State of the Art: Systemic Therapy of Kidney Cancer

Manuela Schmidinger

Medical University of Vienna, Austria

Department of Medicine I

Clinical Division of Oncology and Comprehensive Cancer Centre

Disclosures

Honoraria for lectures and/or advisory boards from:

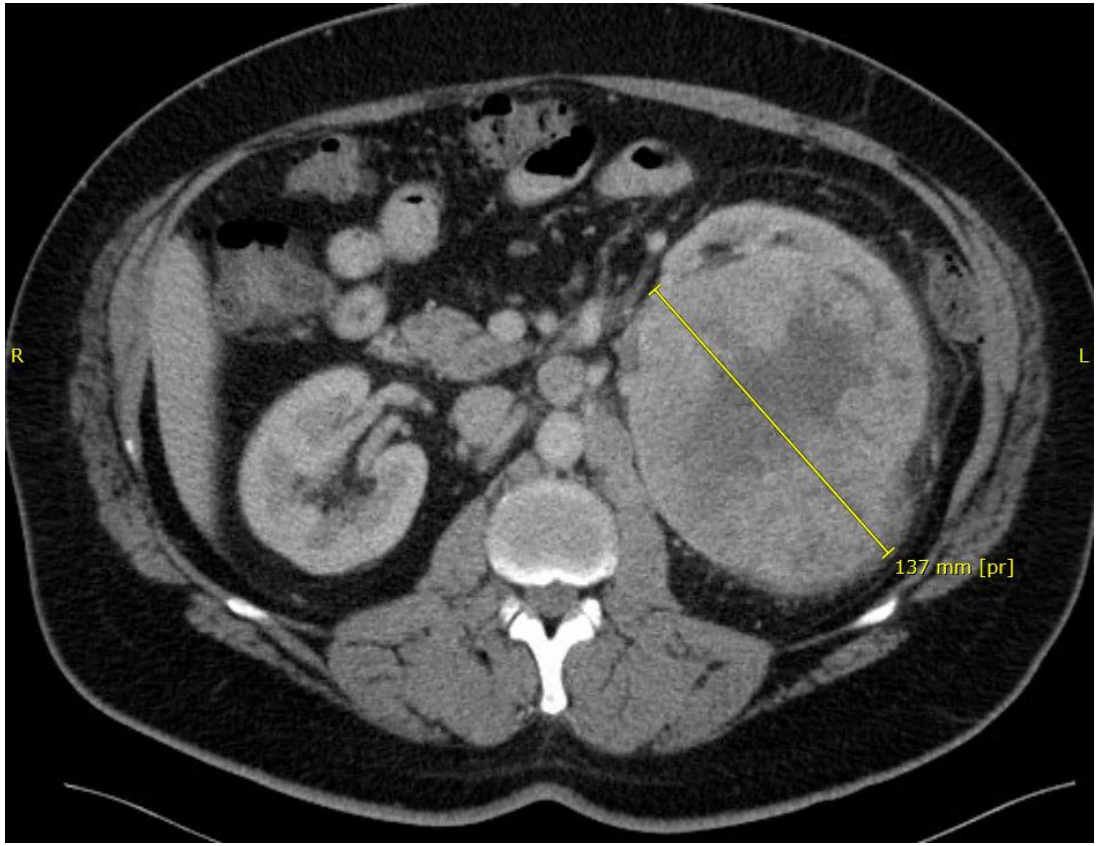
- Pfizer, Novartis, Ipsen, Exelixis, BMS, MSD, EUSA, EISAI, Roche, Alkermes

Patient 1, male, 52 years at diagnosis

- Occasional night sweats, otherwise no symptoms
- Diagnosis of RCC, biopsy: **clear cell**
- CTs: **synchronous metastases lung, pancreas**

KPS <80%
<1 year from diagnosis to treatment
Haemoglobin concentration <lower limit of normal
Calcium concentration >upper limit of normal
Neutrophil count >upper limit of normal
Platelet count >upper limit of normal

IMDC[1,2] Risk: intermediate



Systemic treatment?

1.Heng DY et al., J Clin Oncol 2009
2.Koo JJ et al., Lancet Oncol 2015

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Department of Medicine I, Clinical Division of Oncology and Comprehensive CancerCentre

Patient 1: IMDC intermediate risk, cc-mRCC
Medical Treatment Option 1 according to ESMO Guidelines 2019:

First line/ histology	Risk group/ subtype	Standard	Option
Clear cell	**Good**	Sunitinib [I, A] Pazopanib [I, A] Bevacizumab + IFN [I, A] Tivozanib [II, A]	High dose IL2 [III, B] Bevacizumab + low dose IFN [III, B]
	Intermediate	Nivolumab+ Ipilimumab [I, A]	Cabozantinib [II, A] Sunitinib [I, B] Pazopanib [I, B] Tivozanib [II, B] Bevacizumab + IFN [II, C]
	Poor	Nivolumab+ Ipilimumab [I, A]	Cabozantinib [II, B] Sunitinib [II, C] Pazopanib [II, C] Temsirolimus [I, C]

