Update 2021 – Medical Treatment of (Metastatic) Renal Cell Carcinoma

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Disclosures

- Honoraria for lectures or advisory boards from
- Pfizer, Ipsen, Exelixis, EUSA, EISAI, Roche, BMS, MSD, Merck, Alkermes

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Topics

Prevention of metastasis?

1st-line cc-RCC treatment

Beyond 1st-line

Non-cc RCC treatment

Future strategies

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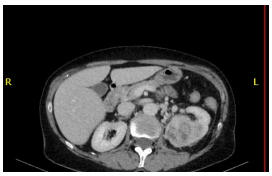
Patient MM

- Female, 69 years
- February 2021 laparoscopic nephrectomy
- Clear cell RCC, ISUP 4
- pT3aN0
- sarcomatoid features 60%, necrosis 50%
- Adjuvant treatment?



- High risk for relapse (8 points)[2]
- Relapse expected in < 2 years
- 5-year MFS 31.2%

6 randomized trials, TKI versus placebo, only one[1] (STRAC) met the primary EP (DFS gain 1,2 years with sunitinib versus placebo); but substantial toxicity
> no recommendation for adjuvant TKI's in Europe

1.Ravaud A et al., New Engl J Med 2016; 2.Leibovich BC et al., Cancer 2003

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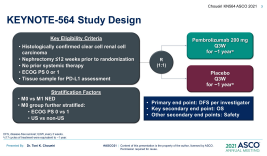
Plenary session ASCO 2021, LBA 5

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

Toni K. Choueiri[1]; Piotr Tomczak[2]; Se Hoon Park[3]; Balaji Venugopal[4]; Thomas Ferguson[5]; Yen-Hwa Chang[6]; Jaroslav Hajek[7]; Stefan Symeonides[8]; Joe Lyon Lee[9]; Naveed Saleem[10]; Antoine Thiery-Vuillemin[11]; Marine Gross-Goupil[12]; Mauricio Maluve[13]; Naomi Haas[14]; Piotr Sawrycki[15]; Rodolfo F. Perini[16]; Pingye Zhang[17]; Jaqueline Wilmanns-Ruperto[18]; Kentaro Inoj[19]; David Quinn[20]; Thomas Powles[21]; on behalf of the KEYNOTE-564 investigators.

KEYNOTE-564 Study Design



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	

Differences in population compared to STRAC

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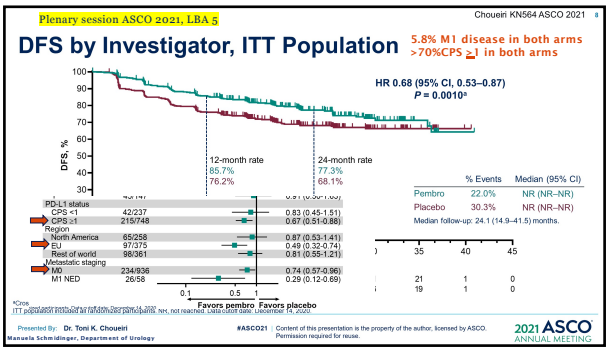
Plenary session ASCO 2021, LBA 5
Choueiri KN564 ASCO 2021
DFS by Investigator, ITT Population
5.8% M1 disease in both arms
>70%CPS ≥1 in both arms
HR 0.68 (95% CI, 0.53–0.87)
P = 0.0010a
12-month rate
85.7%
76.2%
24-month rate
77.3%
68.1%
% Events
Median (95% CI)
Pembro 22.0% NR (NR–NR)
Placebo 30.3% NR (NR–NR)
Median follow-up: 24.1 (14.9–41.5) months.
Favors pembro
Favors placebo
Presented By: Dr. Toni K. Choueiri
Manuela Schmidinger, Department of Urology
#ASCO21
2021 ASCO ANNUAL MEETING

