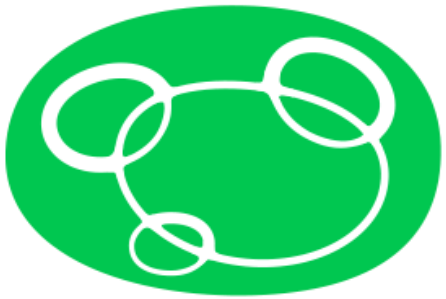

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TREATMENT SEQUENCING IN METASTATIC RENAL CELL CARCINOMA (mRCC)

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BACKGROUND

- Landscape of **treatment for mRCC** has **radically changed in the last few years**
- Treatment with **cabozantinib increased PFS and OS** when **compared with everolimus** in patients previously treated with VEGFR tyrosine kinase inhibitors (TKI)[1]
- Treatment with **nivolumab increased OS** when **compared with everolimus** in patients previously treated with antiangiogenic therapies[2]
- The combination of **nivolumab plus ipilimumab** resulted in **longer PFS and OS** when **compared with sunitinib** in treatment naïve patients with intermediate and poor prognosis based on the IMDC prognostic group[3]
- The combination of **axitinib plus pembrolizumab** resulted in **longer PFS and OS** when **compared with sunitinib** in treatment naïve patients irrespectively of the IMDC prognostic group[4]
- The combination of **axitinib plus avelumab** resulted in **longer PFS** when **compared with sunitinib** in treatment naïve patients irrespectively of the IMDC prognostic group[5]
- **No evidence** from prospective studies are available **for treatment of patients who have progressed after immunotherapy in first line setting**

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

1. Choueiri TK, et al. Lancet Oncol. 2016;17:917-927; 2. Motzer RJ, et al. N Engl J Med. 2015;373:1803-1813; 3. Motzer RJ, et al. N Engl J Med. 2018;378:1277-90; 4. Rini BI, et al. N Engl J Med. 2019;380:1116-27; 5. Motzer RJ, et al. N Engl J Med. 2019;380:1103-15.

VEGFR-TKI AFTER IO: *THE FRENCH EXPERIENCE*

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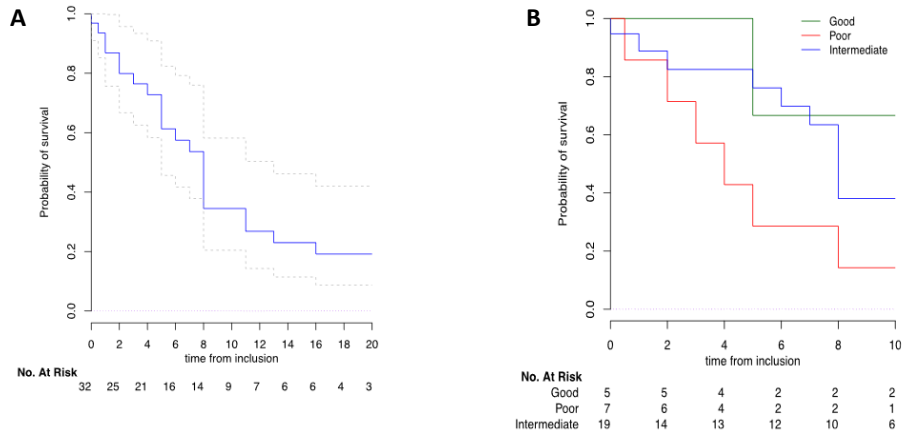
SECOND-LINE THERAPIES AFTER NIVOLUMAB-IPILIMUMAB FAILURE IN mRCC

- Retrospective analysis of patients treated with nivolumab-ipilimumab who received subsequent TKI as part of the Checkmate 214 study
- Overall **33 patients** received subsequent TKI after nivolumab-ipilimumab failure
- Median follow-up from start of subsequent TKI is 22 months (95% CI: 19 -NR)
- **Best response** was assessed in 30 patients: 12 partial responses (36%), 13 stable diseases (39%) and five progressive diseases (15%)

PROGRESSION-FREE SURVIVAL



PFS on first subsequent treatment after double immune checkpoint blockade for a) all population; b) according to IMDC prognostic groups at VEGFR TKI start

PFS BY TYPE OF TKI

Type of TKI	Median PFS
1st generation (suni/pazo)	8 months
2nd generation (axi/cabo)	7 months
	95% CI: 5-NA, p=0.66