Escudier B, Porta C, Schmidinger M et al., Ann Oncol 2019

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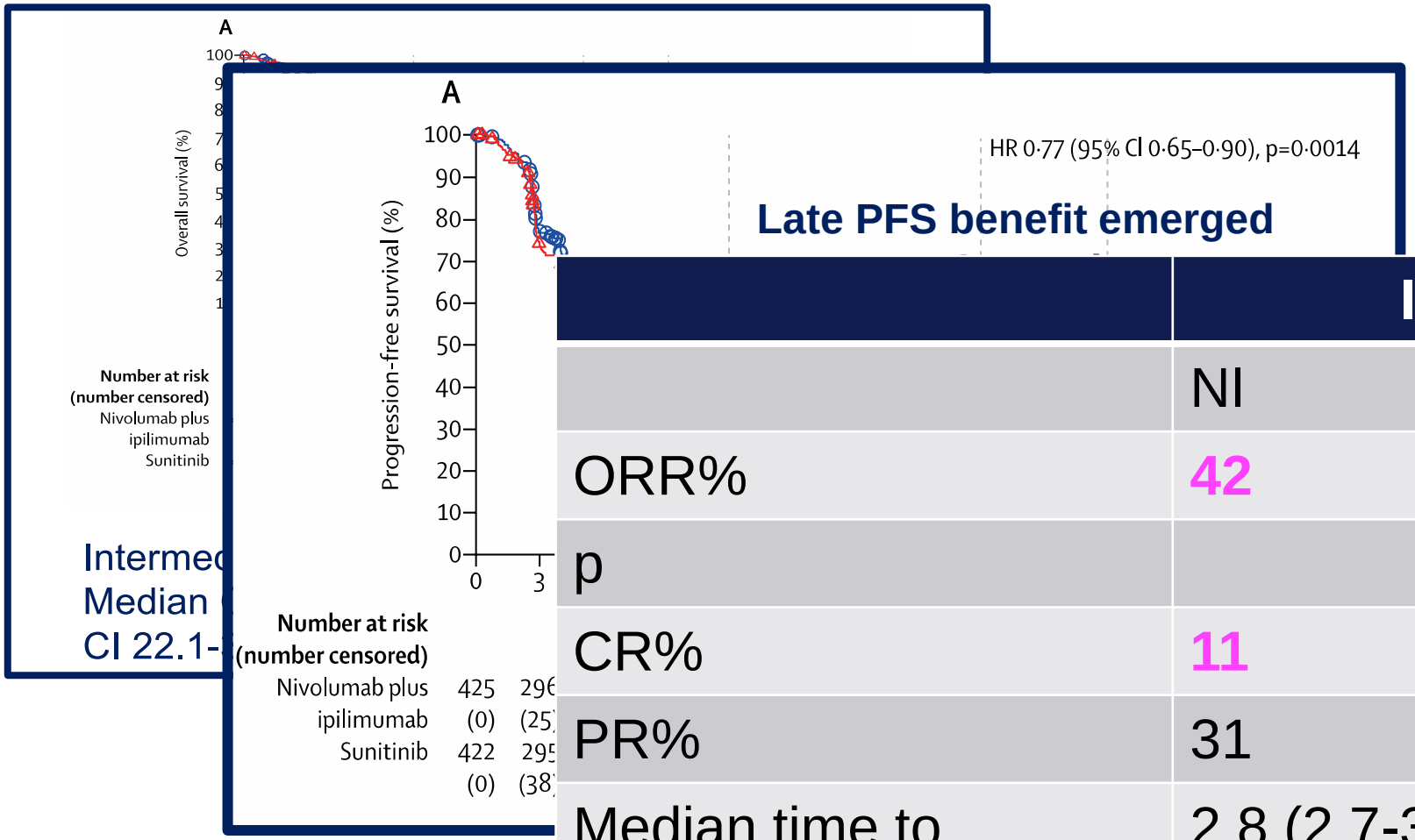
Department of Medicine I, Medical University of Vienna

Updates CheckMate 214, follow up 32.4 months[1]