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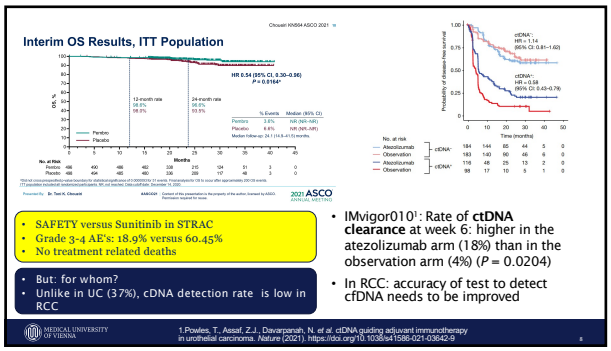
Interim OS Results, ITT Population
HR 0.54 (95% CI, 0.30–0.96)
P = 0.0164a
12-month rate
98.0%
24-month rate
93.5%
SAFETY versus Sunitinib in STRAC
Grade 3-4 AE's: 18.9% versus 60.45%
No treatment related deaths
But: for whom?
Unlike in UC (37%), cDNA detection rate is low in RCC
IMvigor010[1]: Rate of ctDNA clearance at week 6: higher in the atezolizumab arm (18%) than in the observation arm (4%) (P = 0.0204)
In RCC: accuracy of test to detect cfDNA needs to be improved
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1.Powles, T., Assaf, Z.J., Davarpanah, N. et al. ctDNA-guiding adjuvant immunotherapy in urothelial carcinoma. Nature (2021). https://doi.org/10.1038/s41586-021-03642-9

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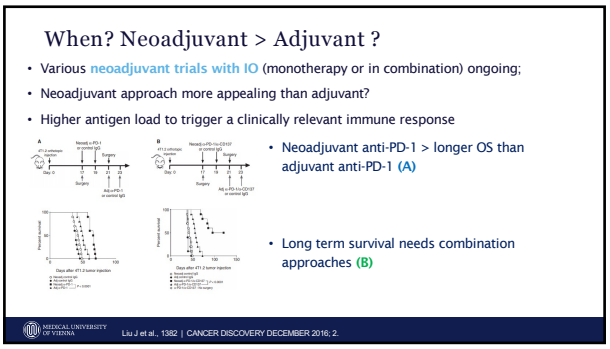
When? Neoadjuvant > Adjuvant ?
Various neoadjuvant trials with IO (monotherapy or in combination) ongoing;
Neoadjuvant approach more appealing than adjuvant?
Higher antigen load to trigger a clinically relevant immune response
Neoadjuvant anti-PD-1 > longer OS than adjuvant anti-PD-1 (A)
Long term survival needs combination approaches (B)
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Liu J et al., 1382 | CANCER DISCOVERY DECEMBER 2016; 2.

