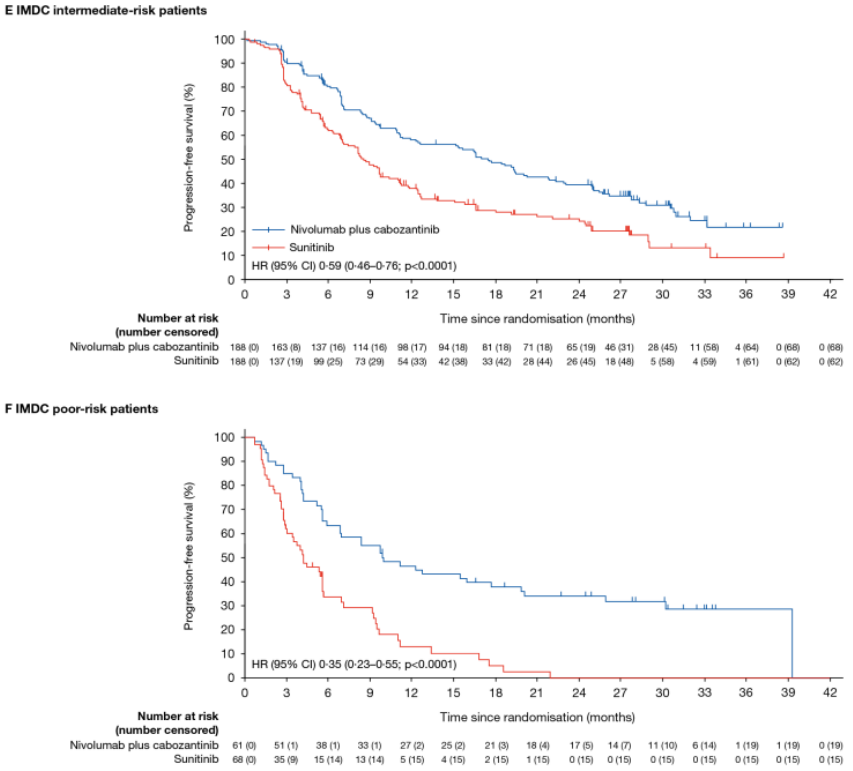
Motzer et al. Cancer 2022
Plimack et al. Eur Urol 2023

CANCER DU REIN METASTATIQUE

La question du « plateau »



- CheckMate 214 (NIVO-IPI)
- PFS pop° pronostic intermédiaire ou mauvais
- Suivi médian 67,7 mois



- CheckMate 9ER (CABO NIVO)
- PFS pop° pronostic intermédiaire et mauvais
- Suivi médian 32,9 mois

Motzer et al. Cancer 2022
Motzer et al. Lancet Oncol 2022

CANCER DU REIN AVANCE

- **Traitements systémiques de première ligne validés**
  - Mise à jour des données de suivi : *bénéfice en survie globale qui semble d'amplitude similaire quelle que soit la combinaison*
  - La question du sous-groupe de pronostic favorable : *pas de bénéfice net en survie globale des combinaisons par rapport au Sunitinib*
  - La question du « plateau » : *lié à l'anti-CTLA4 ou à des différences de population dans les essais?*

CANCER DU REIN AVANCE

- Traitements systémiques de première ligne validés
  - Mise à jour des données de suivi
  - La question du sous-groupe de pronostic favorable
  - La question du « plateau »

- **Intérêt de la poursuite de l'immunothérapie à la progression/rechallenge**

- Données avec le BELZUTIFAN

CANCER DU REIN AVANCE

Intérêt du rechallenge des inhibiteurs de checkpoint immunitaires

2023 ASCO ANNUAL MEETING

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

Sumanta Kumar Pal, Laurence Albiges, Piotr Tomczak, Cristina Suárez, Martin H Voss, Guillermo de Velasco, Jad Chahoud, Anastasia Mochalova, Giuseppe Procopio, Hakim Mahammedi, Friedemann Zengerling, Chan Kim, Takahiro Osawa, Martín Angel, Suyasha Gupta, Omara Khan, Guillaume Bergthold, Bo Liu, Melania Kalaitzidou, Mahrukh Huseni, Christian Scheffold, Thomas Powles, Toni K Choueiri

- Carcinome à cellules rénales métastatique ou localement avancé, à cellules claires ou non (papillaire, chromophobe ou inclassable) avec ou sans composante sarcomatoïde
- Maximum une ligne d'inhibiteur de checkpoint immunitaire (en 1ère ou 2ème ligne avancée ou en adjuvant si progression dans les 6 mois de la dernière injection). 2 lignes de traitement avancé max
- CABOZANTINIB 60mg/j PO + Rand° 1:1 ± ATEZOLIZUMAB 1200 mg IV /3 semaines
- 2 objectifs principaux : PFS selon revue indépendante et OS

Pal et al. Lancet 2023

CANCER DU REIN AVANCE

Intérêt du rechallenge des inhibiteurs de checkpoint immunitaires

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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	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)**

- 522 patients inclus entre juillet 2020 et décembre 2021
- Moins de 1% ont eu l'immunothérapie en adjuvant
- Première ligne : 30% NIVOLUMAB IPILUMUMAB, 13% AXITINIB PEMBROLIZUMAB, le reste SUNITINIB ou PAZOPANIB (Ils ont alors eu du NIVOLUMAB en seconde ligne)
- 36% n'ont reçu aucun ITK anti-VEGF

Pal et al. Lancet 2023

CANCER DU REIN AVANCE

Intérêt du rechallenge des inhibiteurs de checkpoint immunitaires

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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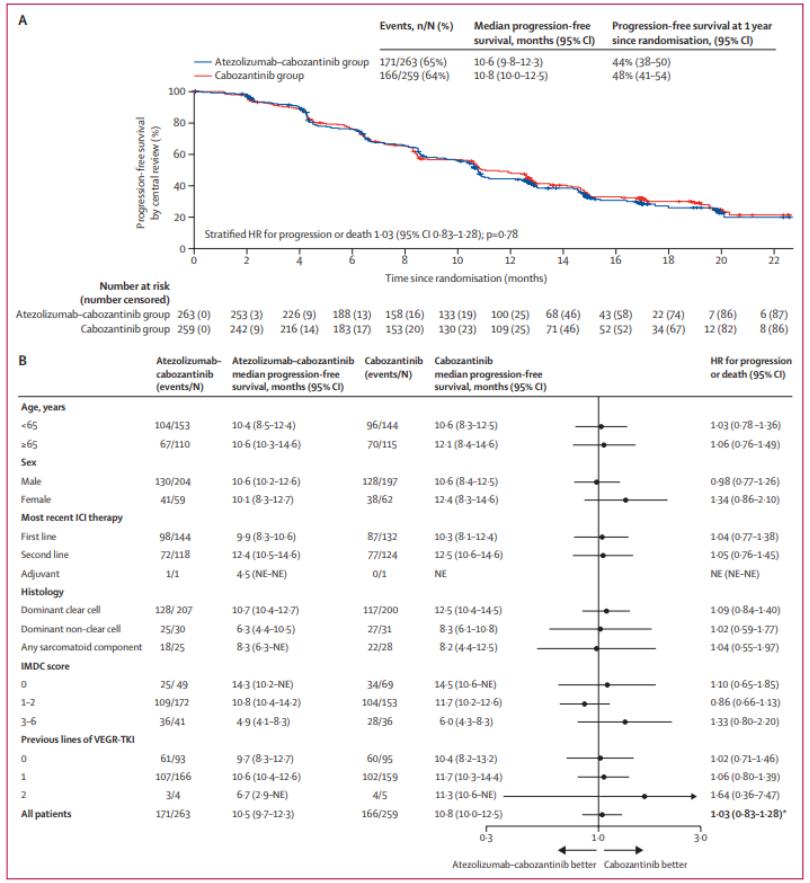

Figure 2: **Progression-free survival per central review**
Kaplan-Meier estimates of progression-free survival as assessed by blinded central review board in the intention-to-treat population (A) and in key subgroups (B). HR values in the subgroup analysis were unstratified. HR=hazard ratio. ICI=immune checkpoint inhibitor. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. NE=not evaluable. TKI=tyrosine kinase inhibitor. *Stratified value.

- 522 patients inclus entre juillet 2020 et décembre 2021
- Suivi médian 15,2 mois
- 65% et 64% ont eu évènement PFS
- PFS médiane 10,6 mois vs 10,8 mois (HR 1,03)
- 34% et 34% sont décédés
- OS : HR 0,94

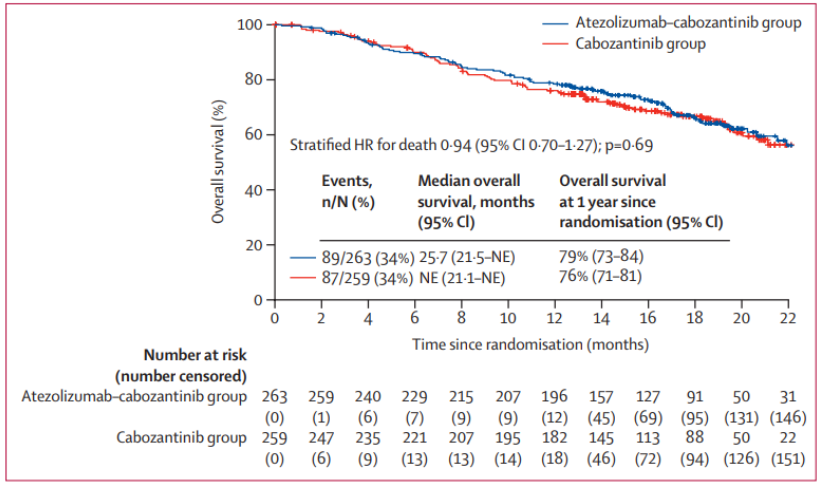

Figure 3: **Kaplan-Meier estimate of overall survival in the intention-to-treat population**
HR=hazard ratio. NE=not evaluable.