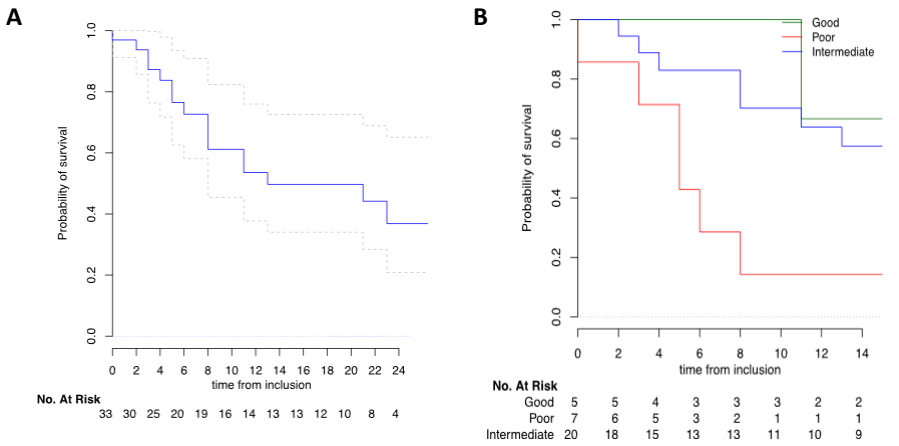
Axi, axitinib; cabo, cabozantinib; CI, confidence interval; IDMC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immuno-oncology; mRCC, metastatic renal cell carcinoma; NA, not available; NR, not reached; pazo, pazopanib; PFS, progression free survival; suni, sunitinib; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

Auvray M, et al. Eur J Cancer. 2019;108:33-40.

VEGFR-TKI AFTER IO: *THE FRENCH EXPERIENCE*

SECOND-LINE THERAPIES AFTER NIVOLUMAB-IPILIMUMAB FAILURE IN mRCC

OVERALL SURVIVAL



OS on first subsequent treatment after double immune checkpoint blockade for a) all population; b) according to IMDC prognostic groups at VEGFR TKI start

OVERALL SURVIVAL BY TYPE OF TKI

Type of TKI	Median OS
1st generation (suni/pazo)	11 months
2nd generation (axi/cabo)	NR
	95% CI: 11-NR, p=0.11

Axi, axitinib; cabo, cabozantinib; CI, confidence interval; IDMC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immuno-oncology; mRCC, metastatic renal cell carcinoma; NR, not reached; OS, overall survival; pazo, pazopanib; suni, sunitinib; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

Auvray M, et al. Eur J Cancer. 2019;108:33-40.

VEGFR-TKI AFTER IO: *THE US EXPERIENCE*

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SECOND-LINE THERAPIES AFTER IMMUNE CHECKPOINT INHIBITOR FAILURE IN mccRCC

- Retrospective study of mccRCC patients treated with second line VEGFR-TKI after progressive disease with first line immune checkpoint inhibitor

Patient characteristics	
Variable	**N (%)**
Gender	
Male	50 (71)
Female	20 (29)
Median age mRCC diagnosis	59
Years (range)	(43.6–74.8)
Stage at initial diagnosis of RCC	
Stage I–III	27 (39)
Stage IV	43 (61)
IMDC risk score at time of 2L TKI start	
Favourable	8 (11)
Intermediate	48 (69)
Poor	14 (20)
Nephrectomy status	
Status after nephrectomy	60 (86)
Primary in situ	10 (14)
Histology	
Clear cell	70 (100)
Sarcomatoid dedifferentiation	14 (20)

Patient characteristics	
Variable	**N (%)**
Sites of metastatic disease at TKI start	
Lung	61 (87)
Bone	35 (50)
Liver	12 (17)
Lymph node	48 (69)
Adrenal	22 (31)
First-line ICI	
Anti–PD-(L)1 single agent	12 (17)
PD-1 + CTLA-4 blockade (followed by maintenance anti-PD-1)	33 (47)
PD-(L)1 + anti-VEGF therapy	25 (36)
Reason for discontinuation of 1L ICI	
Progressive disease	58 (83)
Toxicity	12 (17)
Median duration on ICI, months (range)	5.9 (0.4–25.2)