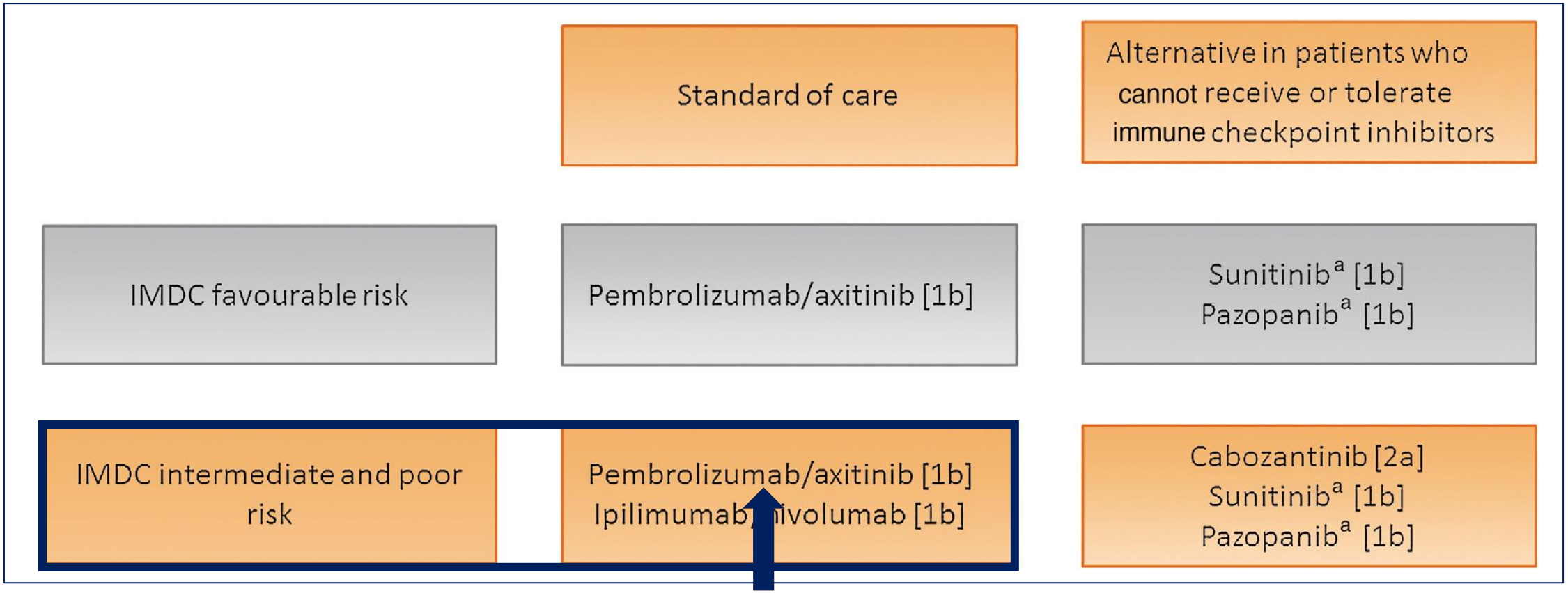


	Intermediate-poor	
	NI	SU
ORR%	42	29
p	0.0001	
CR%	11	1
PR%	31	28
Median time to response months	2.8 (2.7-3.1)	4.0 (2.8-5.5)

Motzer RJ et al., Lancet Oncol 2019

Patient 1: IMDC intermediate risk, cc-RCC: Medical Treatment Option 2 according to updated EAU Guidelines

EUROPEAN UROLOGY 78 (2019) 151–158
available at www.sciencedirect.com
journal homepage: www.europeanurology.com
European Association of Urology



Albiges L et al., Eur Urol 2019

(1) Key efficacy results: pembrolizumab+axitinib[1,2]: median follow up 12.8 months (0.1-22)

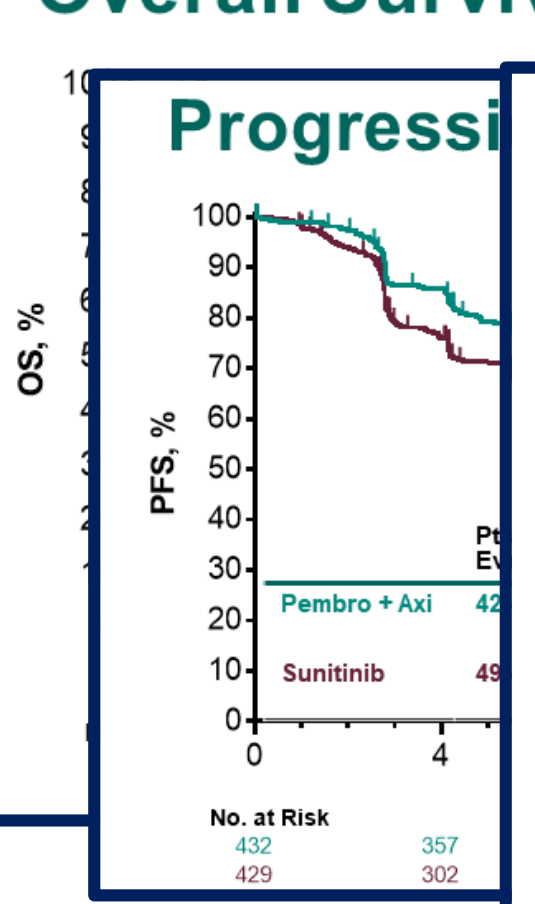
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

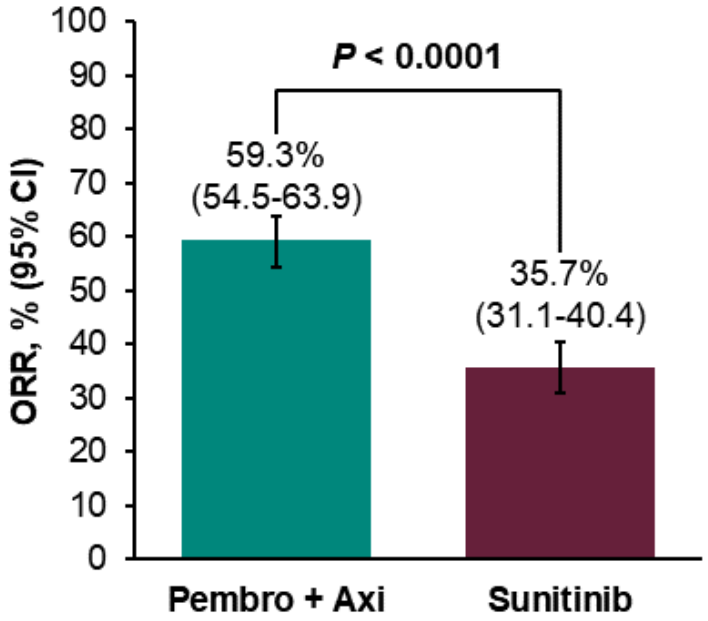
B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot,

Overall Survival



Progressi

Confirmed Objective Response Rate



Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

1. Powles T, et al. ASCO GU 2019 (Abstract No. 543);
2. Rini BI, et al. N Engl J Med 2019;380:1116-1127.

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Medical University of Vienna and Comprehensive Cancer Center

