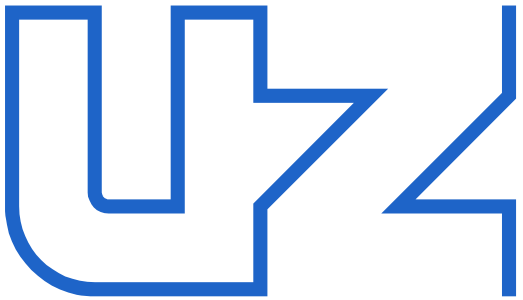

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Sylvie Rottey / Medical Oncology
Drug Research Unit Gent

Therapeutic algorithm in RCC : from adjuvant to advanced disease

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Adjuvant therapy

metastatic disease

Localized setting

Phase 3 clinical trials of VEGF inhibitors in adjuvant treatment of renal cell carcinoma

Trial	treatment arms	n	Disease histology	Disease stage	DFS HR(95%CI)	p	OS HR(95%CI)
Assure	Sunitinib (37,5-50mg) vs Placebo	647	Any	pT1b(G3-4)N0M0 or pT2-4(Gx)N1-3M0	1.02	0.8	1.17
Assure	Sorafenib (400-800mg) vs placebo	540	Any	Intermediate or high risk (Leibovich score, 3-11)	0.72		
S-trac	Sunitinib (50mg) vs Placebo	309	predominantly CC	high risk (modified UISS criteria) pT3-4,N+	0.76	0.03	1.01
Atlas	Axitinib vs placebo	724			0,87	0,32	
Protect	Pazopanib vs placebo	571	CC or predominantly CC	pT2(G3-4)N0 or pT3-4(Gx)N0 or pTx(Gx)N1M0	0.86	0.16	0.79

Disparate results

MUNICH 2018 ESMO Congress

Ravaud et al, NEJM 2016; Haas et al, Lancet 2016; Motzer et al, JCO 2

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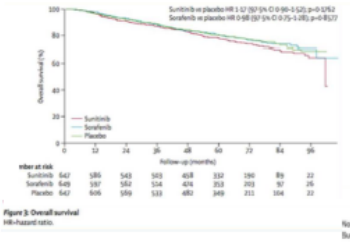
Adjuvant therapy

metastatic disease

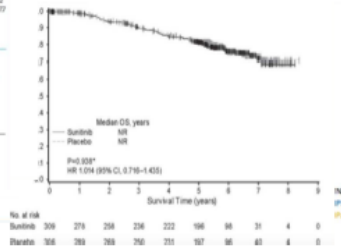
Localized setting

Use of TKI in the adjuvant setting

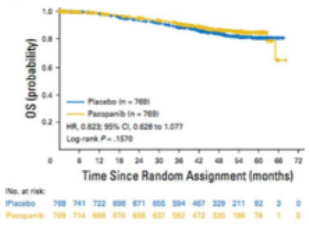
OS In Phase 3 clinical trials of VEGF inhibitors in adjuvant treatment of renal cell carcinoma



Assure Haas Lancet 2016



S-TRAC OS Ravaud, NEJM 2016



Protect OS Motzer JCO 2017

None of those trials improved OS: angiogenesis inhibition does not cure cancer in the adjuvant setting

Use of TKI in the adjuvant setting

What about side effects?

	Sunitinib	Sorafenib	Placebo
grade	>3	>3	>3
ASSURE	63 %	70 %	24 %
S-TRAC	56.9 %	-	19.4 %
	Pazopanib		**Placebo**
grade	>3	-	>3
PROTECT	60 %	-	21 %

Assure Haas Lancet 2016 | Protect OS Motzer JCO 2017 | S-TRAC OS Ravaud, NEJM 2016

Adjuvant TKI therapy is currently NOT standard of care in RCC in Europe (><FDA)

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Adjuvant therapy

met

Localized setting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE FREE PREVIEW

Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

Toni K. Choueiri, M.D., Piotr Tomczak, M.D., Ph.D., Se Hoon Park, M.D., Balaji Venugopal, M.D., Thomas Ferguson, M.D., Yen-Hwa Chang, M.D., Ph.D., Jaroslav Hajek, M.U.Dr., Stefan N. Symeonides, M.D., Ph.D., Jae Lyun Lee, M.D., Ph.D., Naveed Sarwar, M.D., Ph.D., Antoine Thiery-Vuillemin, M.D., Ph.D., Marine Gross-Goupil, M.D., Ph.D., et al., for the KEYNOTE-564 Investigators*

Key Eligibility Criteria

- Histologically confirmed clear cell renal cell carcinoma
- Nephrectomy ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors

- M0 vs M1 NED
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

Pembrolizumab 200 mg Q3W for ~1 year[a]

Placebo Q3W for ~1 year[a]

- Primary end point: DFS per investigator
- Key secondary end point: OS
- Other secondary end points: Safety

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Adjuvant therapy

Keynote 564 study population

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Age, median (range), yrs	60 (27–81)	60 (25–84)
Male	347 (70.0)	359 (72.1)
ECOG PS		
0	421 (84.9)	426 (85.5)
1	75 (15.1)	72 (14.5)
Disease risk category		
M0 intermediate-high risk	427 (86.1)[a]	433 (86.9)
M0 high risk	40 (8.1)	36 (7.2)
M1 NED	29 (5.8)	29 (5.8)

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Geographic location		
North America	113 (26.8)	125 (25.1)
European Union	188 (37.9)	187 (37.6)
Rest of the world	175 (35.3)	186 (37.3)
PD-L1 status[b]		
CPS <1	124 (25.0)	113 (22.7)
CPS ≥1	365 (73.6)	383 (76.9)
Missing	7 (1.4)	2 (0.4)
Sarcomatoid features		
Present	52 (10.5)	59 (11.8)
Absent	417 (84.1)	415 (83.3)
Unknown	27 (5.4)	24 (4.8)