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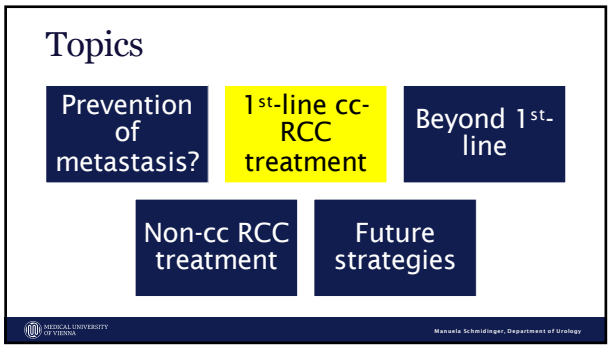
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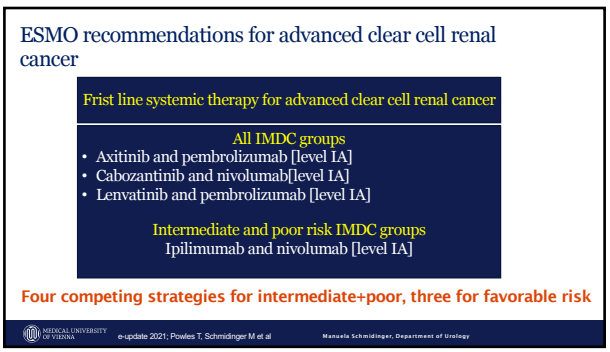
ESMO recommendations for advanced clear cell renal cancer
Frist line systemic therapy for advanced clear cell renal cancer
All IMDC groups
Axitinib and pembrolizumab [level IA]
Cabozantinib and nivolumab[level IA]
Lenvatinib and pembrolizumab [level IA]
Intermediate and poor risk IMDC groups
Ipilimumab and nivolumab [level IA]
Four competing strategies for intermediate+poor, three for favorable risk
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e-update 2021; Powles T, Schmidinger M et al
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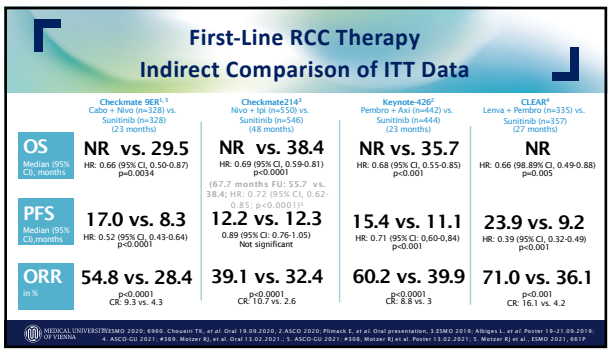
First-Line RCC Therapy
Indirect Comparison of ITT Data
Checkmate 9ER[1,5] Cabo + Nivo (n=328) vs. Sunitinib (n=328) (23 months)
Checkmate214[3] Nivo + Ipi (n=550) vs. Sunitinib (n=546) (48 months)
Keynote-426[2] Pembro + Axi (n=442) vs. Sunitinib (n=444) (23 months)
CLEAR[4] Lenva + Pembro (n=335) vs. Sunitinib (n=357) (27 months)
OS
Median (95% CI), months
NR vs. 29.5
HR: 0.66 (95% CI, 0.50-0.87) p=0.0034
NR vs. 38.4
HR: 0.69 (95% CI, 0.59-0.81) p<0.0001
(67.7 months FU: 55.7 vs. 38.4; HR: 0.72 (95% CI, 0.62-0.85; p<0.0001))
NR vs. 35.7
HR: 0.68 (95% CI, 0.55-0.85) p<0.001
NR
HR: 0.66 (98.89% CI, 0.49-0.88) p=0.005
PFS
Median (95% CI),months
17.0 vs. 8.3
HR: 0.52 (95% CI, 0.43-0.64) p<0.0001
12.2 vs. 12.3
0.89 (95% CI: 0.76-1.05) Not significant
15.4 vs. 11.1
HR: 0.71 (95% CI: 0.60-0,84) p<0.001
23.9 vs. 9.2
HR: 0.39 (95% CI, 0.32-0.49) p<0.001
ORR
in %
54.8 vs. 28.4
p<0.0001 CR: 9.3 vs. 4.3
39.1 vs. 32.4
p<0.0001 CR: 10.7 vs. 2.6
60.2 vs. 39.9
p<0.0001 CR: 8.8 vs. 3
71.0 vs. 36.1
p<0.001 CR: 16.1 vs. 4.2
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Patient Characteristics varied between ICI Trials

	Nivo+Ipi 550 ITT/425 IP	Axi+Pembro	Nivo+Cabo	LenPem
Favorable %	23	31.9	23	31
Intermediate %	61	55.1	58	59.2
Poor %	17	13	19	9.3
Nephrectomy %	82	82.6	69	73.8
Sarcomatoid %	14 (IP-pop)	17.9	10.5	7.9

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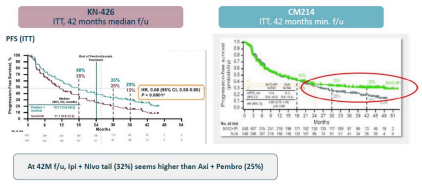
What can drive the treatment decision (1)