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CANCER DU REIN AVANCE

Intérêt du rechallenge des inhibiteurs de checkpoint immunitaires

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	RECIST 1.1 per central review		RECIST 1.1 per investigator	
	Atezolizumab plus cabozantinib group (n=259)	Cabozantinib group (n=254)	Atezolizumab plus cabozantinib group (n=263)	Cabozantinib group (n=259)
Confirmed objective response	105 (41% [35–47%])†	104 (41% [35–47%])†	100 (38% [32–44%])‡	108 (42% [36–48%])‡
Complete response	0	2 (1%)	4 (2%)	2 (1%)
Partial response	105 (41%)	102 (40%)	96 (37%)	106 (41%)
Stable disease	131 (51%)	121 (48%)	127 (48%)	120 (46%)
Progressive disease	11 (4%)	13 (5%)	24 (9%)	17 (7%)
Not evaluable or missing	12 (5%)	16 (6%)	12 (5%)	14 (5%)
Ongoing objective response at data cutoff§	53/105 (50%)	55/104 (53%)	58/100 (58%)	48/108 (44%)
Median duration of response, months (95% CI)	12·7 (10·5–17·4)	14·8 (11·3–20·0)	NE (10·4–NE)	12·2 (9·7–14·5)
Duration of response range, months¶	2·1–22·9	2·3–25·6	2·1–23·2	2·1–25·6

Data are n (% [95% CI]), n (%), n/N (%), median (95% CI), or range. *Included patients who presented with measurable disease according to RECIST 1.1, as assessed by either a central review facility or by investigators. †The estimated difference in objective response rate per central review between the atezolizumab–cabozantinib group and the cabozantinib group was −0·4 (95% CI −9·3 to 8·5). ‡The estimated difference in objective response rate per investigator assessment between the atezolizumab–cabozantinib group and the cabozantinib group was −3·7 (95% CI −12·5 to 5·1). §Included patients with complete or partial response who did not have disease progression and did not die. ¶All value in this row are censored values (ie, all range values were from patients who did not have loss of response but were lost to follow-up or clinical cutoff occurred. NE=not evaluable. RECIST 1.1=Response Evaluation Criteria in Solid Tumours, version 1.1.

Table 2: **Secondary efficacy outcomes***

- Taux de réponse 41% vs 41%
- Tolérance
- SAE 48% vs 33%
- Arrêt pour toxicité : ATEZOLIZUMAB 11%, CABOZANTINIB 10% vs 4%

- *Attente des résultats de l'essai de phase 3 TiNivo-2 testant l'association TIVOZANIB±NIVOLUMAB*

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CANCER DU REIN AVANCE

- **Intérêt de la poursuite de l'immunothérapie à la progression/rechallenge**
  - *Pas d'intérêt au vu des données actuelles*
  - *Attente des résultats d'autres essais (TiNivo-2)*
  - *Quelle va être la première ligne en cas de progression après immunothérapie en adjuvant?*

CANCER DU REIN AVANCE

- Traitements systémiques de première ligne validés
  - Mise à jour des données de suivi
  - La question du sous-groupe de pronostic favorable
  - La question du « plateau »

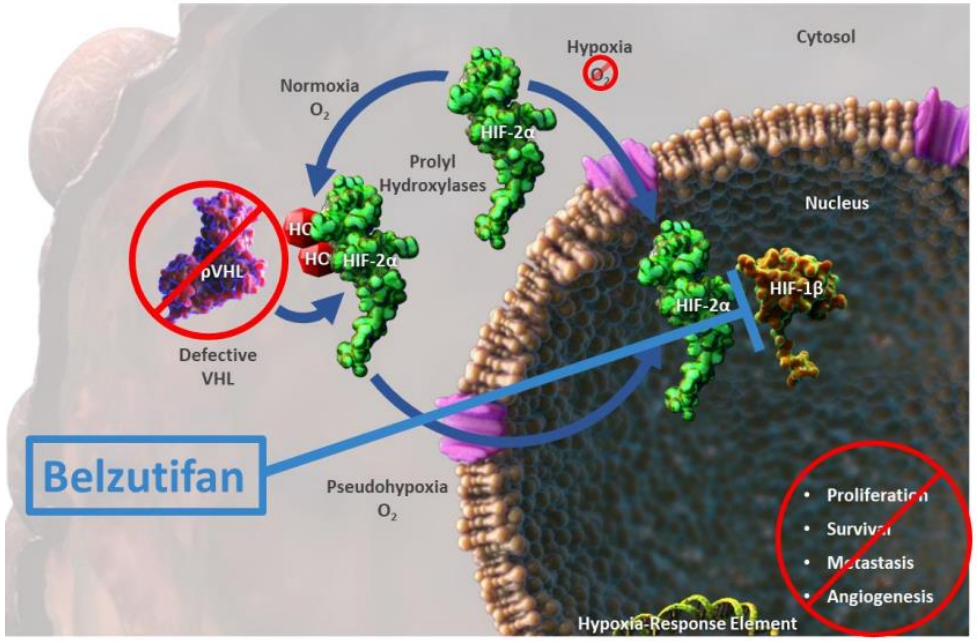
- Intérêt de la poursuite de l'immunothérapie à la progression/rechallenge

- **Données avec le BELZUTIFAN**

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 : Mise à jour des données de phase 1

Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a phase 1 trial and biomarker analysis

Toni K. Choueiri[1,✉], Todd M. Bauer[2], Kyriakos P. Papadopoulos[3], Elizabeth R. Plimack[4], Jaime R. Merchan[5], David F. McDermott[6], M. Dror Michaelson[7], Leonard J. Appleman[8], Sanjay Thamake[9], Rodolfo F. Perini[9], Naseem J. Zojwalla[9], Eric Jonasch[10,✉]

Choueiri et al. Nat Med 2022

Phase I LITESPARK-001 study of belzutifan for advanced solid tumors: Extended 41-month follow-up in the clear cell renal cell carcinoma cohort

Eric Jonasch [a,*], Todd M. Bauer [b], Kyriakos P. Papadopoulos [c], Elizabeth R. Plimack [d], Jaime R. Merchan [e], David F. McDermott [f], M. Dror Michaelson [g], Leonard J. Appleman [h], Ananya Roy [i], Rodolfo F. Perini [i], Yanfang Liu [i], Toni K. Choueiri [j,**]

Jonasch et al. Eur J Cancer 2023

CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Mise à jour des données de phase 1

Phase I LITESPARK-001 study of belzutifan for advanced solid tumors: Extended 41-month follow-up in the clear cell renal cell carcinoma cohort

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Table 1
Demographics and baseline characteristics.

n (%)	ccRCC cohort N = 55
Age, median (range), years	62.0 (39–75)
Sex	
Male	44 (80)
Female	11 (20)
ECOG PS	
0	20 (36)
1	34 (62)
2	1 (2)[a]
Prior systemic therapies, median (range)	3 (1–9)
Prior VEGF-targeted therapy and prior immunotherapy	39 (71)
Number of prior systemic therapies	
1	8 (15)
2	13 (24)
≥ 3	34 (62)
IMDC risk category	
Favorable	13 (24)
Intermediate/poor	42 (76)

ccRCC, clear cell renal carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium; VEGF, vascular endothelial growth factor. Values are n (%) unless otherwise specified.

[a] A waiver was requested by the investigator and approved by the internal review board before enrollment.

- Carcinomes rénaux à cellules claires traités à la dose recommandée de 120 mg/j
- 55 patients (3 de la cohorte d'escalade de dose et 52 de la cohorte d'expansion)
- Suivi médian de 41,2 mois. Durée médiane de traitement de 6,0 mois
- Inclusion possible si prétraités par au moins une ligne
- Nombre médian de lignes reçues : 3
- 85% ont reçu 2 lignes ou plus

Jonasch et al. Eur J Cancer 2023

CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Mise à jour des données de phase 1

Phase I LITESPARK-001 study of belzutifan for advanced solid tumors: Extended 41-month follow-up in the clear cell renal cell carcinoma cohort

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Table 2
Response characteristics per RECIST v1.1 by investigator review in the ccRCC cohort.

	ccRCC cohort N = 55	IMDC favorable risk n = 13	IMDC intermediate or poor risk n = 42	Either prior VEGF or prior PD-1/L1-targeted treatment n = 16	Both prior VEGF and prior PD-1/L1-targeted treatment n = 39	1 prior treatment regimen n = 8	≥ 2 prior treatment regimens n = 47
Objective response rate	14 (25)	4 (31)	10 (24)	6 (38)	8 (21)	3 (38)	11 (23)
Clinical benefit rate	44 (80)	12 (92)	32 (76)	15 (94)	29 (74)	8 (100)	36 (77)
Best objective response							
Complete response	1 (2)	0 (0)	1 (2)	0 (0)	1 (3)	0 (0)	1 (2)
Partial response	13 (24)	4 (31)	9 (21)	6 (38)	7 (18)	3 (38)	10 (21)
Stable disease	30 (55)	8 (62)	22 (52)	9 (56)	21 (54)	5 (63)	25 (53)
Progressive disease	8 (15)	1 (8)	7 (17)	1 (6)	7 (18)	0 (0)	8 (17)
Non-evaluable	3 (6)	0 (0)	3 (7)	0 (0)	3 (8)	0 (0)	3 (6)
Time to response, median (range), months	4.9 (1.7–16.6)	3.7 (3.6–16.6)	5.6 (1.7–12.7)	6.5 (1.7–12.7)	4.0 (1.7–16.6)	5.6 (1.8–7.4)	4.2 (1.7–16.6)
Duration of response, median (range), months	NR (3.1 + to 38.0 +)	NR (23.1 + to 38.0 +)	10.1 (3.1 + to 37.2 +)	9.4 (3.1 + to 29.0 +)	NR (5.0–38.0 +)	3.7 (3.1 + to 3.7)	NR (5.0–38.0 +)

ccRCC; clear cell renal cell carcinoma; IMDC, International Metastatic RCC Disease Consortium; NR, not reached; PD-1/PD-L1; programmed cell death protein 1/programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; VEGF, vascular endothelial growth factor. Values are n (%) unless otherwise specified.