Choueiri et al, NEJM 2021

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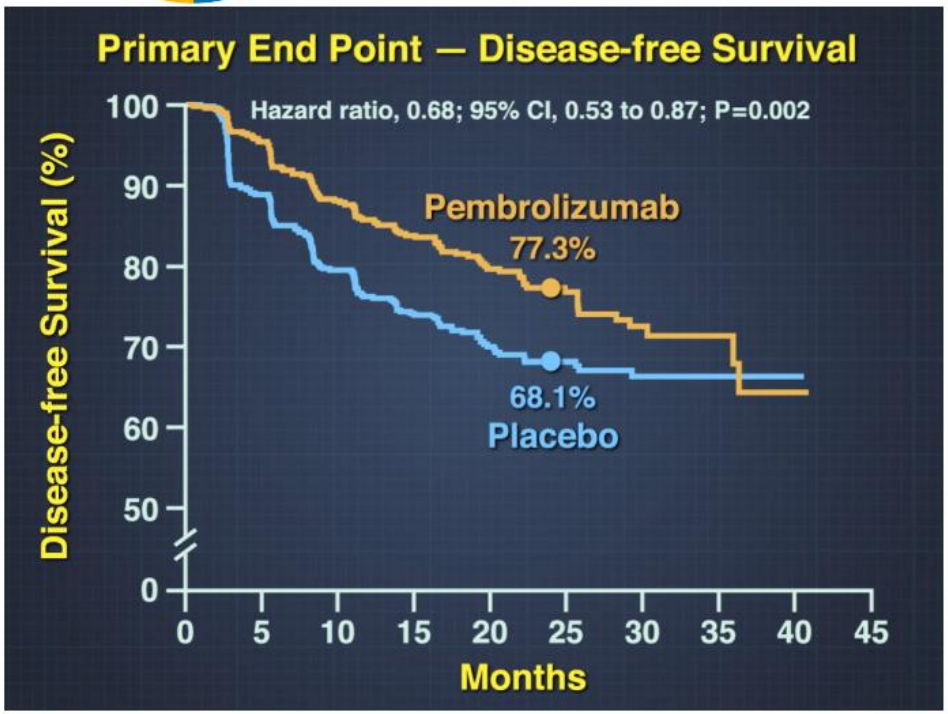
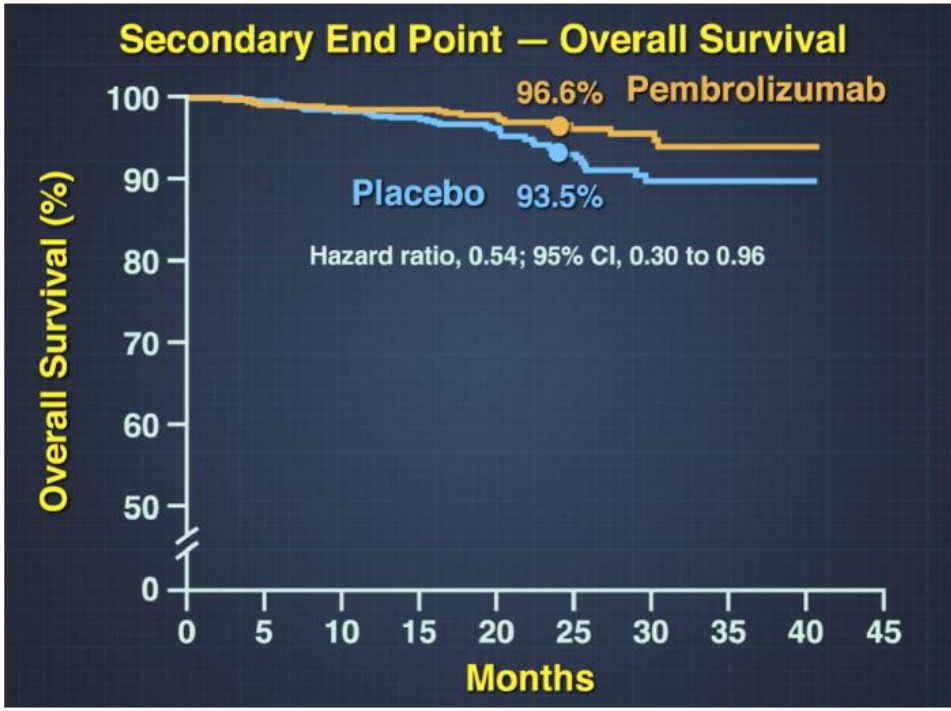
Adjuvant therapy

Keynote 564: results





Choueiri et al, NEJM 2021

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Adjuvant therapy

Localized setting

CONCLUSION

OS data are awaited (uncertain correlation between DFS & OS for operable RCC)

Adjuvant Pembrolizumab is currently not recommended as SOC in the ESMO guidelines Optional (1c) for patients with intermediate or high risk operable ccRCC after careful patients counseling regarding immature OS date & potential long term AE

Regarding the M1-NED population, systemic therapy with PD-1 based combination therapy is SOC for patients who relapse within one year of nephrectomy (Ia)

FDA in august 2021 has granted a priority review designation for pembrolizumab in this indication