- Do we need a fast response or a long term response?
- **Head or tails?**



At 42M f/u, Ipi + Nivo tail (32%) seems higher than Axi + Pembro (25%)

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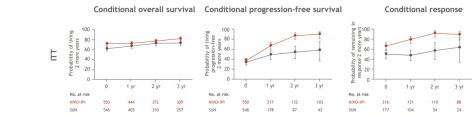
Head or Tails?
„Conditional Survival" CheckMate-214

Definition: conditional survival outcomes: the probability of a patient remaining alive, progression free, or in response for an additional 2 years beyond annual landmark timepoints



With NI, the probability of remaining alive for an additional 2 years increased from time zero (randomization) to
1) landmark year 3 for ITT patients (71% to 81%)
2) beyond 3-years: 81% vs 72%

With NI, the probability of remaining progression free 1) for an additional 2 years increased from time zero to year 3 from 37% to 89%
2) 3-years landmark, PFS estimates NI vs Sun 89% vs 57%

With NI, the probability of remaining in response
1) for an additional 2 years beyond first response increased from time zero (first confirmed response) to year 3 for ITT patients (66% to 89%),
2) response estimates beyond the 3-years landmark higher with NI: 89% vs 63%

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What can drive the treatment decision (2)

- **Likelihood of response, complete response and response duration**
- **or likelihood of progression?**

	Nivo-Ipi IP[1]	Pembro+Axi[2]	Nivo+Cabo[3]	LenPem[4]
Follow up median months	48	30.6	18	27
ORR %	41.9	60.2	47.7	71
CR%	10.4	8.8	8	16.1
DoR	NR (45.8-NE)	23.5 (1.4-34.5)	20.2 (17.3-NE)	25.8 (22.1-27.9)
Primary progression	17.6	11.3	5.6	5.4

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What can drive the treatment decision (3)
Quality of life

HRQoL Summary of Randomized Phase 3 First-Line Combination Studies in cc Renal Cell Carcinoma

	CHECKMATE-214[1] N=847	KEYNOTE-426[2] N=861	CHECKMATE-9ER[3] N=651	CLEAR[4] N=1069	
HRQoL Tools	Nivolumab + Ipilimumab vs. Sunitinib	Axitinib + Pembrolizumab vs. Sunitinib	Cabozantinib + Nivolumab vs. Sunitinib	Lenvatinib + Pembrolizumab vs. Sunitinib	Lenvatinib + Everolimus vs. Sunitinib
	Intermediate and Poor Risk Only	All Risk Groups	All Risk Groups	All Risk Groups	
FKSI-19	✓		✓		
FKSI-DRS		=		=	=
EORTC QLQ-C30		=		=	=
FACT-G	✓				
EQ-5D-3L	✓	=	✓	=	=

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What can drive the treatment decision (4)
Sarcomatoid features

	Nivo+Ipi, n=58[1]	Axi+Pembro, n=51[2]	Cabo+Nivo, n=34[3]	Pembro+Lenva[4] n=28
Median OS	NR (25.2-NE)	NR	NR (22.8-NE)	Not reported
HR	0.45 (0.3-0.7)	0.58 (0.21-1.59)	0.36 (0.17-0.79)	0.91 (0.32-2.58)
Median PFS	26.5	NR	10.3 (5.6-19.4)	Not reported
HR	0.54 (0.33-0.86)	0.54 (0.29-1.0)	0.42 (0.23-0.74)	0.39 (0.18-0.84)
ORR % sarc	60.8	58.8	55.9	Not reported
CR%	18.9	13	8.8	Not reported

1.Tannir NZ et al., Clin Cancer Res 2021; 2. Rini BI et al. Oral presentation at ASCO 2019. Abstract 4500; 3.Motzer RJ et al., ASCO GU 2021, abstract 308; 4. Motzer RJ et al., NR: not reached