- Taux de réponse objective : 25%.
- 15% de progression d'emblée
- Délai réponse 4,9 mois.
- Durée médiane de réponse non atteinte
- Suivi médian de 41,2 mois

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Mise à jour des données de phase 1

Phase I LITESPARK-001 study of belzutifan for advanced solid tumors: Extended 41-month follow-up in the clear cell renal cell carcinoma cohort

Eric Jonasch [a,*], Todd M. Bauer [b], Kyriakos P. Papadopoulos [c], Elizabeth R. Plimack [d], Jaime R. Merchan [e], David F. McDermott [f], M. Dror Michaelson [g], Leonard J. Appleman [h], Ananya Roy [i], Rodolfo F. Perini [i], Yanfang Liu [i], Toni K. Choueiri [j,**]

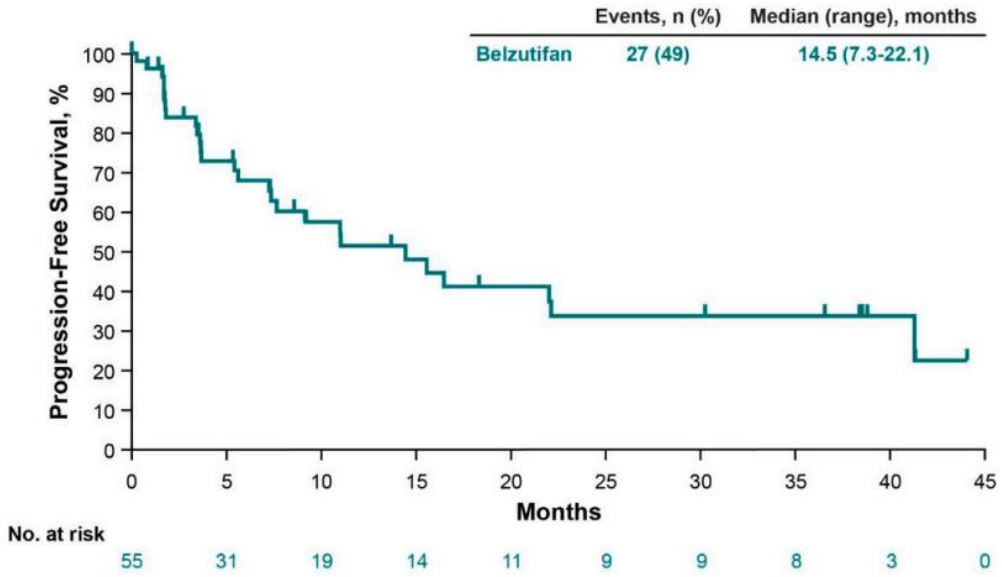

Fig. 2. Kaplan-Meier estimate of progression-free survival per RECIST v1.1 in the ccRCC cohort. ccRCC, clear cell renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

- PFS médiane 14,5 mois

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Table 3
Treatment-related adverse events occurring in ≥ 2 patients and associated grade 3 events in the ccRCC cohort.

Treatment-related adverse event	ccRCC cohort	
	N = 55	
	Grade 1–2	Grade 3[b,c]
Any	31 (56)	22 (40)
Anemia	28 (51)	13 (24)
Fatigue	30 (55)	1 (2)
Hypoxia	5 (9)	7 (13)
Dyspnea	10 (18)	2 (4)
Peripheral edema	9 (16)	0 (0)
Nausea	7 (13)	1 (2)
Increased alanine aminotransferase	5 (9)	1 (2)
Aspartate aminotransferase increased	4 (7)	0 (0)
Decreased lymphocyte count	4 (7)	0 (0)
Vomiting	4 (7)	0 (0)
Cough	3 (6)	0 (0)
Dizziness	3 (6)	0 (0)
Decreased appetite	3 (6)	0 (0)
Headache	2 (4)	1 (2)
Increased weight	3 (6)	0 (0)
Increased blood alkaline phosphatase	3 (6)	0 (0)
Decreased platelet count	2 (4)	1 (2)
Myalgia	3 (6)	0 (0)
Pneumonitis	2 (4)	1 (2)
Proteinuria	3 (6)	0 (0)
Asthenia	2 (4)	0 (0)
Edema	2 (4)	0 (0)
Flushing	2 (4)	0 (0)
Hypercalcemia	2 (4)	0 (0)
Increased blood creatinine	2 (4)	0 (0)
Malaise	2 (4)	0 (0)
Muscular weakness	2 (4)	0 (0)

- <u>Tolérance</u>
- Parmi 44 patients avec anémie, 43% ont eu EPO, 7 une transfusion et 7 transfusion + EPO
- Parmi les 18 pts avec hypoxie, 13 ont reçu une oxygénothérapie, 4 d'autres traitements (ATB, cortico, bronchodilatateurs)
- Réduction de dose chez 5 patients, interruption chez 13, arrêt définitif chez 2 pour hypoxie

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3 en monothérapie

Belzutifan Versus Everolimus in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma: Randomized Open-Label Phase 3 LITESPARK-005 Study

Laurence Albiges[1], Brian Rini[2], Katriina Peltola[3], Guillermo de Velasco[4], Mauricio Burotto[5], Cristina Suarez Rodriguez[6], Pooja Ghatalia[7], Roberto Iacovelli[8], Elaine T. Lam[9], Elena Verzoni[10], Mahmut Gumus[11], Walter M. Stadler[12]; Christian Kollmannsberger[13], Bohuslav Melichar[14], Balaji Venugopal[15], Aobo Wang[16], Rodolfo F. Perini[16], Donna Vickery[16], Thomas Powles[17], Toni K. Choueiri[18]

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Cellules claires : BELZUTIFAN : Données de phase 3

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Belzutifan Versus Everolimus in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma: Randomized Open-Label Phase 3 LITESPARK-005 Study

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LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti–PD-(L)1 mAb and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%

R 1:1

N = 374 → **Belzutifan** 120 mg orally daily

N = 372 → **Everolimus** 10 mg orally daily

Stratification Factors

- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGF/VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

2 objectifs principaux :

- PFS selon relecture centralisée
- OS

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3

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Baseline Characteristics

	Belzutifan (N = 374)	Everolimus (N = 372)
Age, median (range), yrs	62 (22–90)	63 (33–87)
Male	79.4%	76.3%
KPS score[a]		
90/100	63.6%	64.5%
70/80	36.1%	35.2%
IMDC risk categories		
Favorable	21.1%	22.3%
Intermediate	66.6%	65.6%
Poor	12.3%	12.1%
Sarcomatoid features		
Yes	11.2%	8.3%
No/Unknown/Missing	88.8%	91.7%
Prior nephrectomy	69.8%	69.6%
# Prior VEGF/VEGFR-TKIs		
1	50.0%	51.1%
2-3	50.0%	48.9%
# Prior lines of therapy[b]		
1	12.3%	14.0%
2	42.0%	44.6%
3	45.2%	40.3%

- Présentation des résultats de la deuxième analyse intermédiaire
- Délai médian depuis la randomisation : 25,7 mois

Planned analysis	Planned timing	Planned analysis	Data cutoff date
Interim analysis 1 (IA1)	• ~563 PFS events[b], AND • ~7 months after last participant randomized	Interim PFS Interim OS Final ORR	Nov 1, 2022
Interim analysis 2 (IA2)	• ~410 OS events, AND • ~17 months after last participant randomized	Interim OS Final PFS	Jun 13, 2023
Final	• ~483 OS events, AND • ~27 months after last participant randomized	Final OS	

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3

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Belzutifan Versus Everolimus in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma: Randomized Open-Label Phase 3 LITESPARK-005 Study

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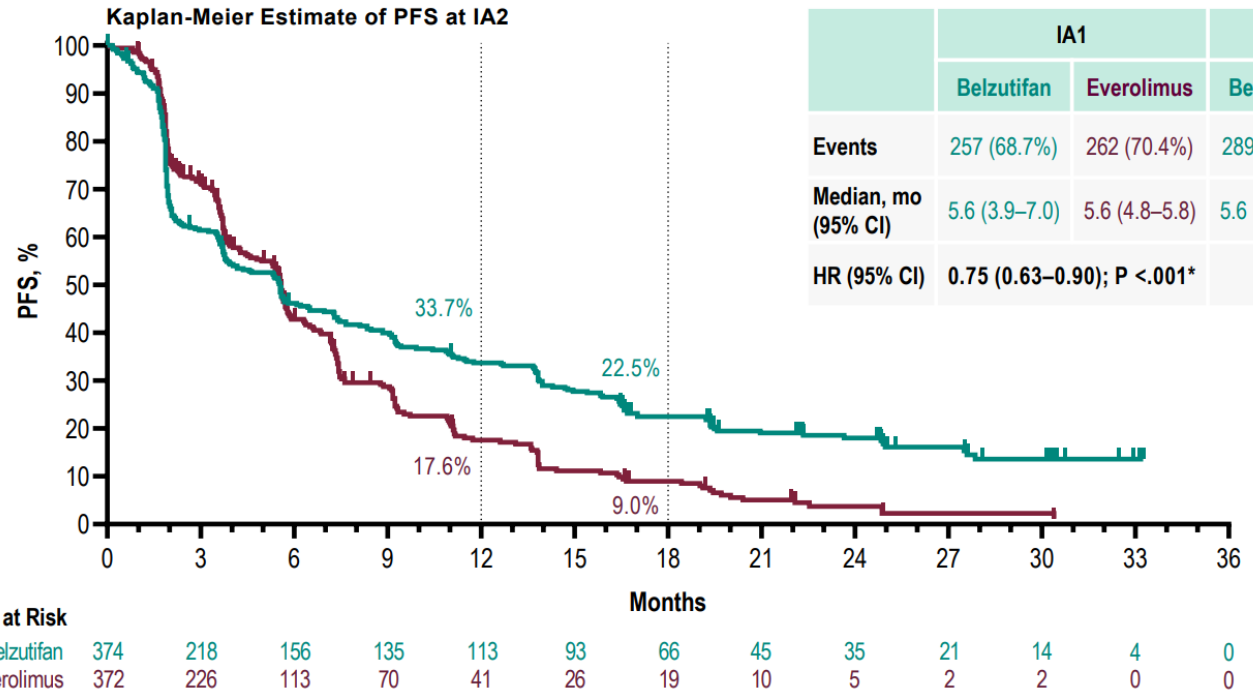
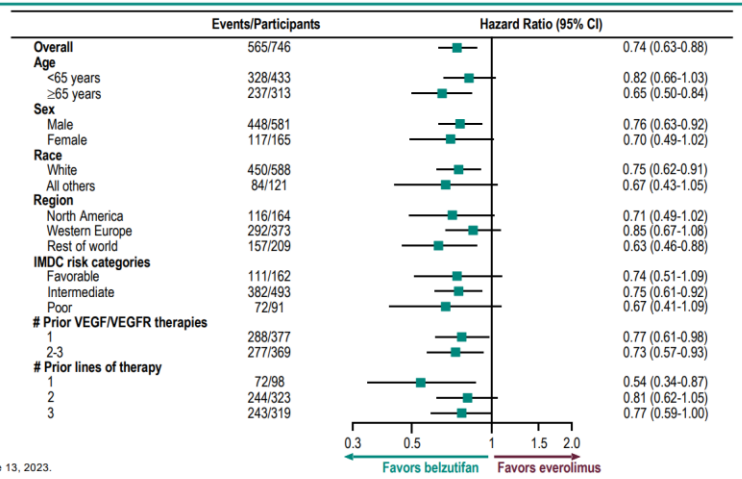
Primary Endpoint: PFS per RECIST 1.1 by BICR