If it becomes a SOC, it will changes our treatment landscape

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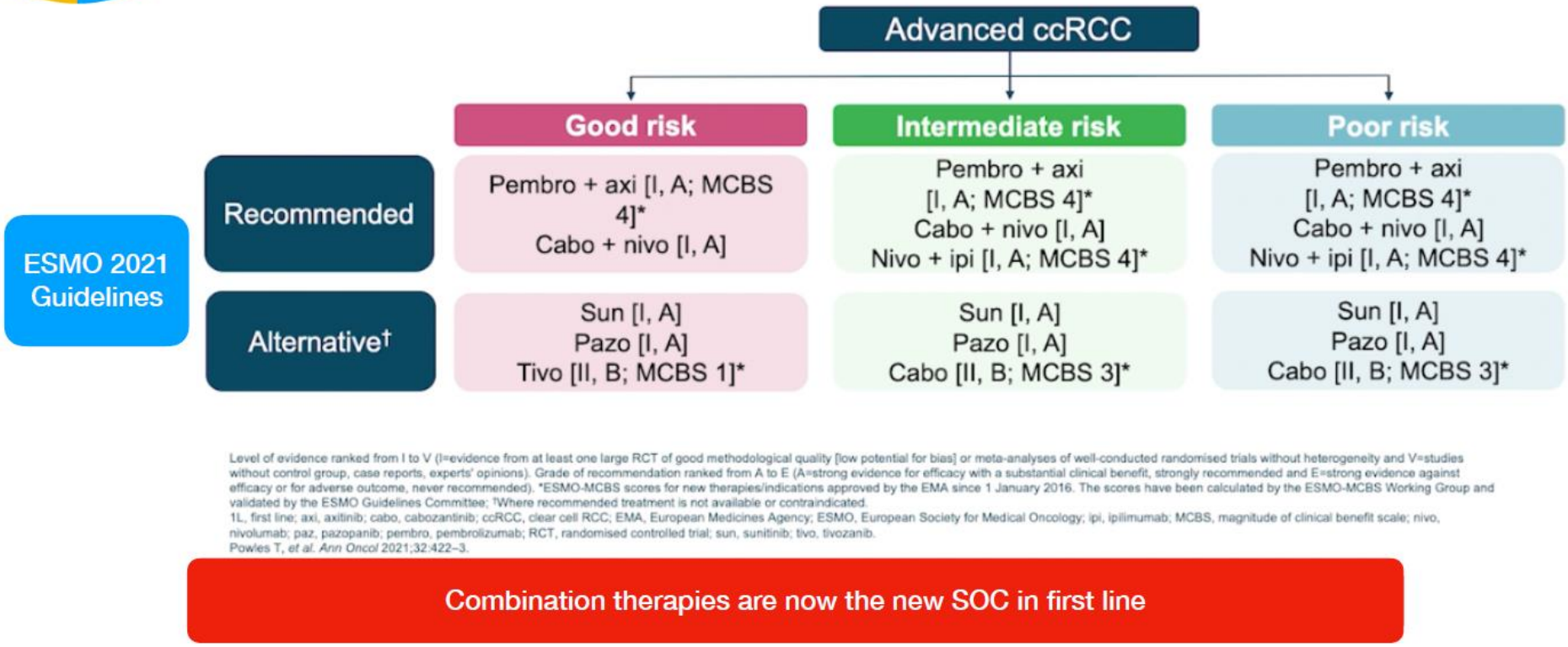
1st line

Metastatic setting



Level of evidence ranked from I to V (I=evidence from at least one large RCT of good methodological quality [low potential for bias] or meta-analyses of well-conducted randomised trials without heterogeneity and V=studies without control group, case reports, experts' opinions). Grade of recommendation ranked from A to E (A=strong evidence for efficacy with a substantial clinical benefit, strongly recommended and E=strong evidence against efficacy or for adverse outcome, never recommended). *ESMO-MCBS scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee; †Where recommended treatment is not available or contraindicated.
1L, first line; axi, axitinib; cabo, cabozantinib; ccRCC, clear cell RCC; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; ipi, ipilimumab; MCBS, magnitude of clinical benefit scale; nivo, nivolumab; paz, pazopanib; pembro, pembrolizumab; RCT, randomised controlled trial; sun, sunitinib; tivo, tivozanib.
Powles T, *et al. Ann Oncol* 2021;32:422–3.

Combination therapies are now the new SOC in first line

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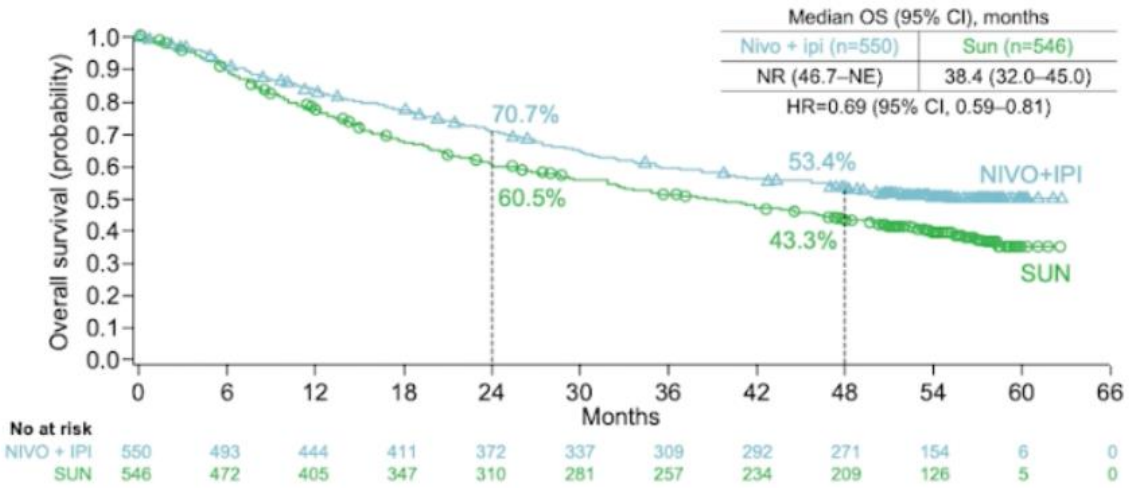
1st line

Metastatic setting

Checkmate 214 phase 3 trial

OS:



Nivolumab + Ipilimumab significantly improved OS vs sunitinib in pts with I/P risk

1L, first line; CI, confidence interval; CPI, immune checkpoint inhibitor; HR, hazard ratio; ipi, ipilimumab; mPFS, median PFS; No, number; NE, not estimated; Nivo, nivolumab; NR, not reached; OS, overall survival; PFS, progression-free survival; Sun, sunitinib.
Albiges L, *et al. ESMO Open* 2020;5:e001079.