Patient 2, male, 66 years, IMDC favorable risk

- March 2005: cytoreductive nephrectomy
- pT3a, pN0, G3, clear cell RCC
- **July 2009**: diagnosis of single liver met

IMDC Risk factors
KPS <80%
<1 year from diagnosis to treatment
Haemoglobin concentration <lower limit of normal
Calcium concentration >upper limit of normal
Neutrophil count >upper limit of normal
Platelet count >upper limit of normal

NONE

- **Do we need to begin medical treatment right away in favorable risk patients?**
- **Is local treatment an option?**
  - Yes in selected patients, although no prospective data
  - Multiple retrospective reports point towards a benefit of complete metastasectomy for OS and CSS, but there is selection bias

Median OS 36.5 to142 months for patients with complete resection

Complete surgical metastasectomy: independent predictor of survival across a priori subgroup and sensitivity analyses, and regardless of whether adjusted for performance status[1]

1.Zaid HB et al., Vol. 197, 44-49, January 2017

Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive CancerCentre

EUROPEAN UROLOGY ONCOLOGY XXX (2019) XXX–XXX

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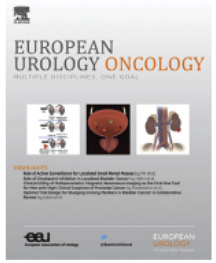


European Association of Urology

Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies

Nicholas G. Zaorsky [a,b,*], *Eric J. Lehrer* [c], *Gargi Kothari* [d], *Alexander V. Louie* [e], *Shankar Siva* [d]

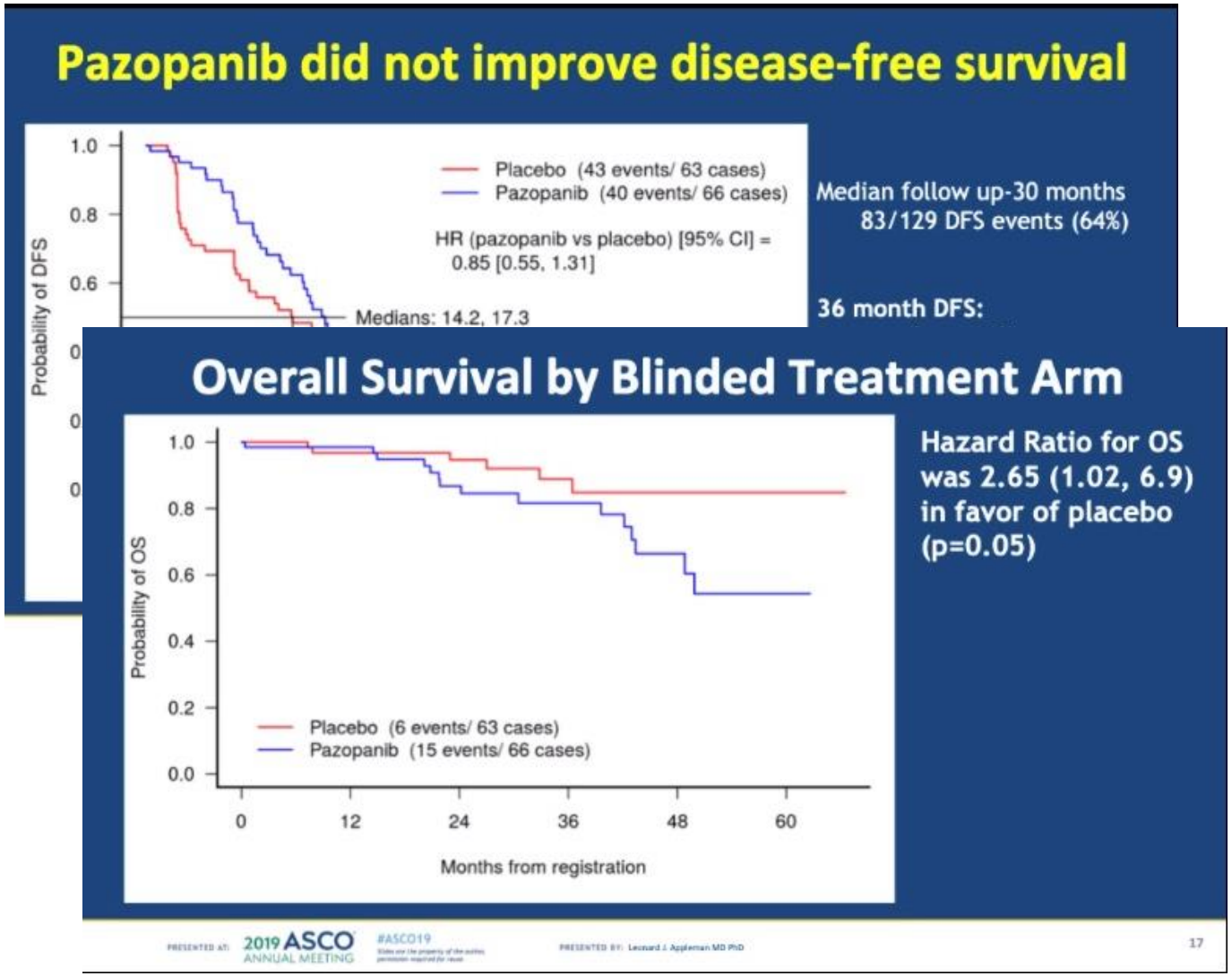
Population	Patients with metastatic renal cell carcinoma
Intervention	Stereotactic radiation therapy, defined as a treatment that couples a high degree of anatomic targeting accuracy and reproducibility with very high doses (ie, >8 Gy/fraction) of extremely precise and accurate, externally generated, ionizing radiation, thereby maximizing the cell-killing effect on the target(s), while minimizing radiation-related injury in adjacent tissues
Control	Either no control group or a multiarm study where stereotactic radiation therapy was used
Outcomes	Primary outcome: 1-yr local control and 1-yr overall survival Secondary outcome: incidence of any acute or late Common Terminology Criteria for Adverse Events grade 3–4 toxicity
Study design	Prospective or retrospective clinical study