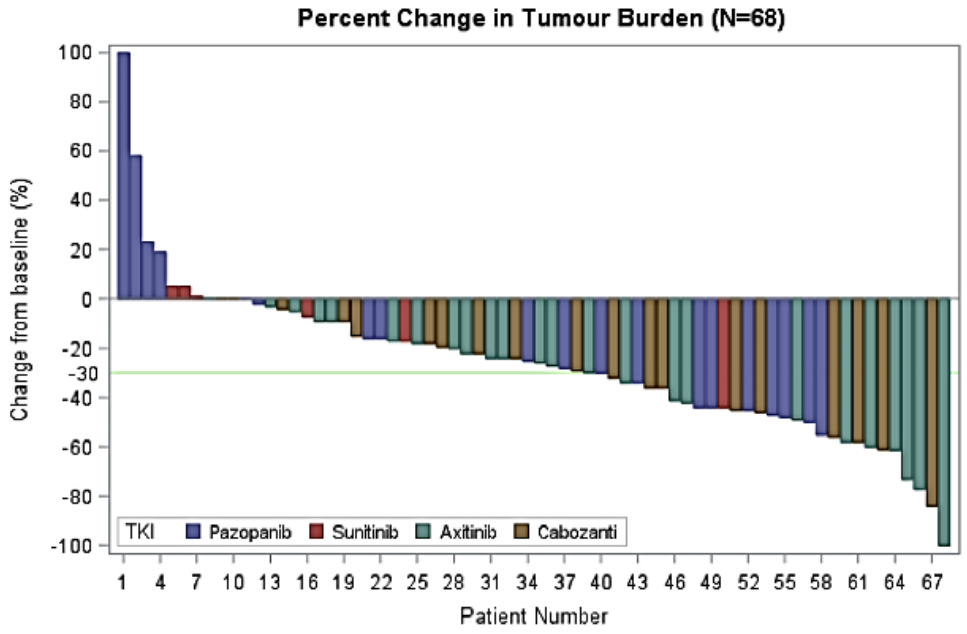
1L, first line; 2L, second line; CTLA-4, cytotoxic T-lymphocyte associated protein 4, ICI, immune checkpoint inhibitor; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immuno-oncology; mccRCC, metastatic clear cell renal cell carcinoma; mRCC, metastatic renal cell carcinoma; PD-1, programmed death-1; PD-(L)1, programmed death ligand-1; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitors; VEGF(R), vascular endothelial growth factor (receptor)

Shah AY, et al. Eur J Cancer. 2019;114:67-75.

VEGFR-TKI AFTER IO: *THE US EXPERIENCE*

SECOND-LINE THERAPIES AFTER IMMUNE CHECKPOINT INHIBITOR FAILURE IN mccRCC

BEST OVERALL RESPONSE BY SECOND LINE TKI



Best overall response to second line TKI (n=68)	Patients (n,%)
CR	1 (1.5%)
PR	27 (39.7%)
SD	36 (52.9%)
PD	4 (6%)
DCR	94%

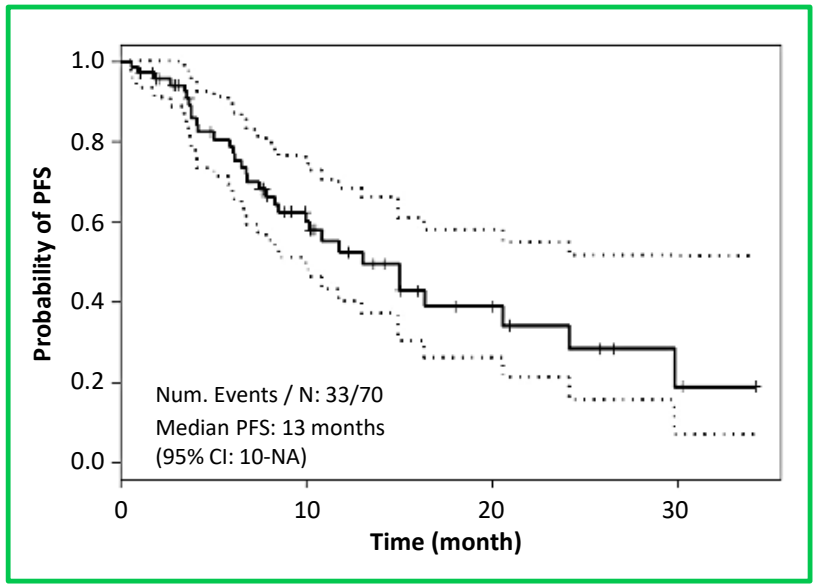
CR, complete response; DCR, disease control rate; mccRCC, metastatic clear cell renal cell carcinoma; mRCC, metastatic renal cell carcinoma; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitors

Shah AY, et al. Eur J Cancer. 2019;114:67-75.