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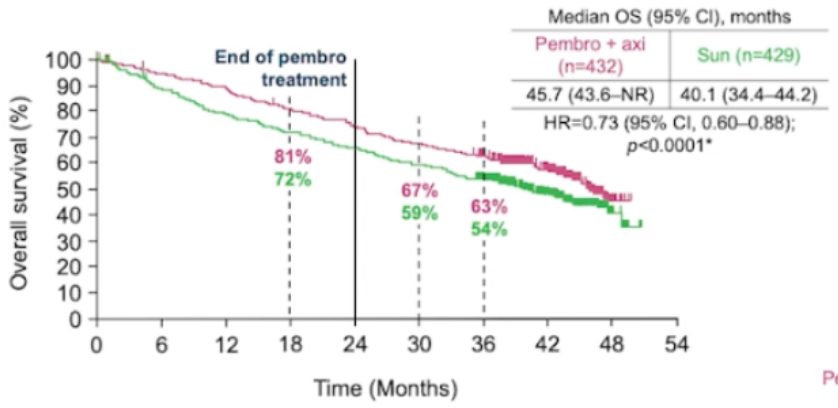
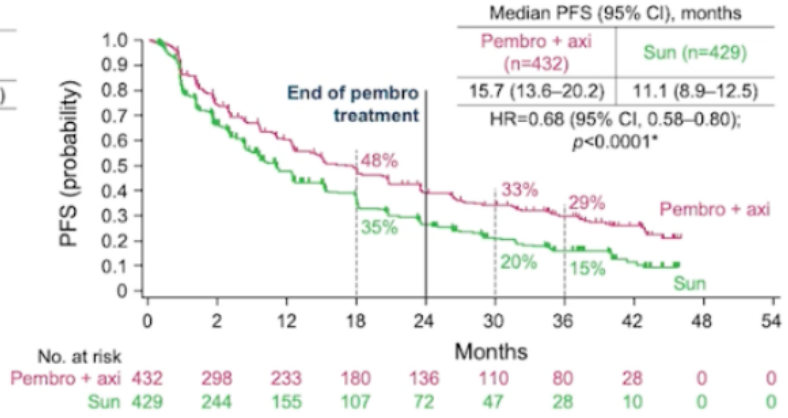
Keynote 426 of Axitinib / Pembrolizumab vs Sunitinib

OS:



PFS:



ORR: Axi+Pembro 60,4% (55,6-65,1) vs sunitinib 39,6% (35,0-44,4); p<0,0001

Median follow-up 42.8 months (minimum 35.6 months), data cut off: 11th January 2021.*Because superiority of pembro + axi was demonstrated at interim analysis, no alpha was allocated to OS or PFS; only nominal p values are reported.
Axi, axitinib; CI, confidence interval; HR, hazard ratio; No, number; NR, not reached; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; sun, sunitinib.

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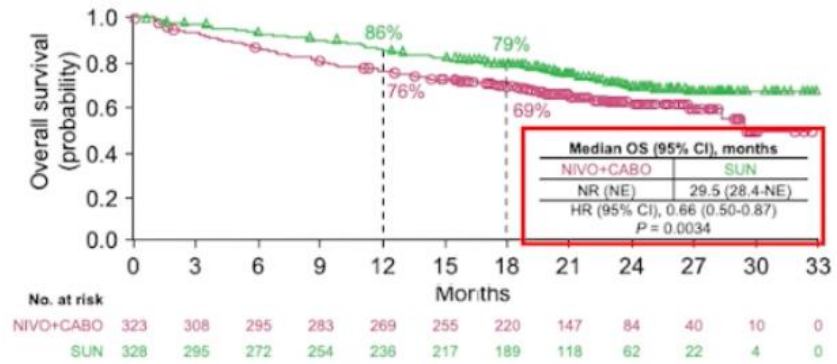
1st line

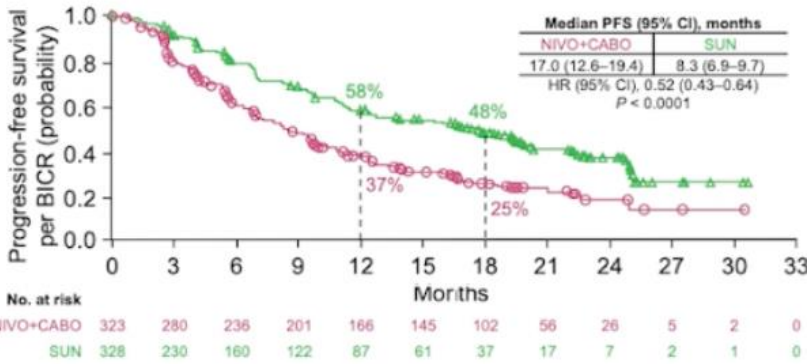
Metastatic setting

Checkmate 9 ER phase 3 trial of Cabo/Nivo vs Sunitinib

OS:



PFS:



ORR: Cabo+Nivo 54,8% (49,2-60,3) vs sunitinib 28,4% (23,5-33,6)

Median follow-up 23.5 months (minimum 16.0 months)[1]

*p value not reported. cabo, cabozantinib; CI, confidence interval; CPI, immune checkpoint inhibitor; HR, hazard ratio; NE, not estimated; No, number; nivo, nivolumab; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; sun, sunitinib; TKI tyrosine kinase inhibitor.

Motzer RJ, *et al. J Clin Oncol* 39, 2021 (suppl 6; abstr 308). Presented at ASCO GU 2021. Available at: https://meetinglibrary.asco.org/record/195192/abstract. Accessed August 2021.