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ESMO Algorithm second-line[1]

- „*A VEGFR systemic therapy that has not been given previously*"
- (axitinib, cabozantinib, lenvatinib+everolimus, pazopanib, sunitinib, tivozanib)
- All IIIB recommendations
- Some are likely to become more important than others (if not used in 1st-line and if confirmed in larger trials):
- **Cabozantinib**[2]: post IO: PR 43%, PFS 9.3 months
- **Lenvatinib+pembrolizumab**[3] : post IO: PR 55.8%, PFS 11.1 months

 1. e-update 2021; Powles T, Schmidinger M et al 2.Procoppio G et al., ASCO 2021, abstract 4569; 3.Lee CH et al., ASCO 2021, abstract e16542

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ESMO recommendations for advanced papillary renal cancer

Frist line systemic therapy for advanced papillary renal cancer → Second line systemic therapy for advanced papillary renal cancer

Preferred option
- Cabozantinib [level IIB]

Alternative option
- Sunitinib [level IIB]
- Pembrolizumab [level IIIB]
- Savolitinib in MET altered tumors [level IIIB]

A systemic therapy that has not been given previously
- Cabozantinib Sunitinib [level IVC]
- Everolimus [level IVC]
- Pembrolizumab Savolitinib in MET altered tumors[level IVC]
- Sunitinib [level IVC]

 e-update 2021; Powles T, Schmidinger M et al

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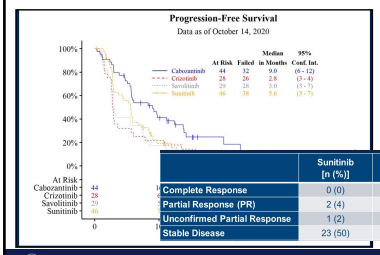
Sunitinib versus cabozantinib, crizotinib or savolitinib in papillary mRCC: randomized phase II SWOG 1500 study



	Sunitinib [n (%)]	Cabozantinib [n (%)]	Crizotinib [n (%)]	Savolitinib [n (%)]
Complete Response	0 (0)	2 (5)	0 (0)	0 (0)
Partial Response (PR)	2 (4)	8 (18)	0 (0)	1 (3)
Unconfirmed Partial Response	1 (2)	2 (5)	1 (4)	2 (7)
Stable Disease	23 (50)	23 (51)	7 (25)	8 (28)

CABO	SUN
9.0	5.6
HR 0.60; 95%CI 0.37-0.97, p=0.019	
OS not significant	

Crizotinib and savolitinib arm closed for futility in Dec 2018

 Presented By Sumanta Pal at 2021 Genitourinary Cancers Symposium

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Other non-cc subtypes

Collecting Duct[1]

- BONSAI: Phase II trial, **cabozantinib** in treatment naive CDC patients
- Primary EP: ORR
- N=25, median follow up 8 months
- ORR 35% including 1 CR, SD 26%
- Median PFS 6 months

Unclassified or translocation associated and Chromophobe[2]

- **Cabo+Nivo** in unclassified (cohort 1) and chromophobe (cohort 2)
- Single center oben label phase II
- N= 40 cohort 1 and 7 cohort 2
- **ORR and PFS cohort 1**: **47.5%** (31.5, 63.9); **12.5** (6.3-15.9) months
- **ORR cohort 2: 0**

 1.Procopio G et al; ASCO 2021, abstract 4571; 2.Lee CH ASCO 2021, abstract 4509

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Other non-cc subtypes

HLRCC associated papillary RCC

- HLRCC: familial disorder with germline loss of function in the fumarate hydratase gene > **increased levels of HIF** → predisposes to aggressive papillary RCC
- Phase I study, bevacizumab+erlotinib, n= 43 HLRCC group, n=40 pRCC group, no more than 2 prior VEGF-targeting agents
- **Primary EP: ORR:**
- Median age: 49.8 years, **67.5% treatment-naive**