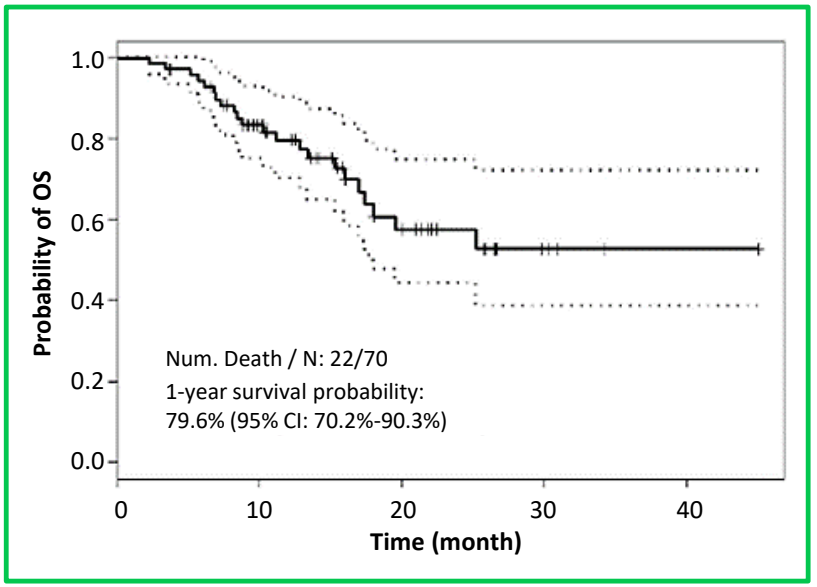
VEGFR-TKI AFTER IO: *THE US EXPERIENCE*

SECOND-LINE THERAPIES AFTER IMMUNE CHECKPOINT INHIBITOR FAILURE IN mccRCC

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



CI, confidence interval; IO, immuno-oncology; mccRCC, metastatic clear cell renal cell carcinoma; NA, not available; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

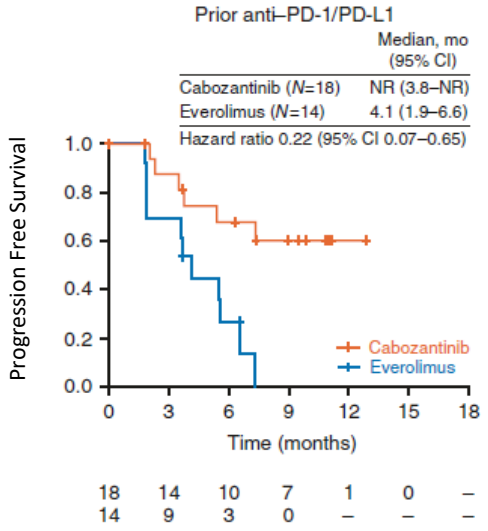
Shah AY, et al. Eur J Cancer. 2019;114:67-75.

VEGFR-TKI AFTER IO: *CABOZANTINIB AFTER IO*

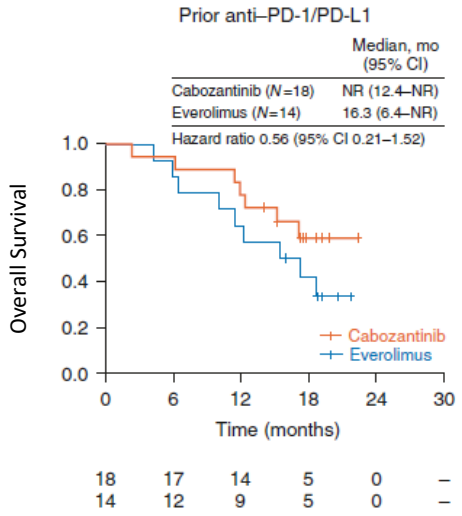
OUTCOMES BASED ON PRIOR THERAPY IN THE METEOR TRIAL IN ADVANCED RCC

- A post hoc analysis of patients enrolled in the METEOR trial who received cabozantinib or everolimus after progression on a VEGFR TKI or anti-PD1/PD-L1 therapy
- In the prior anti-PD-1/PD-L1 subgroup, cabozantinib retained its activity over everolimus in terms of PFS, while data are not mature for OS

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



CI, confidence interval; IO, immuno-oncology; NR, not reached; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression free survival; RCC, metastatic renal cell carcinoma; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

Powles T, et al. Br J Cancer. 2018;119:663-9.