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1st line

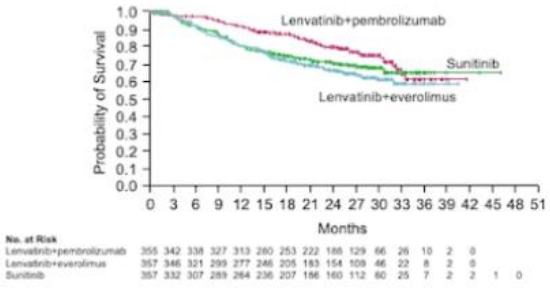
Metastatic setting

CLEAR trial

CLEAR: TKI + CPI combination (lenvatinib + pembrolizumab) demonstrates improved PFS, OS and ORR *vs* sun[1]

OS:

A Kaplan-Meier Analysis of Overall Survival



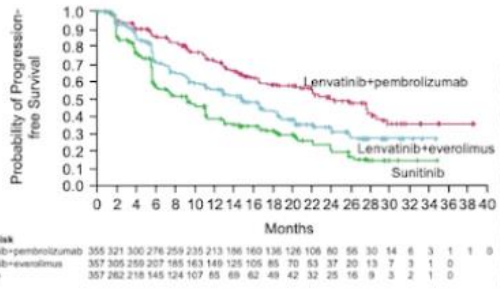
	Median Overall Survival (95% CI) *mo*
Lenvatinib + Pembrolizumab	NR (33.6–NE)
Lenvatinib + Everolizumab	NR (NE–NE)
Sunitinib	NR (NE–NE)

Hazard ratio for death (Lenvatinib + pembrolizumab *vs* sunitinib), 0.66 (95% CI, 0.49–0.88); P=0.005

Hazard ratio for death (Lenvatinib + everolimus *vs* sunitinib), 1.15 (95% CI, 0.88–1.50); P=0.30

PFS:

A Kaplan-Meier Analysis of Progression-free Survival



	Median Progression-free Survival (95% CI) *mo*
Lenvatinib + Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib + Everolizumab	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0))

Hazard ratio for disease progression or death (Lenvatinib + pembrolizumab *vs* sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

Hazard ratio for disease progression or death (Lenvatinib + everolimus *vs* sunitinib), 0.65 (95% CI, 0.53–0.80); P<0.001

ORR: Len+Pembro 71,0% (66,3-75,7) vs sunitinib 36,1% (31,2-41,1); p<0,0001

Median follow-up 26.6 months. CI, confidence interval; eve, everolimus; HR, hazard ratio; len, lenvatinib; mo, months; mOS, median OS; mPFS, median PFS; NE, not estimated; No, number; NR, not reached; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; sun, sunitinib.

Motzer R, *et al. N Engl J Med* 2021;384:1289–300.

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1st line

ESMO 2021 Guidelines

Pivotal Phase 3 trials of guideline-recommended 1L combination therapies in aRCC: key efficacy results

Study 1° endpoint(s) 2° endpoint(s)	Tx arms (n)	Median FU, mo	PFS			OS			ORR	
			mPFS, mo (95% CI)	HR vs sun (95% CI)	P value	mOS, mo (95% CI)	HR vs sun (95% CI)	P value	ORR, % (95% CI)	P value (vs sun)
CheckMate 214[1] OS, PFS, ORR (all in IMDC I/P risk pts)	Nivo + ipi (550 [425 I/P])	55	11.2 (8.4–16.1)	0.74 (0.62–0.88)	Not reported*	48.1 (35.6–NE)	0.65 (0.54–0.78)	Not reported*	41.9 (37.1–46.7)	<0.0001
	Sun (546 [422 I/P])		8.3 (7.0–10.8)			26.6 (22.1–33.5)			26.8 (22.6–31.3)	
KEYNOTE-426[2] OS, PFS (both ITT) ORR (ITT)	Axi + pembro (432)	42.8	15.7 (13.6–20.2)	0.68 (0.58–0.80)	<0.0001†	45.7 (43.6–NR)	0.73 (0.60–0.88)	<0.001†	60.4 (55.6–65.1)	<0.0001†
	Sun (429)		11.1 (8.9–12.5)			40.1 (34.3–44.2)			39.6 (35.0–44.4)	
CheckMate 9ER[3] PFS OS, ORR	Cabo + nivo (323)	23.5	17.0 (12.6–19.4)	0.52 (0.43–0.64)	<0.0001	NR (NE)	0.66 (0.50–0.87)	0.0034	54.8 (49.2–60.3)	Not reported*
	Sun (328)		8.3 (6.9–9.7)			29.5 (28.4–NE)			28.4 (23.5–33.6)	
CLEAR[4] PFS OS, ORR	Lenva + pembro (355)	26.6	23.9	0.39 (0.32–0.49)	<0.001	NR (33.6–NE)	0.66 (0.49–0.88)	0.005	71.0 (66.3–75.7)	<0.001
	Lenva + eve (357)		14.7	0.65 (0.53–0.80)	<0.001	NR (NE)	1.15 (0.88–1.50)	0.30 (NS)	53.5 (48.3–58.7)	<0.001
	Sun (357)		9.2			NR (NE)			36.1 (31.2–41.1)	