Conclusions: Stereotactic radiotherapy is safe and efficacious for RCC oligometastases, with local control at 90% and any significant toxicity at 1%, reported at 1 yr.

Patient WP, male, 66 years

- March 2005: cytoreductive nephrectomy
- pT3a, pN0, G3, clear cell RCC
- July 2009: diagnosis of a single liver metastasis
- **Resection liver metastasis**

Should this patient receive medical treatment after resection of metastasis?



Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: A trial of the ECOG-ACRIN cancer research group (E2810)

Patient WP, male, 66 years, IMDC favorable risk

- March 2005: cytoreductive nephrectomy
- pT3a, pN0, G3, clear cell RCC
- July 2009: diagnosis of a single liver metastasis > Resection
- **August 2010: diagnosis of lung metastasis**
- **Begin medical treatment?**

The proper time to start systemic therapy is not well defined, some patient have an indolent course of disease,
median time on observation: 14.9 months (95%C) 10.6-25.0)[1]
median OS 44.5 months (95%Ci 37.6-not reached)

1.Rini BI et al., Lancet Oncol 2016;17:1317-23

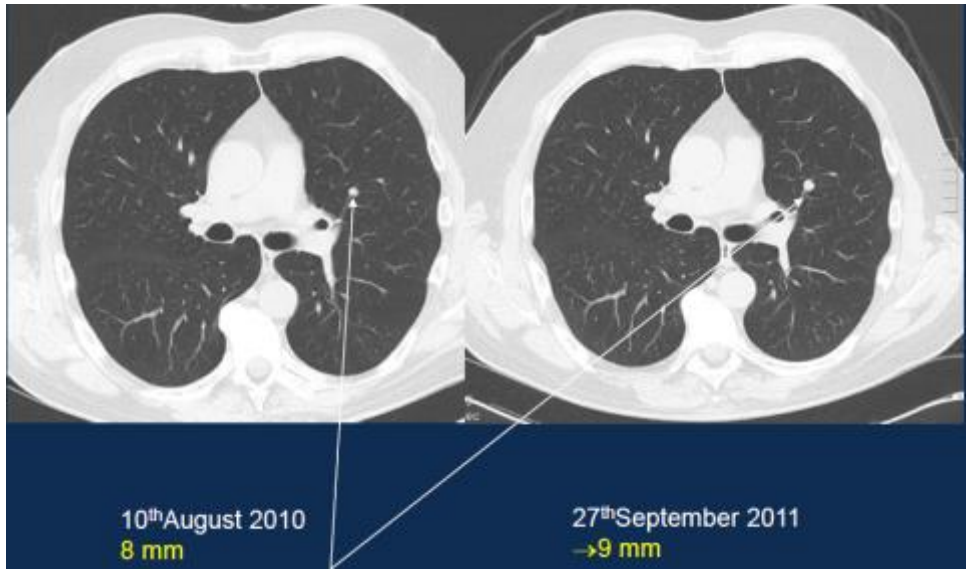
Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive CancerCentre

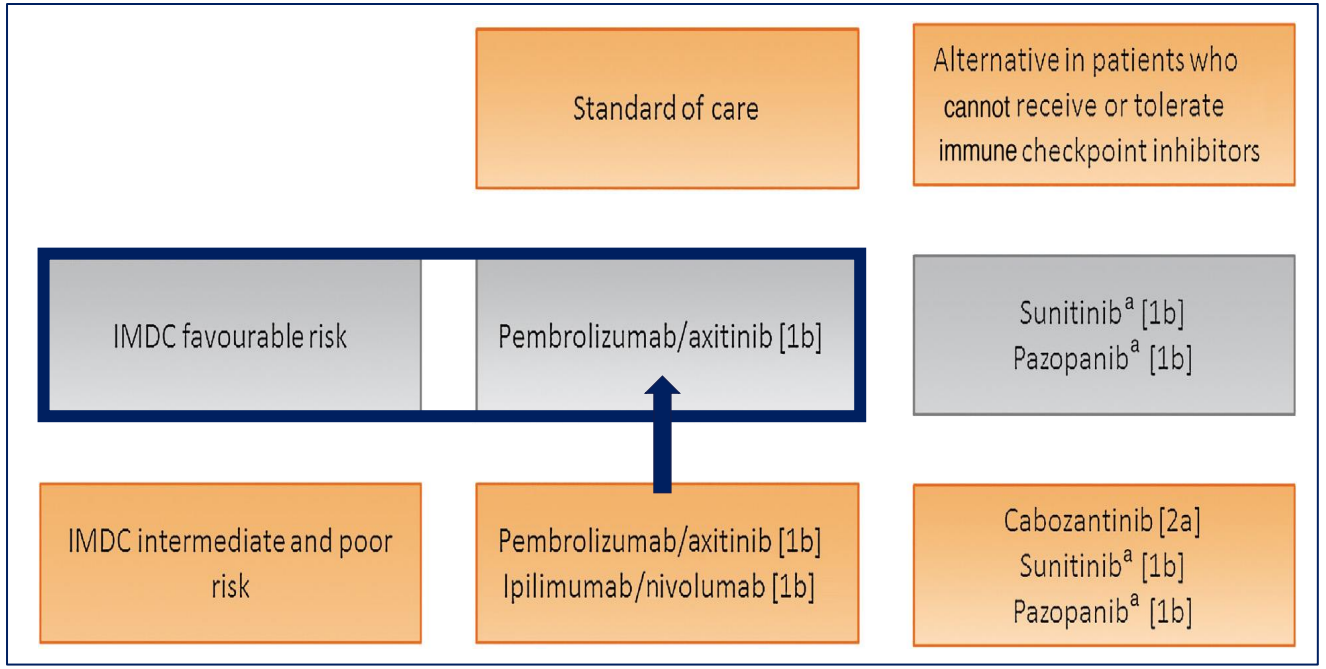
Patient WP, male, 66 years, IMDC favorable risk