AXITINIB AFTER IO: *A PROSPECTIVE STUDY*

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- A prospective study of patients with mRCC who received checkpoint inhibitor therapy as the most recent treatment. There was no limit on number of previous therapies received
- Patients received oral axitinib at a starting dose of 5 mg twice daily with dose titration every 14 days in 1 mg increments (up to 10 mg twice daily maximum dose)

Previous therapies and response to immune checkpoint inhibitor	Participants, n=40
Number of previous therapies*	
1	11 (28%)
2	19 (48%)
3	9 (23%)
4	1 (3%)
Most recent therapy	
Nivolumab	25 (63%)
Ipilimumab plus nivolumab	6 (15%)
Nivolumab plus hypoxia-inducible factor inhibitor	3 (8%)
Atezolizumab	2 (5%)
Bevacizumab plus atezolizumab	2 (5%)
Durvalumab plus tremelimumab	1 (3%)
Durvalumab	1 (3%)
Best response to checkpoint inhibitor therapy†	8 (20%)
Partial response	21 (53%)
Stable disease	10 (25%)
Progressive disease	

Previous therapies and response to immune checkpoint inhibitor	Participants, n=40
Duration on previous checkpoint inhibitor	
<6 months	25 (63%)
≥6 months	15 (38%)
Median duration, months	4.8 (2.0-8.7)
Reason for checkpoint inhibitor discontinuation	37 (93%)
Disease progression	3 (8%)
Toxicity‡	
Time from checkpoint inhibitor discontinuation to axitinib initiation, months	1.1 (0.7-1.7)

Values are n (%) or median (IQR). *The majority of patients (28 [70%]) received previous VEGF-directed therapy. †Unknown for one patient.
‡One patient each: fatigue, pneumonitis and colitis.

IO, immuno-oncology; IQR, interquartile range; mRCC, metastatic renal cell carcinoma; VEGF, vascular endothelial growth factor

Ornstein MC, et al. Lancet Oncol. 2019;20:1386-94.

AXITINIB AFTER IO: *A PROSPECTIVE STUDY*

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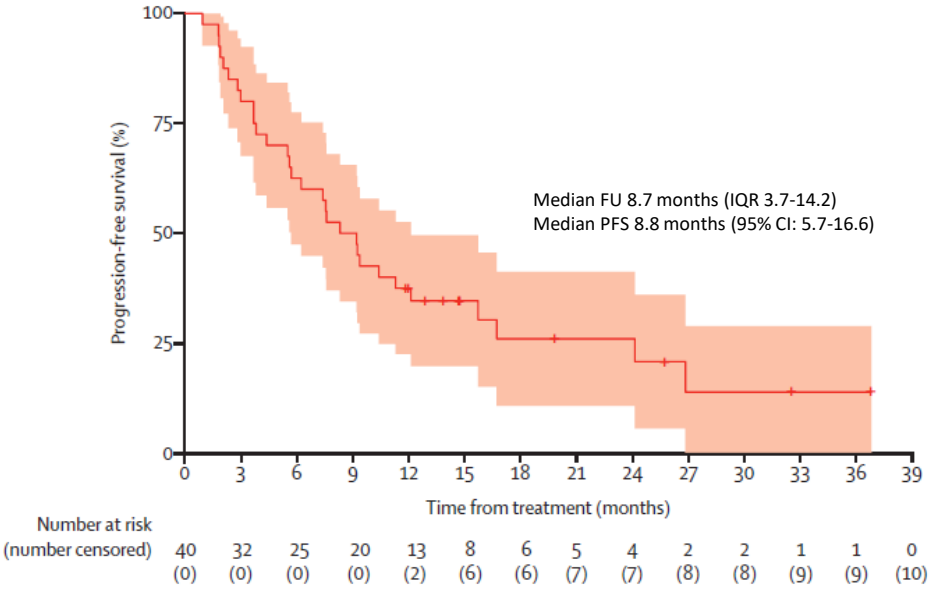
PROGRESSION-FREE SURVIVAL



BEST RESPONSE

Best response to axitinib treatment (N=40)	Patients n (%)
Complete	1 (3%)
Partial	17 (43%)
Stable	18 (45%)
Progression	4 (10%)

CI, confidence interval; FU, follow up; IO, immuno-oncology; IQR, interquartile range

Ornstein MC, et al. Lancet Oncol. 2019;20:1386-94.