No head to head trials comparing different 1L treatment combination regimens

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1st line

Metastatic setting

Axi/pembro

Cabo/Nivo

Lenva/ Pembro

PD-1 + CTLA 4

PD-1 + VEGF

PROS

How to choose between IO/VEGF or IO/IO

Intermediate or bad prognosis group

Improved OS

Durable responses

Potential to stop therapy

QOL during maintenance

Improved OS

High ORR Low PD rate

Longer PFS

Lower irAE rate

Mature Follow up data available

CONS

Lower PFS /response rate

HIgher irAE rate

Unclear AE attribution

Less mature Follow up

Chronic TKI toxicity

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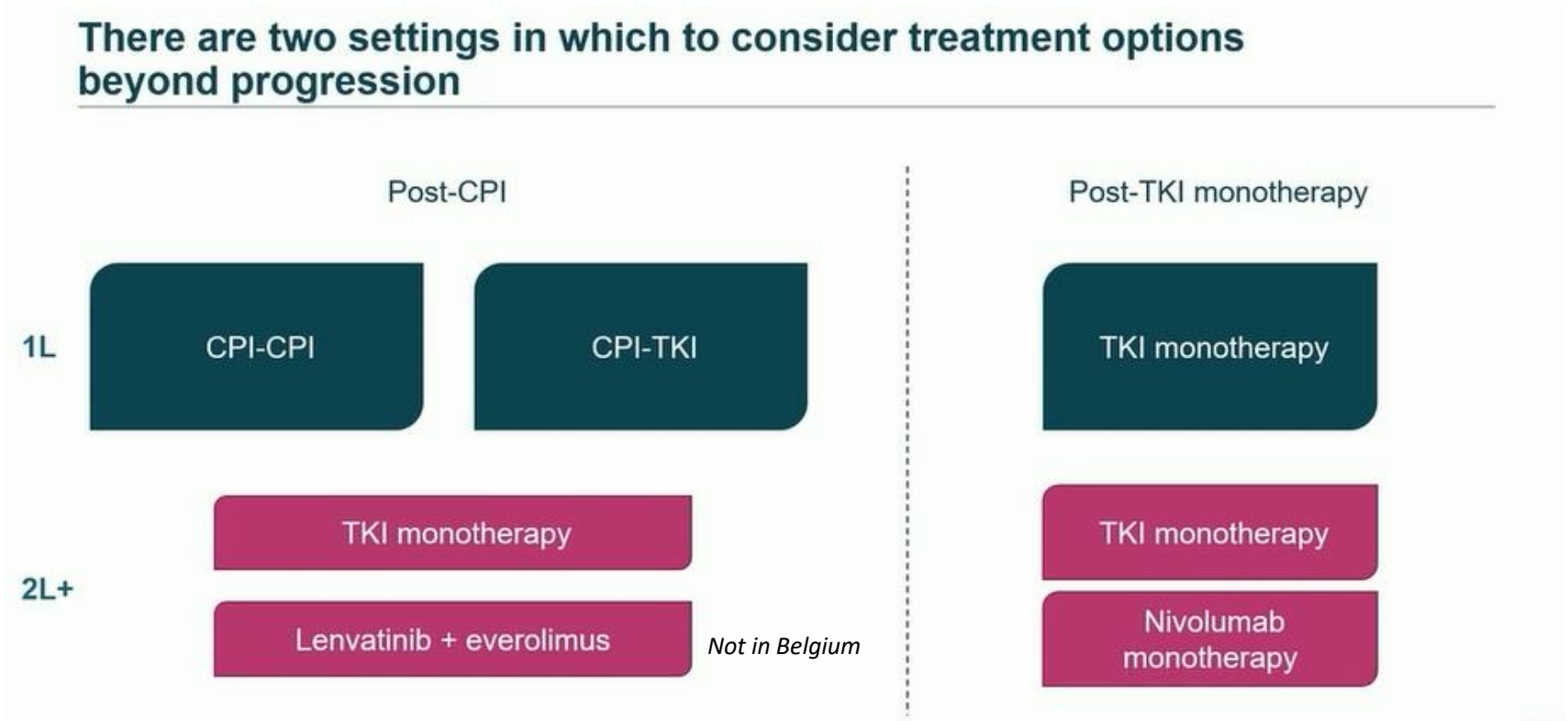


Daniel Y. Heng. Where are we now? Optimising treatment beyond first line. – Ipsen Industry Satellite Symposium: Spotlight on emerging therapies – ESMO 2021

EUROPEAN UROLOGY 76 (2019) 861–867

Kidney Cancer

First-line Immuno-Oncology Combination Therapies in Metastatic Renal-cell Carcinoma: Results from the International Metastatic Renal-cell Carcinoma Database Consortium

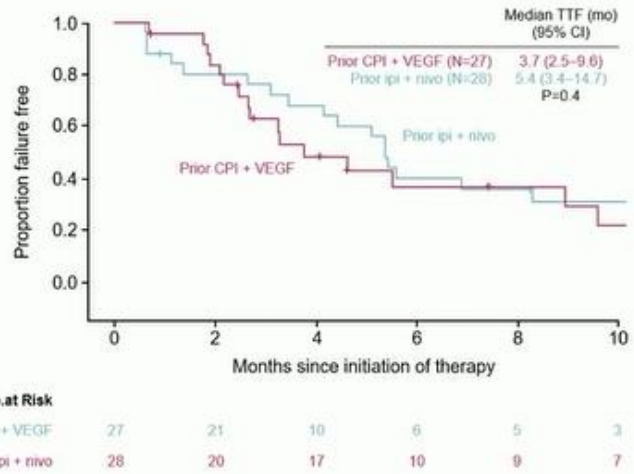
Retrospective database analysis

VEGF-based therapy is efficacious following 1L ipilimumab + nivolumab

Key background:

2L treatment* (% of patients treated)	1L CPI+VEGF (N=113)	1L Ipi+nivo (N=75)
Axitinib	15	7
Cabozantinib	26	7
Lenvatinib + everolimus	6	0
Nivolumab	15	0
Pazopanib	6	30
Sunitinib	26	50
Other	6	7

Key results:



2L response rates were higher in the post- ipi+nivo cohort compared with the post- CPI+VEGF cohort (45% vs 15%, p=0.04)

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ORIGINAL RESEARCH

Cancer Medicine WILEY

Cabozantinib real-world effectiveness in the first-through fourth-line settings for the treatment of metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Cancer Medicine. 2021;10:1212–1221.