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

- Amélioration significative de PFS (courbes qui se croisent?)
- Bénéfice plus marqué selon nombre de lignes antérieures?

PFS by BICR per RECIST 1.1 in Subgroups



Data cutoff date for IA2: June 13, 2023.

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3

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Belzutifan Versus Everolimus in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma: Randomized Open-Label Phase 3 LITESPARK-005 Study

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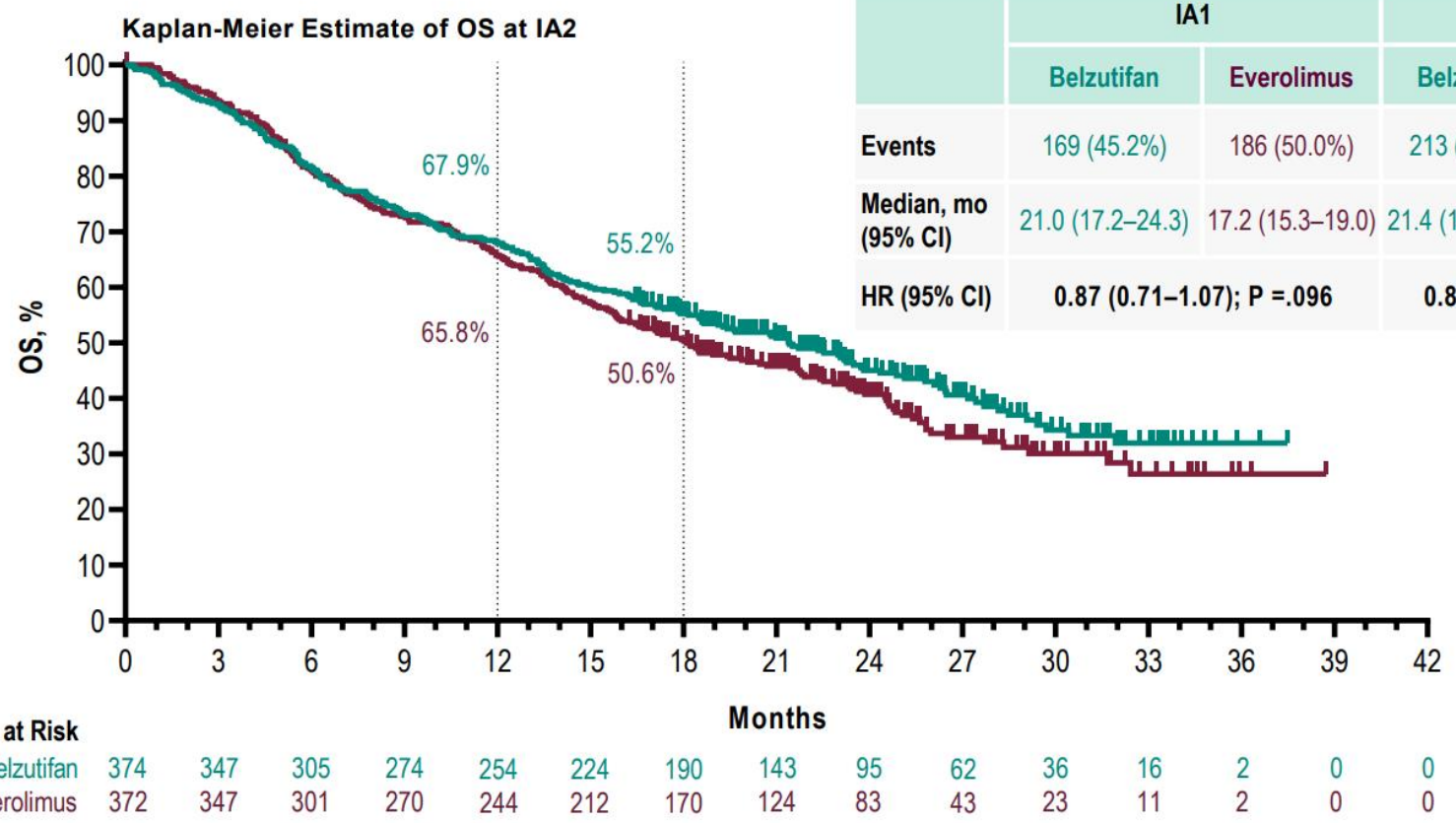
Primary Endpoint: OS



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

- Pas de bénéfice significatif en survie globale dans cette analyse intermédiaire

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3

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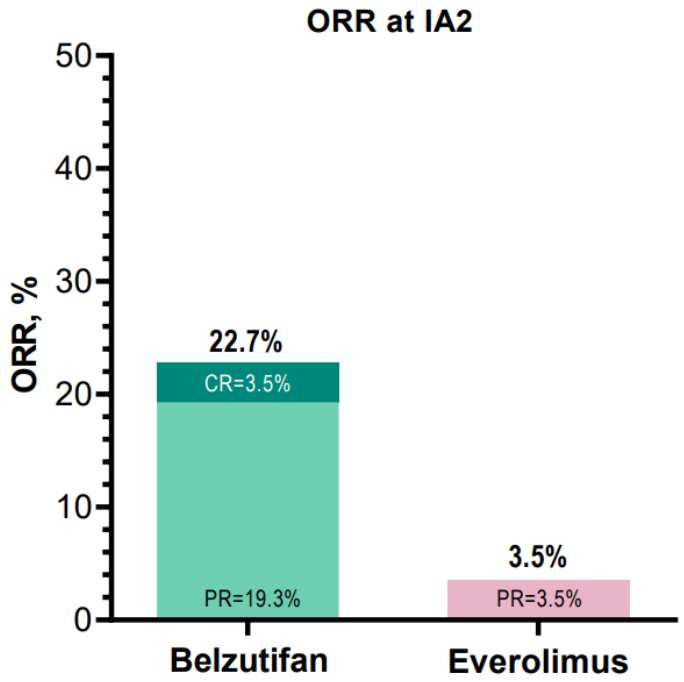
Key Secondary Endpoint: ORR by BICR per RECIST 1.1

	Belzutifan (N = 374)	Everolimus (N = 372)
	IA1	
ORR, % (95% CI)	**21.9% (17.8–26.5)**	**3.5% (1.9–5.9)**
Estimated difference in % (95% CI)	**18.4 (14.0–23.2); P <.00001***	
CR	2.7%	0
PR	19.3%	3.5%
SD	39.3%	65.9%
PD	33.7%	21.5%
Non-evaluable[a]	1.3%	2.2%
No assessment[b]	3.7%	7.0%
	IA2	
ORR, % (95% CI)	**22.7% (18.6–27.3)**	**3.5% (1.9–5.9)**
Estimated difference in % (95% CI)	**19.2 (14.8–24.0)**	