VEGFR-TKI AFTER IO: *THE LENVATINIB/EVEROLIMUS COMBINATION*

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- Retrospective analysis of mRCC patients with lenvatinib alone, or in combination with everolimus, after at least 2 prior lines of therapy, including ICI and VEGFR-TKI

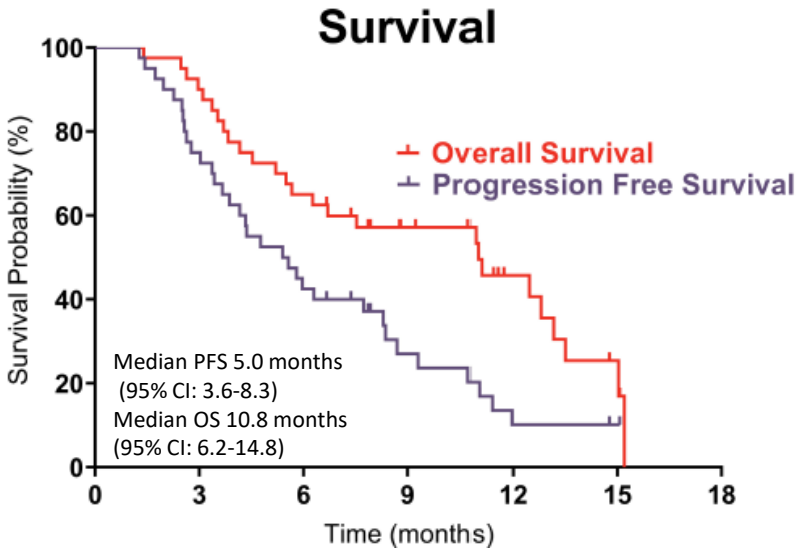
Baseline Patient and Disease Characteristics	
Median age, year (range)	59 (34-76)
Sex, no. (%) Male Female	 25 (62.5) 15 (37.5)
ECOG performance status, no. (%) 0 1 2 3	 4 (10) 21 (52.5) 14 (35) 1 (2.5)
IMDC prognostic risk, no. (%) Favorable Intermediate Poor	 1 (2.5) 35 (87.5) 4 (10)
Clear cell histology, no. (%)	31 (77.5)
Prior nephrectomy, no. (%)	34 (85)
Three or more sites of metastatic disease, no. (%)	38 (95)

Baseline Patient and Disease Characteristics	
Three or more sites of metastatic disease, no. (%)	38 (95)
Prior immune checkpoint inhibitor treatment, no. (%) Nivolumab Nivolumab + Ipilimumab Other ICI combination therapy	 28 (70) 4 (10) 8 (20)
Prior cabozanitinib treatment, no. (%)	35 (87.5)
Prior lines of therapy, no. (%) 2-3 4-5 6-10	 15 (37.5) 17 (42.5) 8 (20)
Treatment received, no. (%) Lenvatinib with everolimus Lenvatinib alone	 30 (75) 10 (25)

ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immuno-oncology; mRCC, metastatic renal cell carcinoma; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

Wiele AJ, et al. Ann Oncol. 2019; 30(suppl_5): Abstract 964P (poster presentation)

VEGFR-TKI AFTER IO: *THE LENVATINIB/EVEROLIMUS COMBINATION*



Antitumor Activity of Lenvatinib +/– Everolimus	
Best overall response – no. (%)	
Complete response	0 (0)
Clinical benefit	27 (67.5)
Partial response	12 (30)
Stable disease	15 (37.5)
Progressive disease	13 (32.5)

CI, confidence interval; IO, immuno-oncology

Wiele AJ, et al. Ann Oncol. 2019; 30(suppl_5): Abstract 964P (poster presentation)