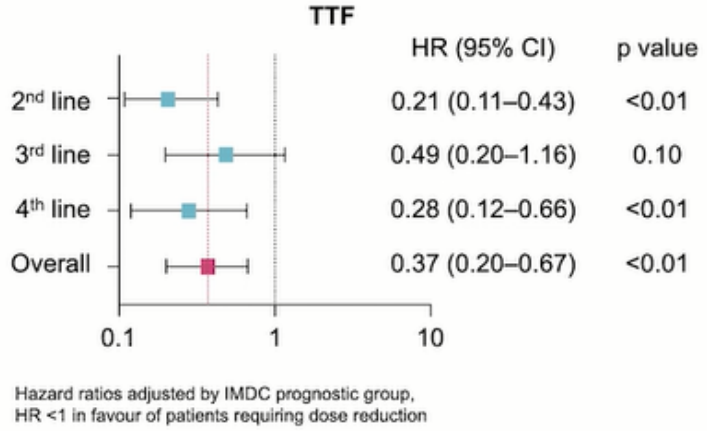
Retrospective database analysis

Efficacy of cabozantinib maintained regardless of prior systemic therapy*

Key background:

	Treatment line		
	2L (n=143)	3L (n=142)	4L (n=94)
Percentage of patients per prior therapy			
Prior CPI any line, %	23	75	88
Single agent CPI, %	1	61	77
CPI-CPI, %	7	6	11
CPI-VEGF, %	15	8	1
Response to therapy†			
ORR, %	26	25	29

Key results:



Hazard ratios adjusted by IMDC prognostic group,
HR <1 in favour of patients requiring dose reduction

The efficacy of cabozantinib is maintained regardless of number or type of prior therapy, including for prior-CPI

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Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study

Lancet Oncol 2019; 20: 1386–94

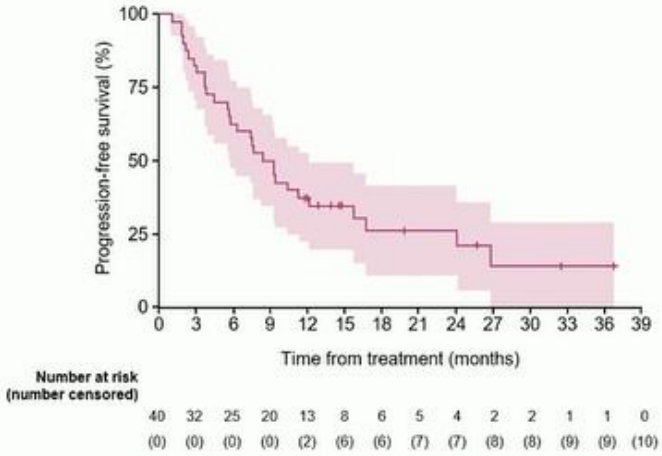
Multi-centre, Phase II, single arm study

Axitinib shows beneficial clinical activity in patients treated with prior-CPI

Key background:

	Axitinib (N=40)
Prior lines of therapy,* %	
1	28
2	48
3	23
4	3
Most recent therapy, %	
Nivolumab	63
Ipilimumab + nivolumab	15
Other	24

Key results:



36% of patients who received axitinib as 2L therapy, and 48% treated with axitinib as ≥3L therapy, achieved an objective response

*The majority of patients (28 [70%]) received previous VEGF-directed therapy

Daniel Y. Heng. Where are we now? Optimising treatment beyond first line. – Ipsen Industry Satellite Symposium: Spotlight on emerging therapies – ESMO 2021

GENITOURINARY CANCER—KIDNEY AND BLADDER 2021 ASCO ANNUAL MEETING

CANTATA: Primary analysis of a global, randomized, placebo (Pbo)-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus Pbo + cabozantinib in advanced/metastatic renal cell carcinoma (mRCC) patients (pts) who progressed on immune checkpoint inhibitor (ICI) or anti-angiogenic therapies.

Phase III, double-blind randomised controlled trial (CANTATA)

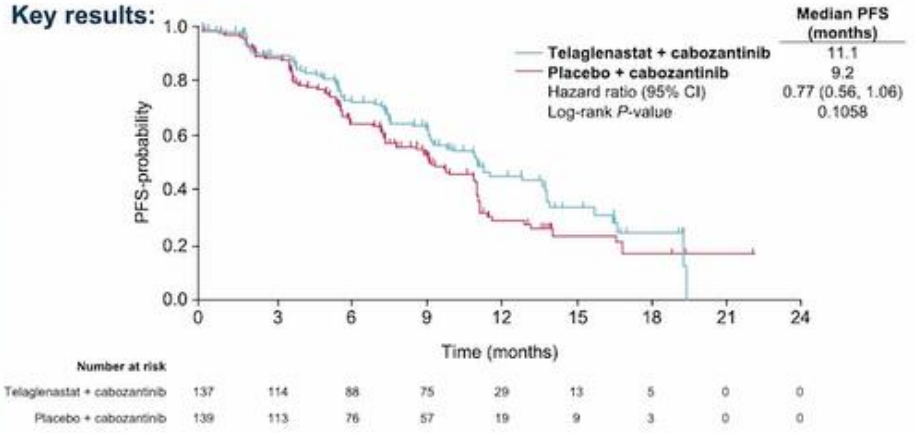
Cabozantinib is efficacious following prior-CPI or prior ipilimumab + nivolumab*†

Key background:

Glutaminase 1 splice variant inhibitor

	Tela + cabo (n=221)	Placebo + cabo (n=223)
Prior lines of therapy, %		
1	57	57
2	43	42
3	0	1
Prior CPI, %	62	62
Prior ipi + nivo, %	29	29

Key results:



	Tela + cabo (n=221)	Placebo + cabo (n=223)
ORR, n (%)	69 (31.2)	62 (27.8)

Though cabozantinib demonstrates a clinical benefit, telaglenastat in combination with cabozantinib is no more efficacious than cabozantinib plus placebo (p=0.1058)

*Cabozantinib + telaglenastat in combination is off-label and not approved for use. †Cabozantinib is not approved for use in patients with aRCC who have received only prior-CPI.