- March 2005: cytoreductive nephrectomy
- pT3a, pN0, G3, clear cell RCC
- July 2009: diagnosis of a single liver metastasis
- Resection
- **August 2010: lung metastases: observation for 30 months**

February 2013:

- **disease progression,**
- **decision to begin medical treatment**

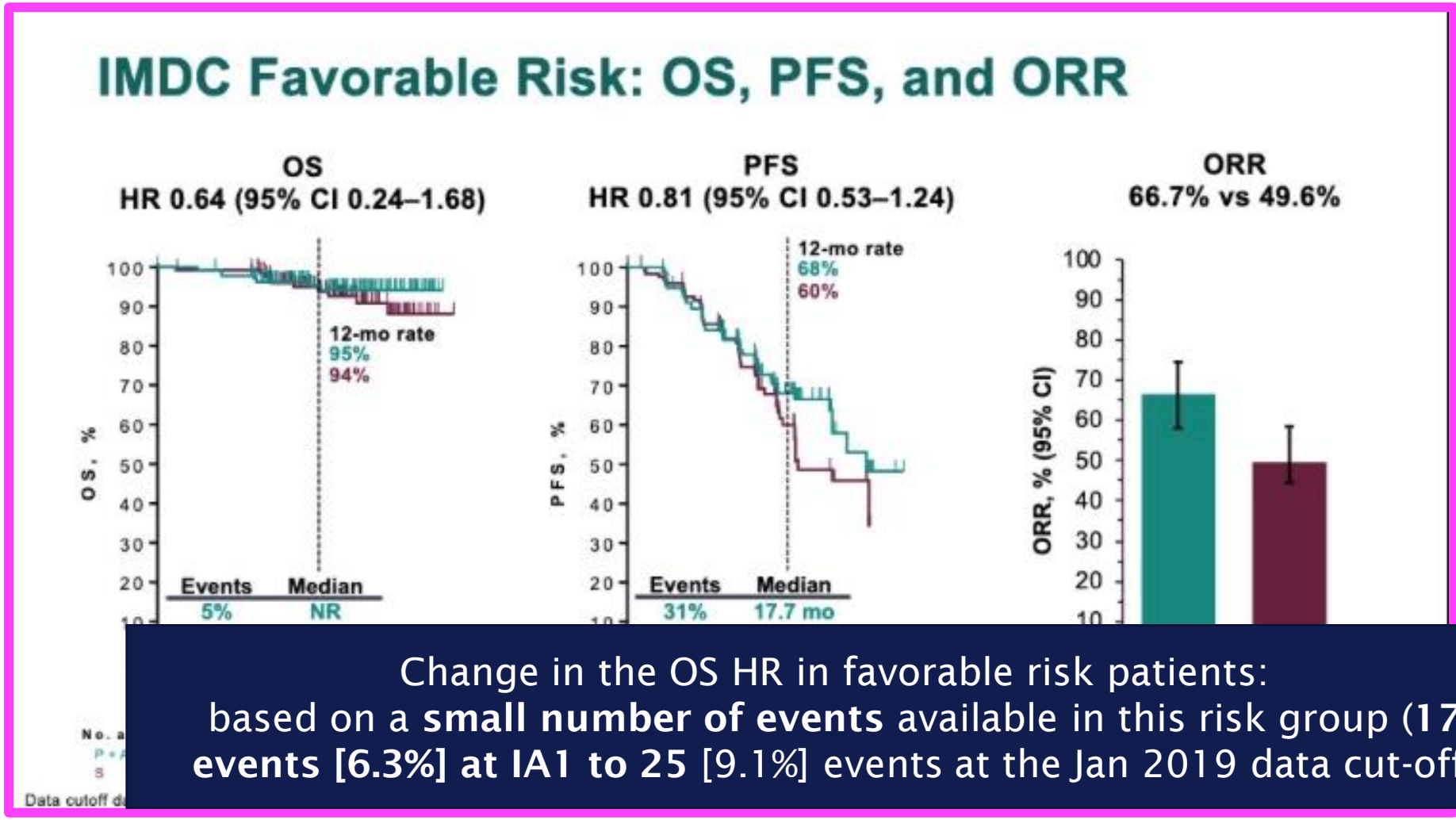




Albiges L et al., Eur Urol 2019

Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive CancerCentre

Key Efficacy results: Pembro+Axi in favorable risk



OS HR 16.6 months follow up 0.94 (95%CI 0.43-2.07)

Role of ICPI in favorable IMDC risk remains unclear

Change in the OS HR in favorable risk patients:
based on a **small number of events** available in this risk group (**17 events [6.3%] at IA1 to 25** [9.1%] events at the Jan 2019 data cut-off)

Rini BI et al., Clin Oncol 37, 2019 (suppl; abstr 4500)

2 attractive IO-based strategies in 1st-line: IO Doublet or IO+TKI

- **What we know:**
- Different biological approaches to address immune escape
- **What we don‘t know:**
- Which is better?