	All N=88	HLRCC (%) N=43	Sporadic p (%) N=40
ORR %	54.2	72.1	35
CR %	2.4	4.7	0
PR %	52	67	35
SD	40	28	53
PFS months	14.3	21.1	8.3

Srinivasan R et al., ASCO 2020, abstract 5004

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Future strategies (1)

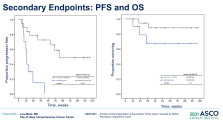
New agents: Belzutifan

- Potent, selective HIF-2α inhibitor
- 90% of clear cell RCC patients have defective VHL function, leading to activation of HIF-2α
- Belzutifan may become a second-line strategy either alone[1] (ORR 25%, PFS 14.5 months in heavily pretreted patients) or in combination with cabozantinib[2]
- **FDA approval for VHL disease associated clear cell RCC** (phase II study)[3] (ORR 49% and 56% maintained a response lasting at least 12 months; ORR in pNETs 83% (95% CI, 52%-98%), CNS hemangioblastoma 63%

Microbiome manipulation

- Open label randomized phase IB study comparing nivo+ipi+CBM-588 versus nivo+ipi alone[4]
- N=39

Secondary Endpoints: PFS and OS



ORR 58% vs 20%
PFS 5.5 vs 10.7 weeks
P<0.001

1. Bauer T et al., ASCO GU 2021; 2.Choueiri TK et al., ASCO GU 2021; 3.Srinivasan R et al ASCO 2021 and ClinicalTrials.gov Identifier: NCT03401788. 4.Meza LA et al., ASCO 2021, abstract 4513

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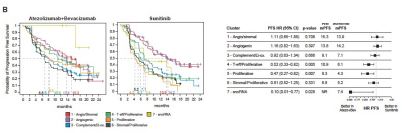
Future Strategies (2) moving toward personalized medicine?

- **Integrated multi-omics analyses** (RNA sequencing (RNA-seq) and targeted somatic variant analysis: **7 molecular subtypes in 823 tumors of patients from Immotion 151: association of transcriptomic clusters and outcome to atezo+bev or sun**



Motzer RJ et al., Cancer Cell 2020

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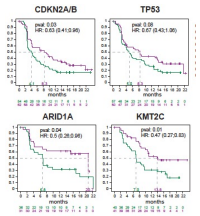
Future Strategies (2) Identifying medicine that has not been on our radar yet



CDKN2A/loss and/or TP53 mutations:
- overall worse prognosis
- benefit from therapeutic approaches that target these specific abberations such as stroma disruptors (telmisartan), cytotoxic agents or CDK46 inhibitors (palbociclib, ribociclib) which arrest tumor cycle and trigger antitumor immunity

LOF in ARID1A and KMT2C:
- improved PFS with atezobev versus sun
- these alterations implicated in epigenetic dysregulation and DNA repair deficiency >combining epigenetic regulators with CPI?

Motzer RJ et al., Cancer Cell 2020

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Take Home Messages

- Pembrolizumab demonstrates improved DFS versus placebo in high risk localized RCC and in M1 resected patients:
  - Patient selection? Neoadjuvant and combination better?
- 4 first-line strategies in clear cell mRCC: tumor and disease characteristics drive the treatment choice; active microbiome manipulation may become a standard of care
- For VHL-syndrome associated RCC: belzutifan
- Second-line: „what has not been given before"-recommendations (IIIB); cabo and pembro+lenva promising
- Non clear cell: cabozantinib is the new SoC in papillary RCC based (SWOG1500 study); erlotinib+bevacizumab: unprecedented ORR and PFS data in HLRCC-associated papillary RCC; chromophobe appears not to benefit from IO
- Genomics of 823 RCC tumors revealed 7 subtypes associated with different outcomes to VEGF blockade alone or in combination with anti-PD-L1[3]
- > We may eventually offer personalized treatment in mRCC

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