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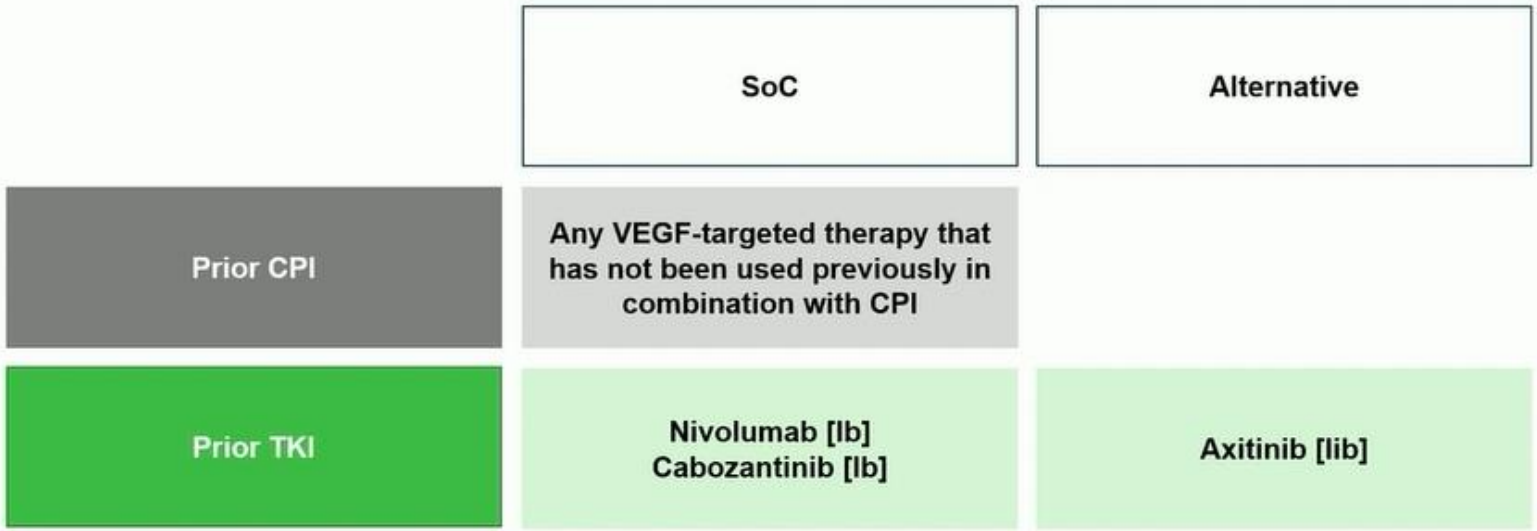
EAU guidelines recommend any VEGF-targeted therapy not used in 1L combination or monotherapy can be used in 2L



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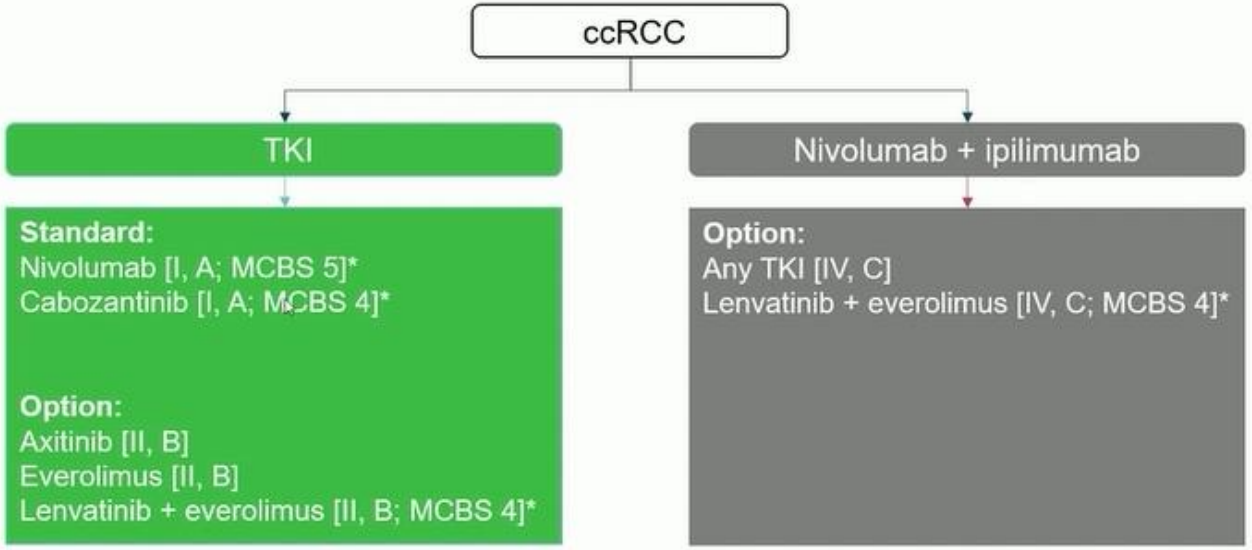
Latest ESMO guidelines recommend any TKI or lenvatinib + everolimus can be used in the post nivolumab + ipilimumab setting



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Clinical perspectives: experience from my clinic

- There is efficacy and activity in 2nd,3rd and 4th line
  - There is attrition: not everyone gets to 4th line therapy – choose your best drugs
- Choice of drugs often driven by reimbursement
- Know your agents:
  - Understand how to effectively perform and manage dose reductions
  - Utilise pharmacokinetics to inform decision making
- Looking forward to clinical trials pushing the needle of PFS/OS by combining therapies
- Real world data are helpful to inform practice and to assess effectiveness of all lines of therapy

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Ongoing clinical trials will continue to improve our understanding of how to optimally sequence treatment in the 2L+ setting

Cabopoint:*[1]
- **Phase II** (N=250)
- Cabo after: 1L ipi + nivo (cohort A) OR CPI + VEGFR-TKI (cohort B)
- Final analysis: Q1 2023
- Primary endpoint: ORR (ICR)

CONTACT-3:[2,3]
- **Phase III** (N=500)
- Cabo + atezo† OR cabo* 1L/2L progression, with CPI immediately prior to study treatment
- Final analysis: Q4 2024
- Primary endpoint: OS + PFS (BICR)

NCT04586231:[4]
- **Phase III** (N=708)
- Belzutifan + lenvatinib vs cabozantinib, after 1L or 2L anti-PD-1/L1
- Final analysis: Q4 2024
- Primary endpoint: PFS (BICR) + OS

TiNivo-2:[2]
- **Phase III** (N=326)
- Tivo + nivo OR tivo, after 1L CPI
- Final analysis: TBC
- Primary endpoint: PFS

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