Taux de réponse objective : 22,7% vs 3,5%

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

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3

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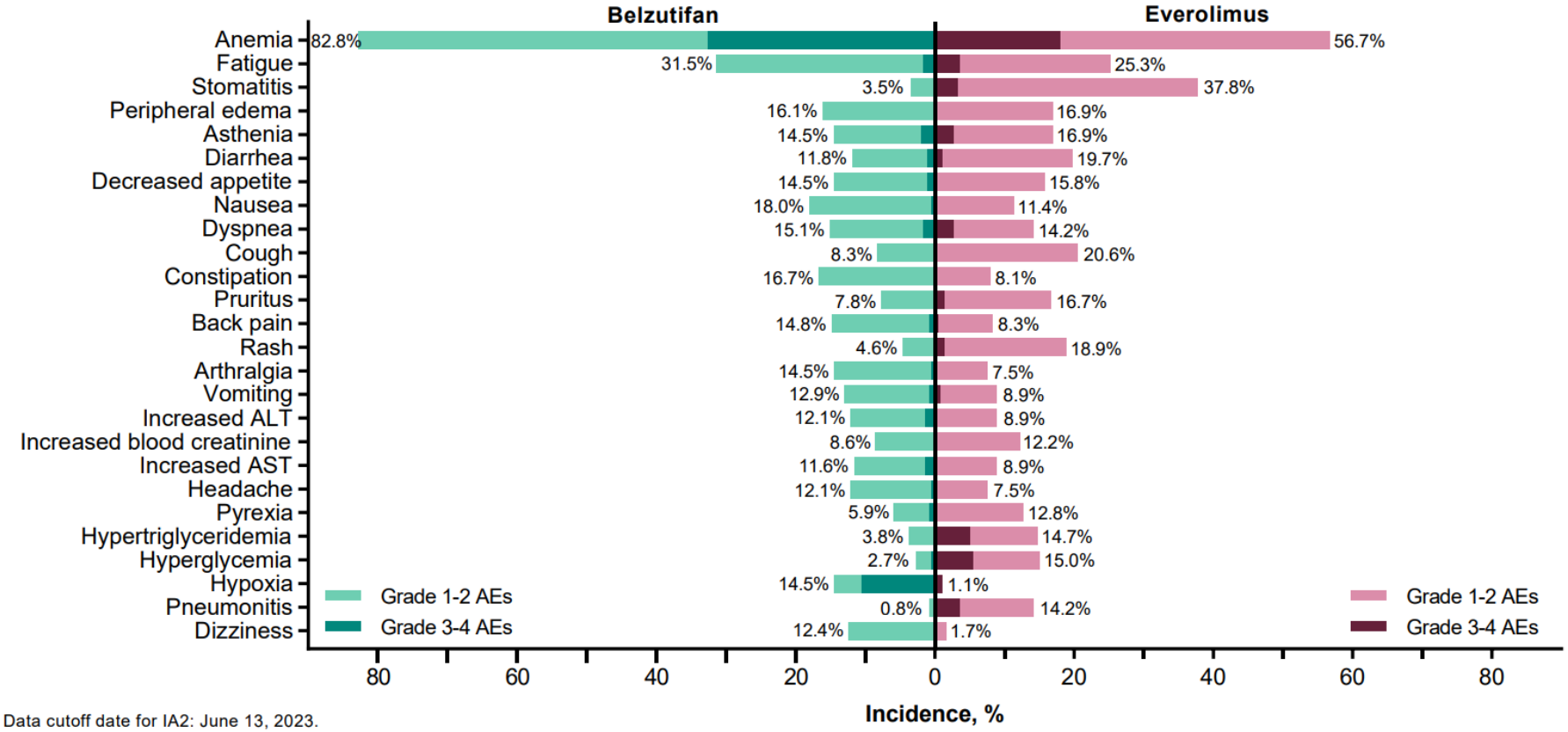
All-Cause AEs in ≥10% of Patients in Either Arm



Data cutoff date for IA2: June 13, 2023.

Tolérance : anémie et hypoxie surtout

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3

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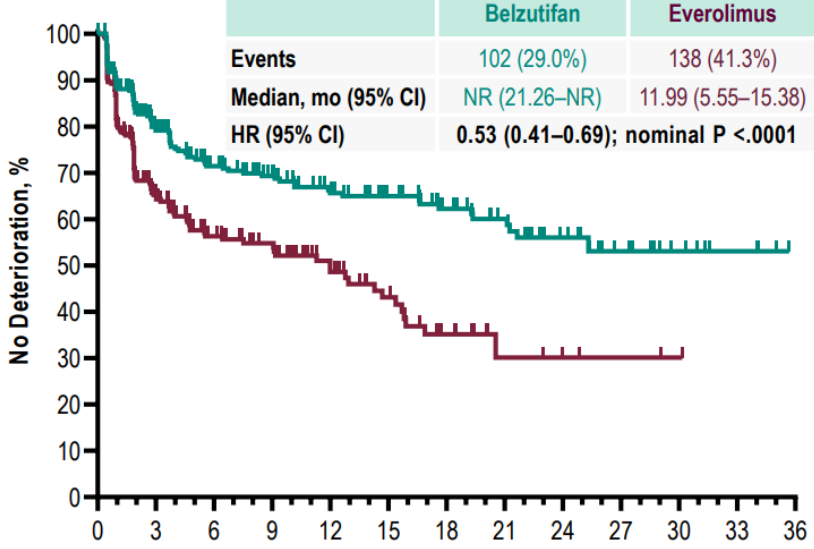
Patient-Reported Outcomes: Time to Confirmed Deterioration

FKSI-DRS: TTD

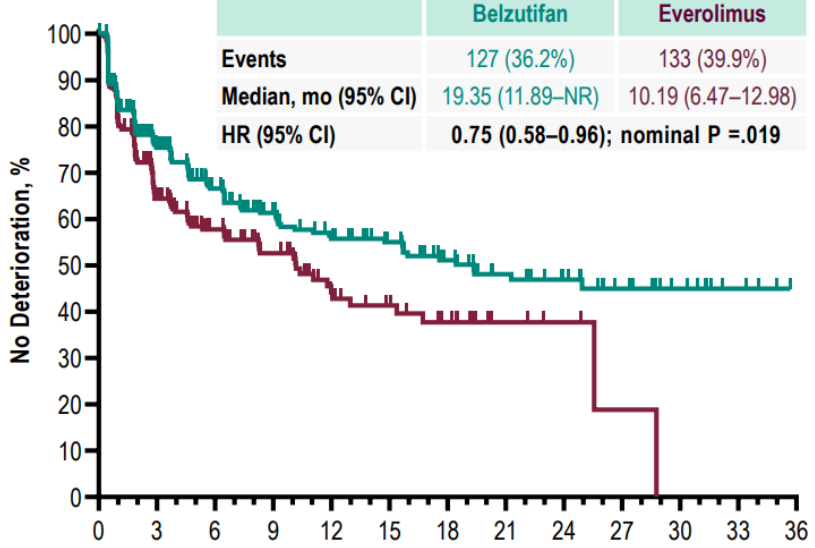
	Belzutifan	Everolimus
Events	102 (29.0%)	138 (41.3%)
Median, mo (95% CI)	NR (21.26–NR)	11.99 (5.55–15.38)
HR (95% CI)	0.53 (0.41–0.69); nominal P <.0001	



No. at Risk													
Belzutifan	352	192	143	123	100	84	62	46	25	14	8	4	0
Everolimus	334	137	83	62	41	30	15	6	3	2	1	0	0

QLQ-C30 GHS/QoL: TTD

	Belzutifan	Everolimus
Events	127 (36.2%)	133 (39.9%)
Median, mo (95% CI)	19.35 (11.89–NR)	10.19 (6.47–12.98)
HR (95% CI)	0.75 (0.58–0.96); nominal P =.019	



No. at Risk													
Belzutifan	351	184	131	105	86	75	55	41	28	17	10	4	0
Everolimus	333	130	80	53	32	25	17	5	3	1	0	0	0

Time to confirmed deterioration (TTD) was defined as time from baseline to first onset of ≥3 points for FKSI-DRS or ≥10 points for EORTC QLQ-C30 with confirmation by the subsequent visit.
NR, not reached. Data cutoff date for IA2: June 13, 2023.

- Données de qualité de vie:
- Dégradation plus tardive sous Belzutifan que sous Everolimus

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 3

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- Belzutifan : bénéfice en PFS comparativement à un comparateur actif (Everolimus) après anti-angiogénique et immunothérapie
- Pas de bénéfice en survie globale pour l'instant (analyse intermédiaire)
- Meilleur taux de réponse et durée de réponse prolongée
- Bénéfice en qualité de vie
- Profil de tolérance qui semble correct

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 2 en association

Phase 2 LITESPARK-003 Study of Belzutifan in Combination With Cabozantinib for Advanced Clear Cell Renal Cell Carcinoma

Toni K. Choueiri[1]; Todd Bauer[2]; Jaime Merchan[3]; David McDermott[4]; Robert Figlin[5]; Edward Arrowsmith[6]; Marc Dror Michaelson[7]; Elisabeth I. Heath[8]; Anishka D'Souza[9]; Song Zhao[10]; Leila Mhamdi[11]; Rodolfo Perini[11]; Donna Vickery[11]; Scott S. Tykodi[12]

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 2

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Phase 2 LITESPARK-003 Study of Belzutifan in Combination With Cabozantinib for Advanced Clear Cell Renal Cell Carcinoma

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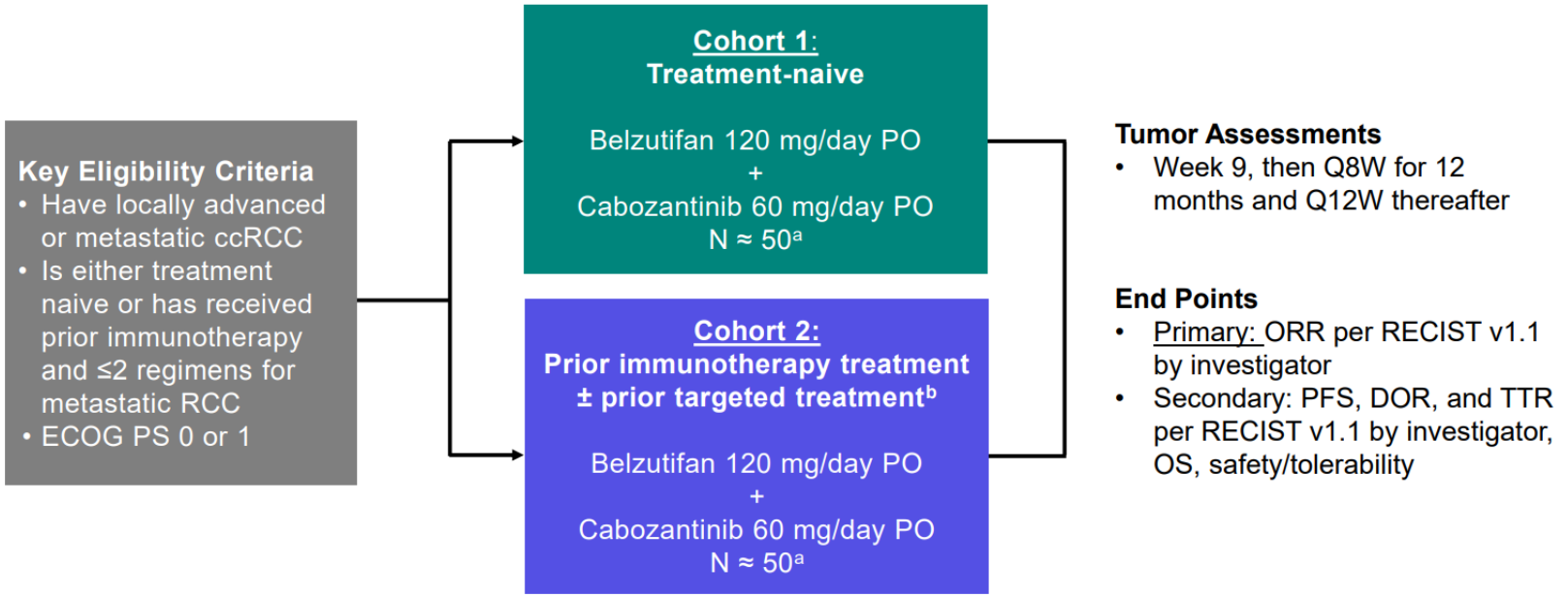
Study Design of LITESPARK-003 (NCT03634540)