No head to head comparison,

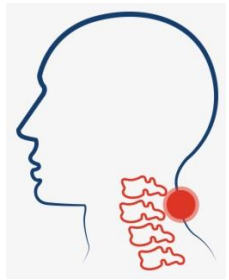
Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Centre

The current challenge: new agents are introduced fast…

- Too fast for our current understanding of how to use them best
- Treatment decisions for now: based on patients, disease and tumor related factors

Manuela Schmidinger, MD
Department of Medicine I, Medical University of Vienna

Treatment decisions in clinical practice: which factors may influence our decision between IO+IO or IO+TKI or TKI in 1st- and 2nd-line



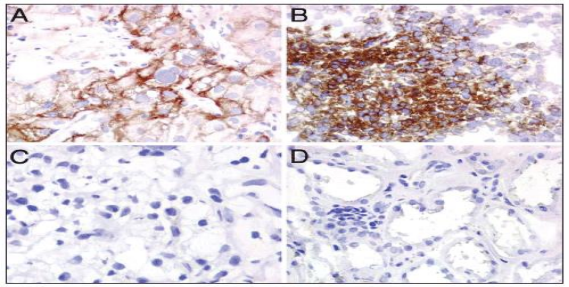
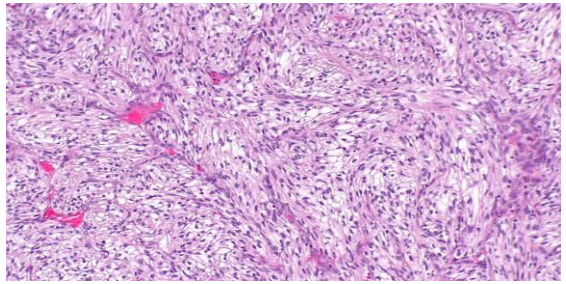
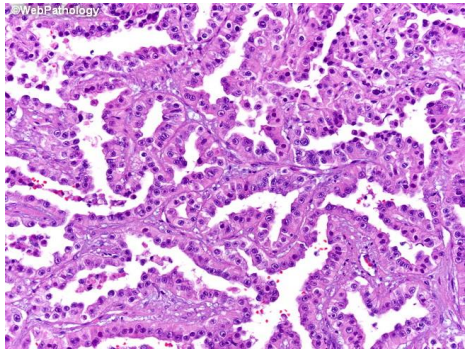


Figure 2: Expression of Programmed Death 1 Ligand (PD-L1) in Kidney Cancer and Normal Kidney—PD-L1 can be expressed on tumor cells (**A**) or infiltrating immune cells (**B**) (using 5H1 anti–PD-L1 antibody for staining); both findings are associated with worse prognosis in patients with kidney cancer compared with lack of tumor PD-L1 expression (**C**). This anti–PD-L1 antibody does not stain PD-L1 in the proximal kidney of a normal kidney specimen (**D**). (Photomicrographs at ×400.) From Thompson et al. Proc Natl Acad Sci USA. 2004.[47] Used with permission.





Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Centre

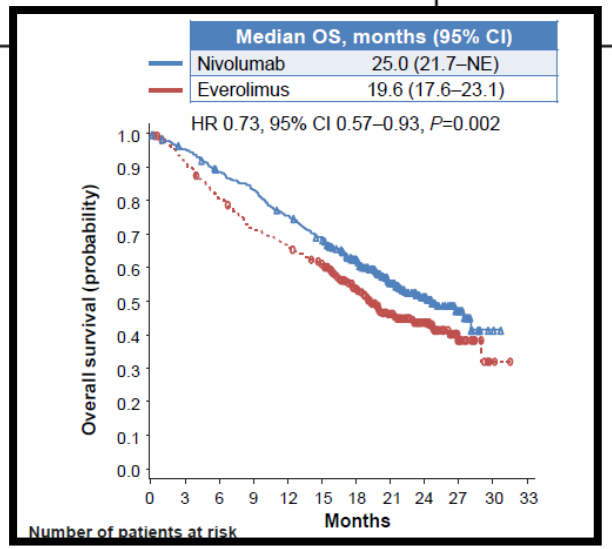
And the same criteria may apply for later lines…