RENAL CELL CARCINOMA: ESMO CLINICAL PRACTICE GUIDELINES

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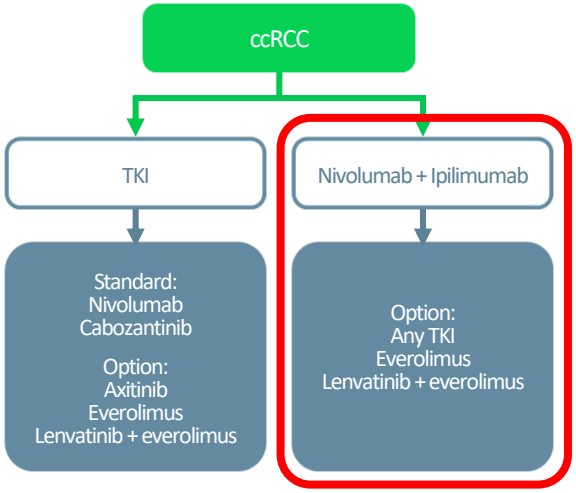
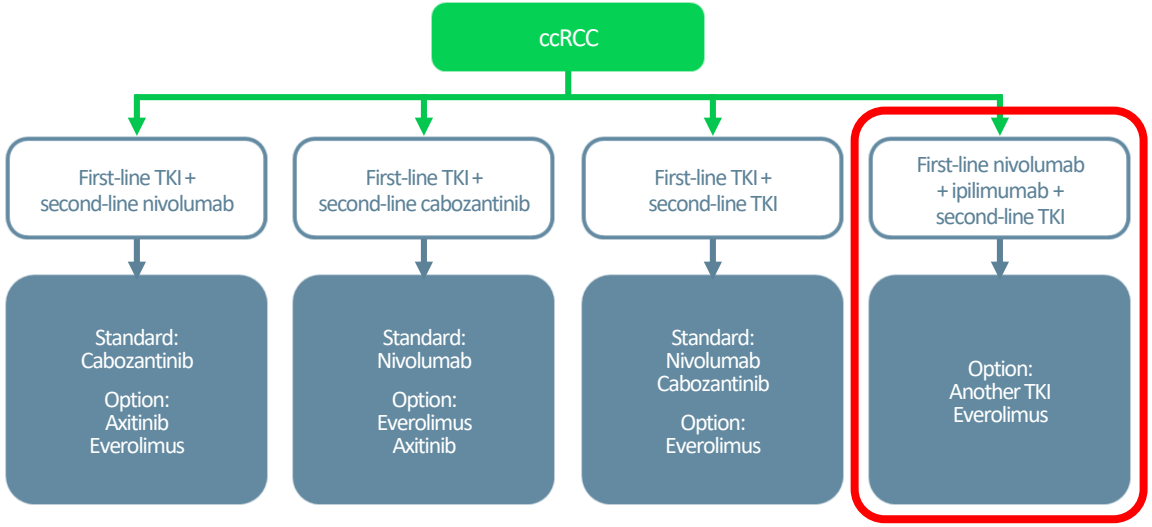
Second-line treatment of ccRCC

- ESMO guidelines recommend the use of any TKI after progression on Nivolumab + Ipilimumab and the use of nivolumab or cabozantinib after progression on a TKI



Third-line treatment of ccRCC

- For patients who progressed after first line with nivolumab + ipilimumab and second line with a TKI the use of another TKI or everolimus is recommended
- Beyond second line treatment, enrolment into clinical trials is strongly encouraged



1L, first line; 2L, second line; ccRCC, clear cell renal cell carcinoma; ESMO, European society for medical oncology; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

Escudier B, et al. Annals of Oncology 2019;30:706-20.

NCCN GUIDELINES – KIDNEY CANCER

- NCCN guidelines do not recommend specific treatment for patients who progressed on an IO-based first-line and simply report the available options for first and subsequent lines.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred regimens**	**Other recommended regimens**	**Useful under certain circumstances**
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	**Other recommended regimens**	**Useful under certain circumstances**
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

IL-2, interleukin-2; IO, immuno-oncology; NCCN, national comprehensive cancer network

NCCN guidelines for kidney cancer v 2.2020 August 5,2019.