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CANCER DU REIN AVANCE

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Baseline Characteristics

	Cohort 1 N = 50	Cohort 2 N = 52
Age, median (range), years	64.0 (33-89)	63.0 (43-79)
≥65 years	23 (46)	24 (46)
Male	40 (80)	38 (73)
ECOG performance status 0/1, n (%)	33 (66)/17 (34)	23 (44)/29 (56)
IMDC risk group		
Favorable	28 (56)	11 (21)
Intermediate/poor	22 (44)	41 (79)
Prior nephrectomy	40 (80)	42 (81)
Number of prior lines of anticancer therapy		
1	0 (0)	29 (56)
2	0 (0)	23 (44)
Prior type of anticancer therapy		
Immunotherapy[a]	0 (0)	28 (54)
Immunotherapy + anti-VEGF/VEGFR therapy[b]	0 (0)	24 (46)

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 2

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Phase 2 LITESPARK-003 Study of Belzutifan in Combination With Cabozantinib for Advanced Clear Cell Renal Cell Carcinoma

Toni K. Choueiri[1]; Todd Bauer[2]; Jaime Merchan[3]; David McDermott[4]; Robert Figlin[5]; Edward Arrowsmith[6]; Marc Dror Michaelson[7]; Elisabeth I. Heath[8]; Anishka D'Souza[9]; Song Zhao[10]; Leila Mhamdi[11]; Rodolfo Perini[11]; Donna Vickery[11]; Scott S. Tykodi[12]

ORR by Investigator in All Patients and by IMDC Risk

	Cohort 1			Cohort 2		
	Overall N = 50	IMDC risk category		Overall N = 52	IMDC risk category	
		Favorable n = 28	Intermediate/ poor n = 22		Favorable n = 11	Intermediate/ poor n = 41
ORR (CR + PR)	**35 (70)**	22 (79)	13 (59)	**16 (31)**	3 (27)	13 (32)
DCR (CR + PR + SD)	49 (98)	28 (100)	21 (96)	48 (92)	11 (100)	37 (90)
Best response						
CR	4 (8)	3 (11)	1 (5)	2 (4)	0	2 (5)
PR	31 (62)	19 (68)	12 (55)	14 (27)	3 (27)	11 (27)
SD	14 (28)	6 (21)	8 (36)	32 (62)	8 (73)	24 (59)
PD	1 (2)	0 (0)	1 (5)	3 (6)	0 (0)	3 (7)
Not available[a]	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 2

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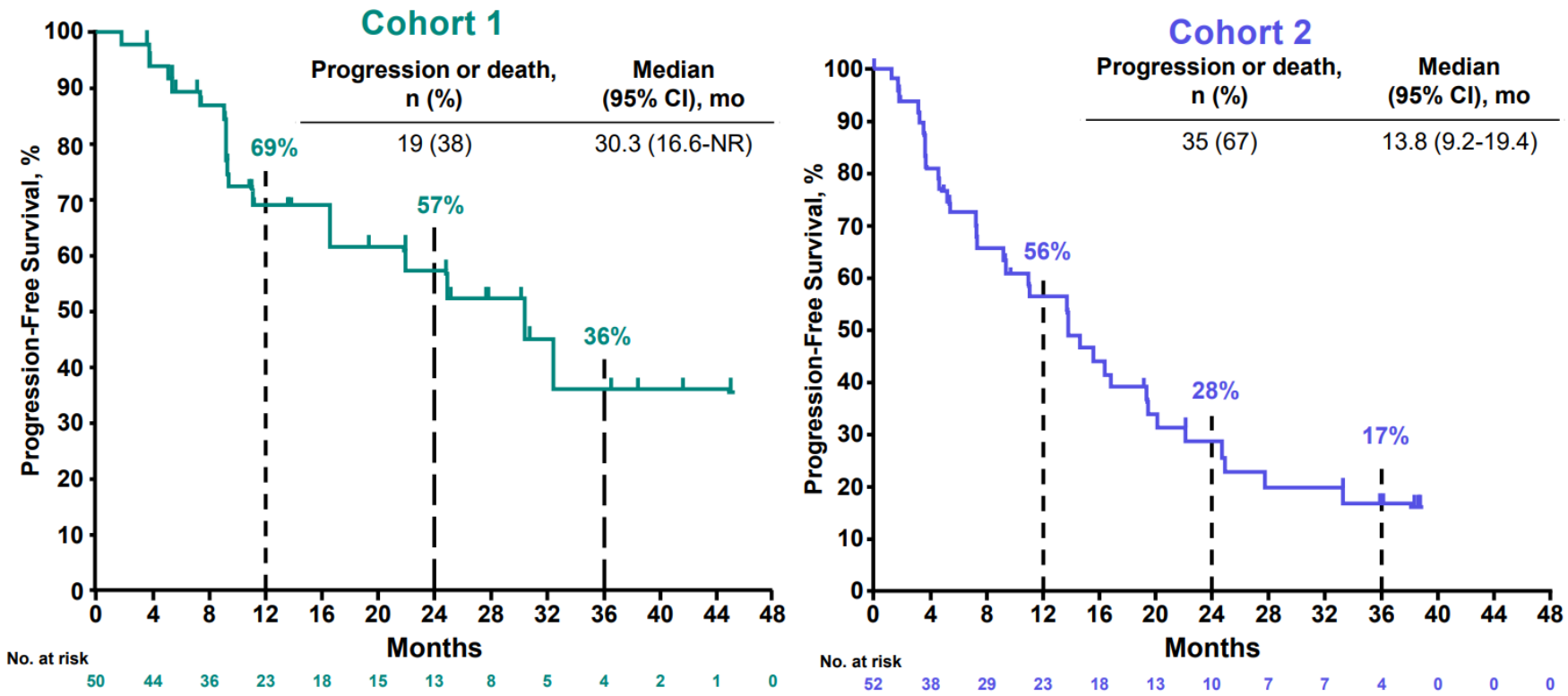
Progression-Free Survival by Investigator



- PFS cohorte 1 : 30,3 mois
- PFS cohorte 2 : 13,8 mois (médianes)

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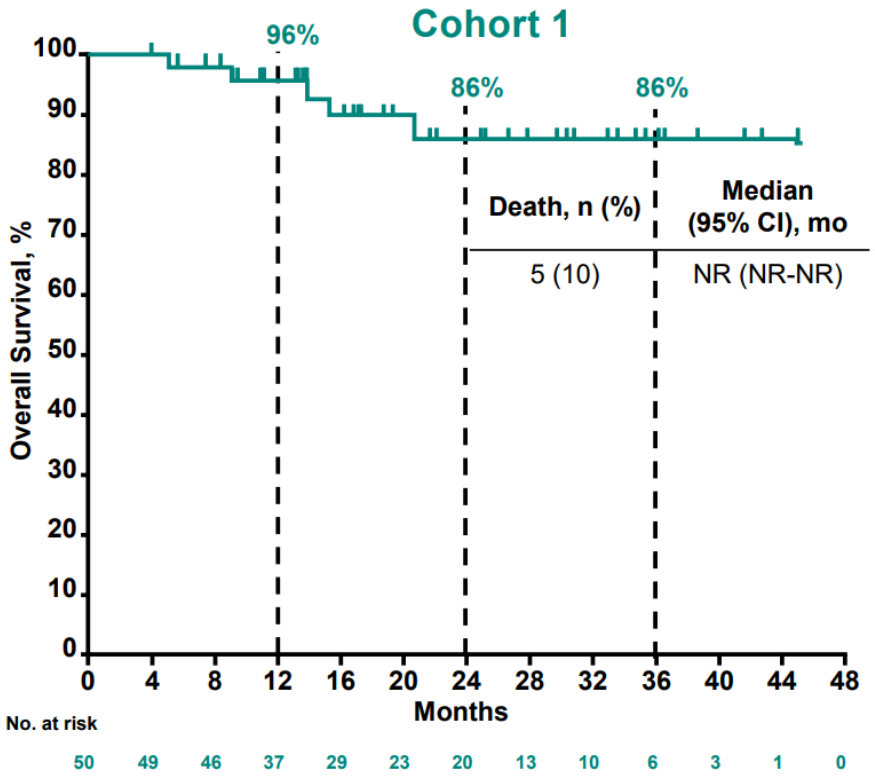
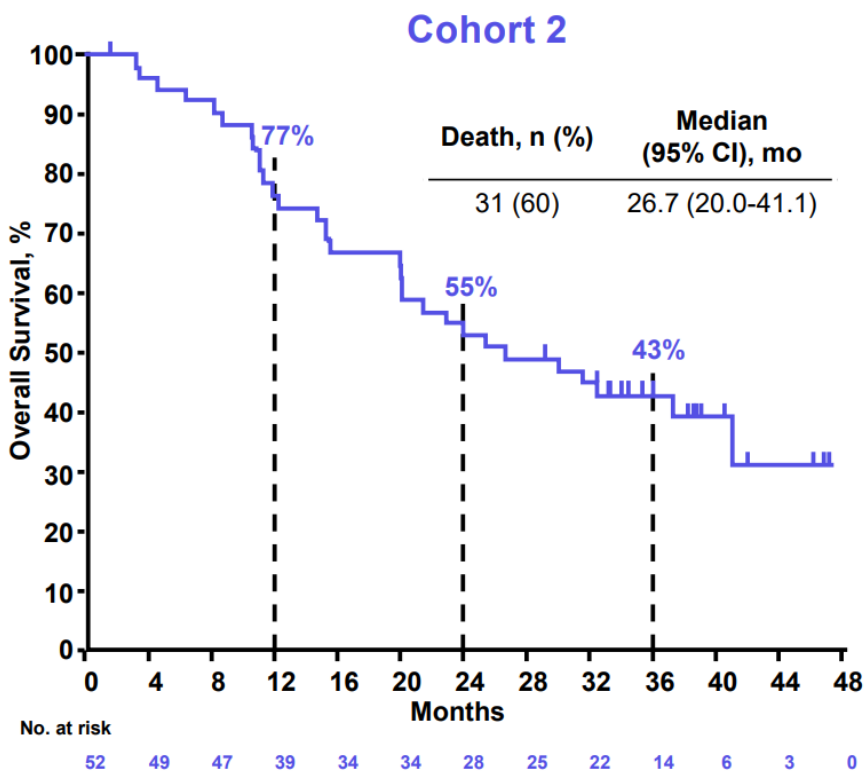
Overall Survival





- OS cohorte 1 : NA
- OS cohorte 2 : 26,7 mois (médianes)

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CANCER DU REIN AVANCE

Cellules claires : BELZUTIFAN : Données de phase 2

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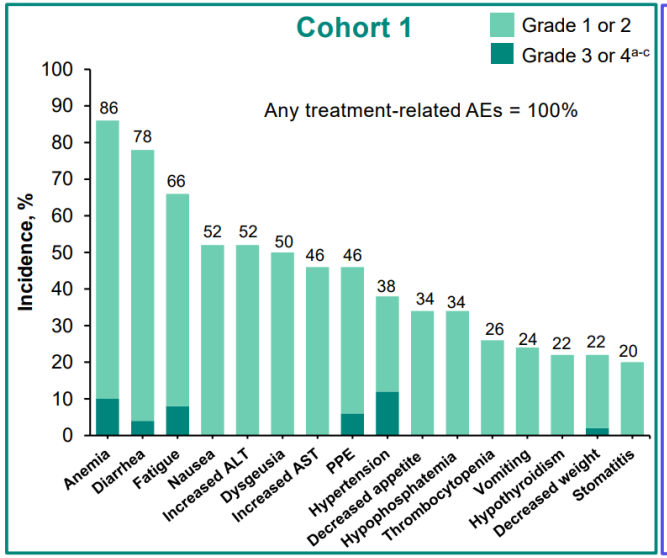
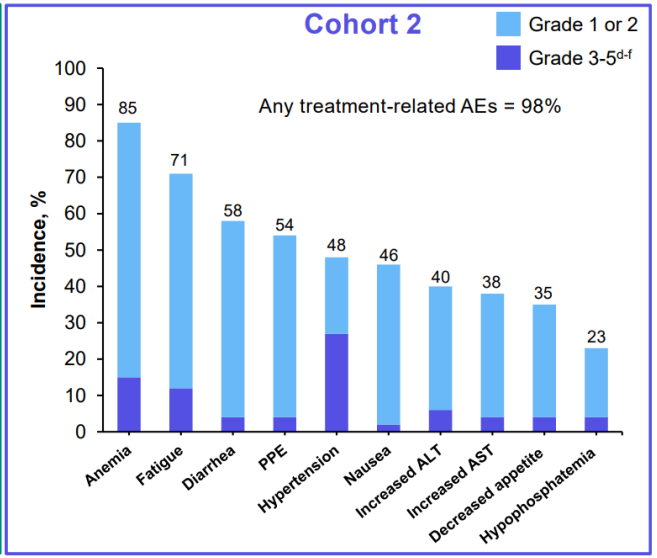
Summary of Treatment-Related Adverse Events

	Cohort 1 N = 50	Cohort 2 N = 52
Any-grade treatment-related AE	50 (100)	51 (98)
Grade ≥3 treatment-related AE	23 (46)	33 (64)
Grade 5 treatment-related AE	0 (0)	1 (2)[a]
Discontinued any drug because of a treatment-related AE	7 (14)	11 (21)
Serious treatment-related AE	7 (14)	16 (31)
Dose reduction because of a treatment-related AE	38 (76)	37 (71)

Treatment-Related Adverse Events With Incidence of ≥20%





Data cutoff date: May 15, 2023

[a]No grade 5 treatment-related AEs occurred in cohort 1. [b]Grade 4 treatment-related hypertension occurred in 1 patient (2%) in cohort 1. [c]Grade 3 hypoxia occurred in 3 patients (6%) in cohort 1. [d]Grade 5 treatment-related respiratory failure occurred in 1 patient (2%) in cohort 2. [e]No grade 4 treatment-related AEs occurred in cohort 2. [f]Grade 3 hypoxia occurred in 3 patients (6%) in each cohort 2.

- Toxicités G3+ : 46% et 64%
- Arrêt pour tox 14% et 21%
- Réduction dose 76% et 71%

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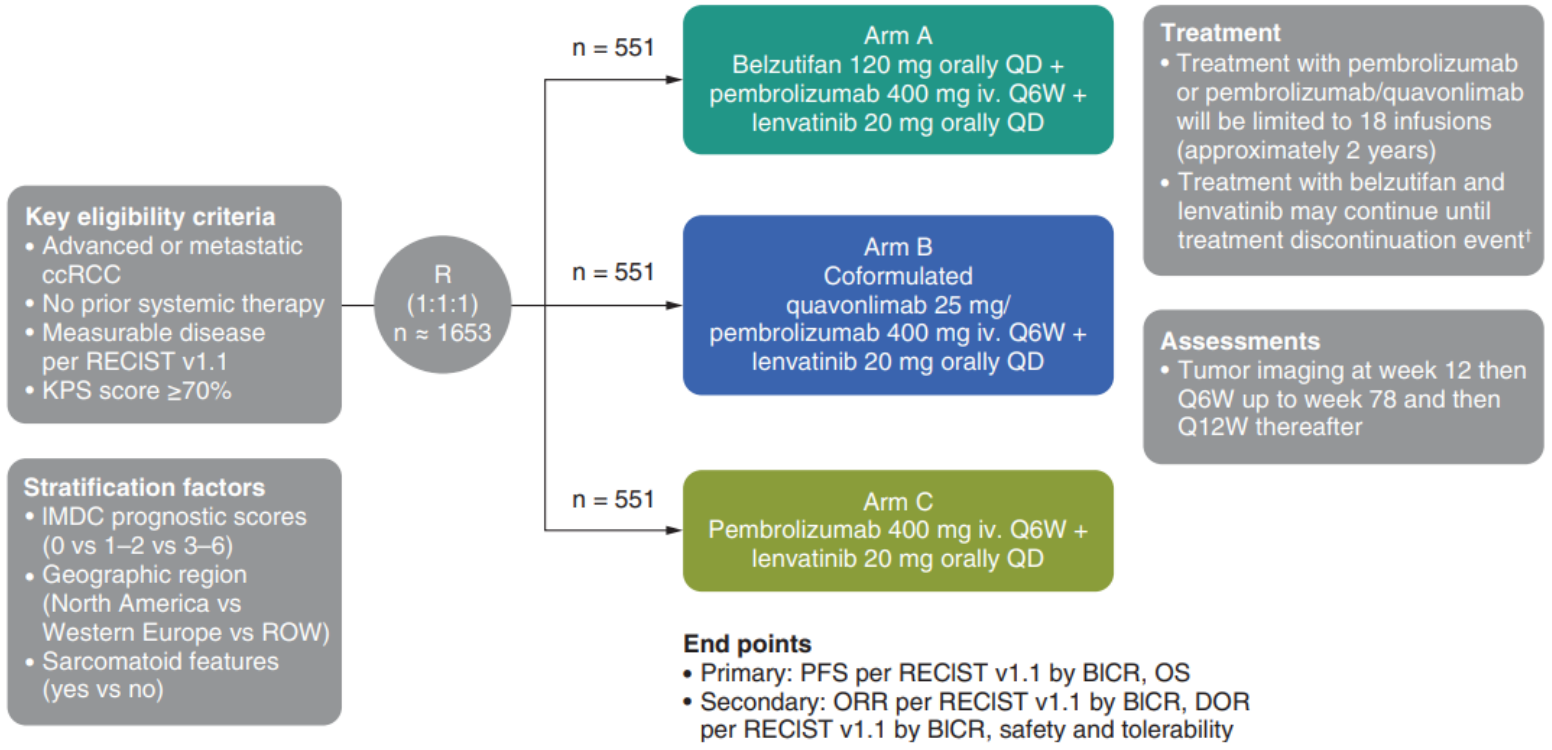
Cellules claires : BELZUTIFAN : Exemples d'essais en cours