CONCLUSIONS

- **No prospective data for second-line of therapy after progression on an IO-based first-line therapy**
- The **difference in reimbursement** regulations in each country **might increase the heterogeneity in clinical approach** to treatment of mRCC **and sequencing of agents** across multiple lines of treatment
- The **VEGFR TKIs retain their activity after IO** with a PFS from 7 to 13 months and a response rate of 35-40%[1, 2]

  …but available studies are heterogeneous for type of TKI used
- **Enrolment** of patients **in clinical trial should be encouraged**
- In clinical practice, based on data from the CABOSUN[3] and METEOR[4] trials, **cabozantinib can be considered the best TKI after progression on an IO-based first-line therapy**

IO, immuno-oncology; mRCC, metastatic renal cell carcinoma; PFS, progression-free survival; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor

1. Auvray M et al. Eur J Cancer. 2019;108:33-40; 2. Shah AY et al. Eur J Cancer. 2019;114:67-75; 3. Choueiri TK, et al. JCO 2017;35(6):591-597; 4. Powles T, et al. Br J Cancer. 2018;119:663-9

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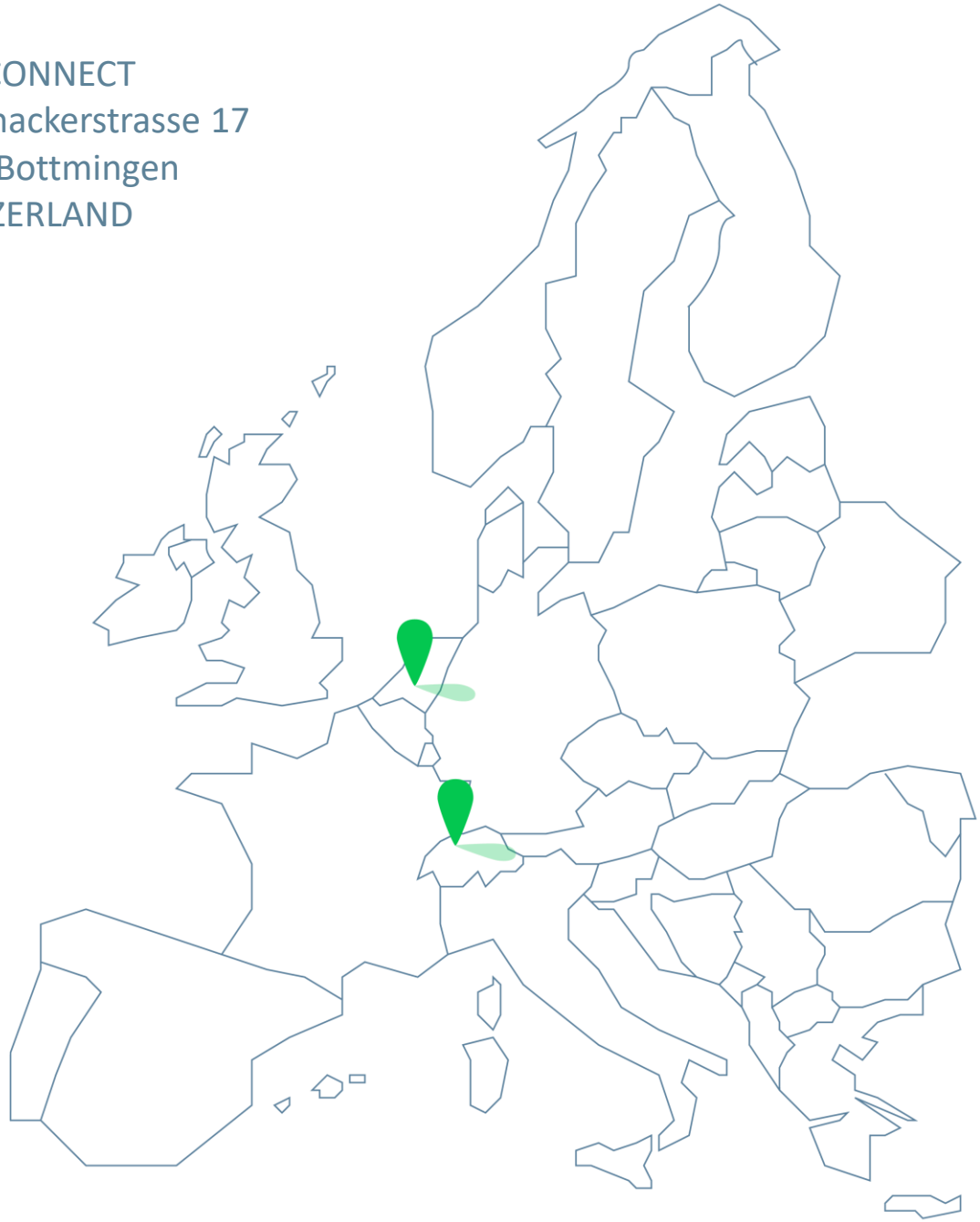

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