- Métastatique naïf de traitement : LITESPARK-012



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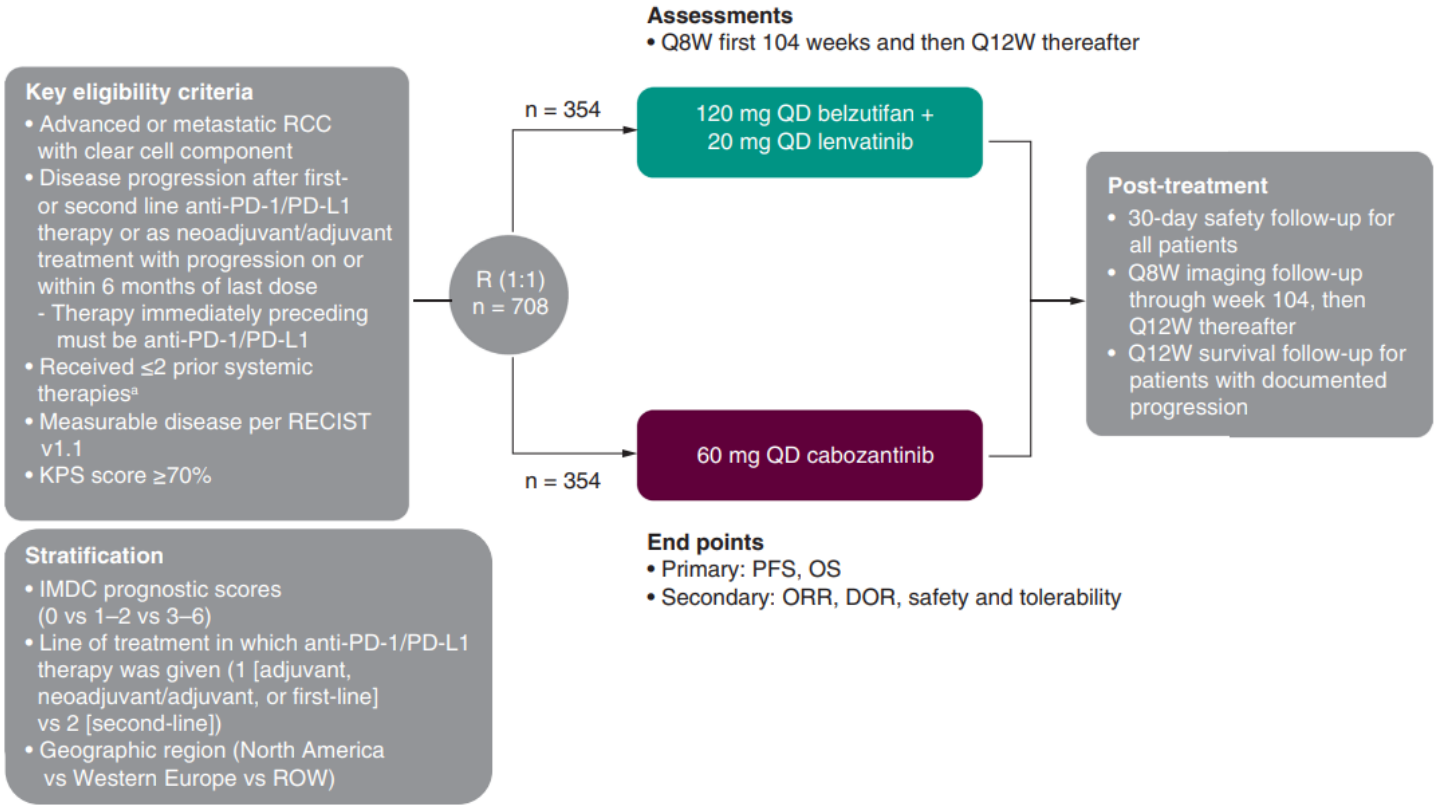
Cellules claires : BELZUTIFAN : Exemples d'essais en cours

- Métastatique post-immunothérapie LITESPARK-011



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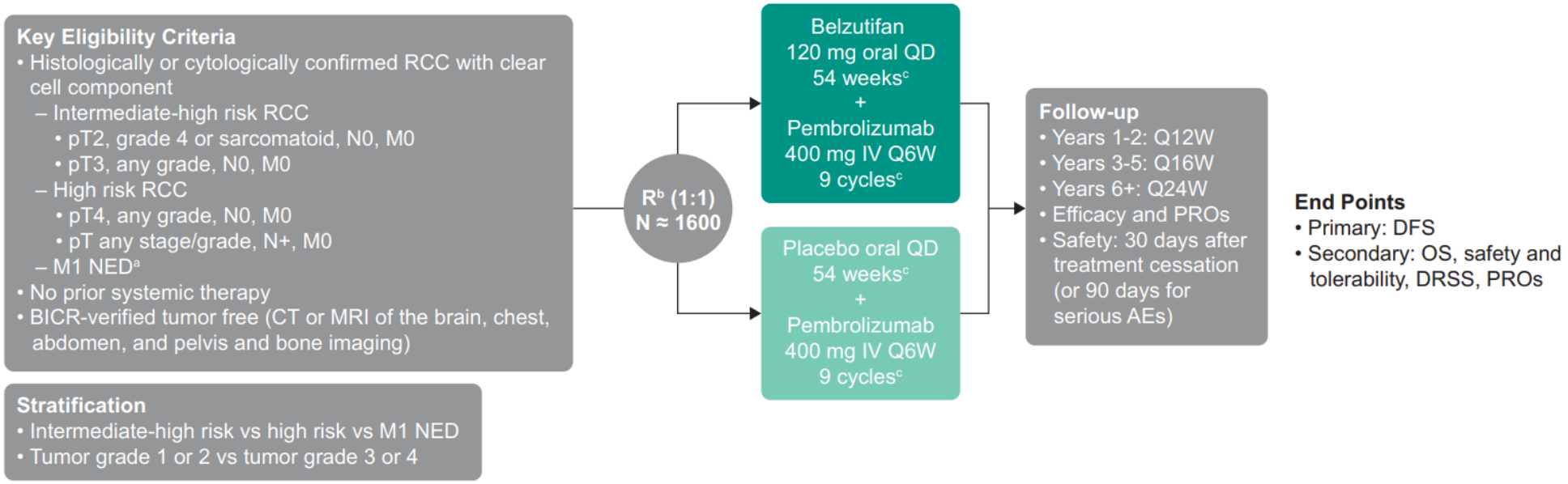
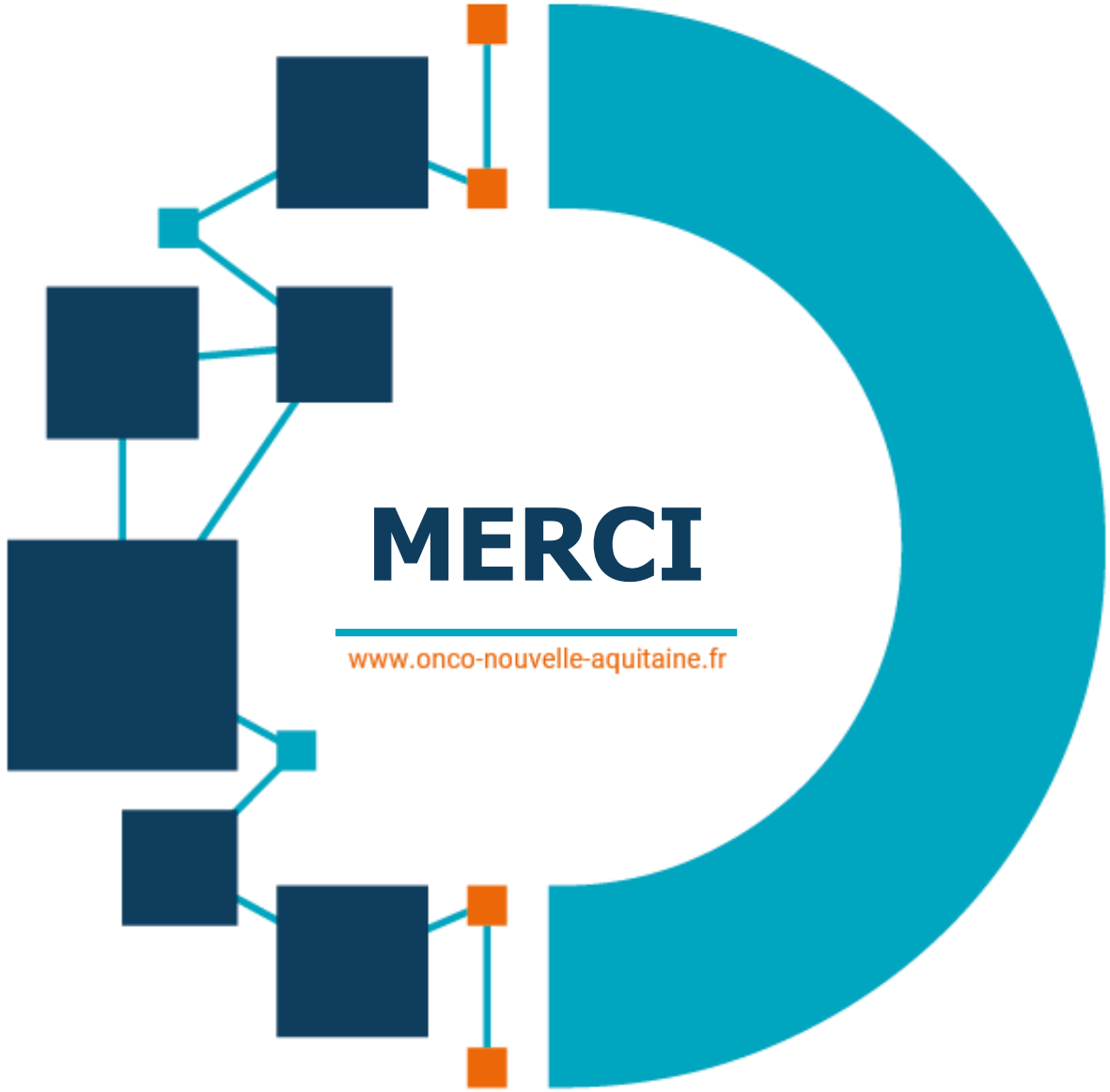
Cellules claires : BELZUTIFAN : Exemples d'essais en cours

- Adjuvant : LITESPARK-022



CANCER DU REIN AVANCE

- **Données avec le BELZUTIFAN**
  - *Données convaincantes en monothérapie après immunothérapie et ITK?*
  - *Nouvelle classe thérapeutique avec des résultats positifs*
  - *Combinaisons pouvant trouver leur place notamment après immunothérapie adjuvante ou en cas de contre-indication*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