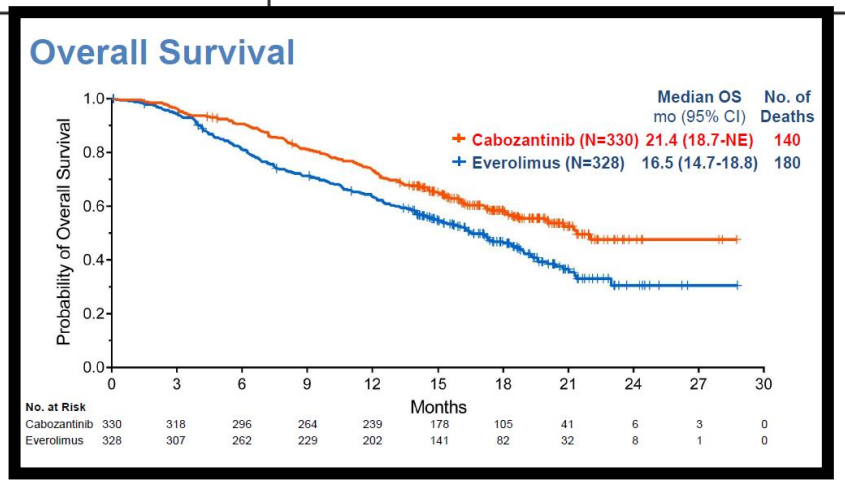
Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Centre

Second-Line Standard of Care in mRCC According to the ESMO 2019 Guidelines

Patient 2, after TKI

First line	Standard	Option
TKI	Nivolumab [I, A] Cabozantinib [I, A]	Axitinib [IIB] Everolimus [IIB] Lenvatinib + Everolimus [V, C]





1.Escudier B, Porta C; Schmidinger M et al., Ann Oncol 2019;

Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive CancerCentre

The Hope trial: randomized phase 2 trial Summary of Efficacy

	Lenvatinib/Everolimus (n=51)	Lenvatinib (n=52)	Everolimus (n=50)
Progression-free survival			
Median, months	14.6	7.4	5.5
95% CI	5.9-20.1	5.6-10.2	3.5-7.1
Benefit vs everolimus	P<0.001	P=0.048	NA
Objective response rate, %	43	27	6
95% CI	29-58	16-41	1-17
Benefit vs everolimus	P<0.001	P=0.007	NA
Overall survival (updated)			
Median, months	25.5	19.1	15.4
95% CI	16.4-32.1	13.6-26.2	11.8-20.6
Benefit vs everolimus	P=0.065	P=0.130	P=0.309

Motzer et al, Lancet Oncol 2015; 16: 1473-82

Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Centre

Second-Line Standard of Care in mRCC According to the ESMO 2019 Guidelines

Patient 2, after TKI

Patient 1, after Nivo+Ipi

First line	Standard	Option
TKI	Nivolumab [I, A] Cabozantinib [I, A]	Axitinib [IIB] Everolimus [IIB] Lenvatinib + Everolimus [V, C]
Nivolumab + Ipilimumab	X	Any TKI [IV, C] Lenvatinib + Everolimus [V, C]

What else?

1.Escudier B, Porta C; Schmidinger M et al., Ann Oncol 2019;

Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive CancerCentre

Lenvatinib+Pembrolizumab in patients who have progressed on ICPI±ICPI or ± TKI

Poster No. 1187PD

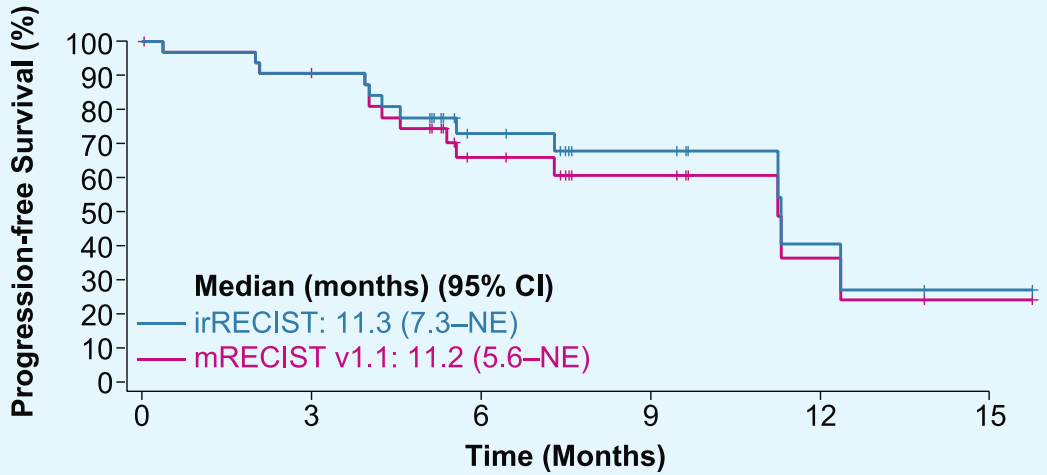
Phase 2 Study of Lenvatinib Plus Pembrolizumab for Disease Progression After PD-1/PD-L1 Immune Checkpoint Inhibitor (ICI) in Metastatic Clear Cell (mcc) Renal Cell Carcinoma (RCC): Results of an Interim Analysis

Chung-Han Lee[1], Amishi Y. Shah[2], Vicky Makker[1], Matthew Taylor[3], David Shaffer[4], James J. Hsieh[5], Allen L. Cohn[6], Chris DiSimone[7], Alvaro Pinto Marin[8], Drew Rasco[9], Sara Gunnestad Ribe[10], Donald A. Richards[11], Daniel E. Stepan[12]*, Corina E. Dutcus[12], Jane Wu[12], Emmett V. Schmidt[13], Rodolfo Perini[13], Robert Motzer[1]

- All (n=33) patients **had progressed on IO-based treatment**
- The initial evidence of disease progression needed to be confirmed by a second assessment, ≥ 4 weeks from the date of the first documented disease progression
- Primary endpoint: ORR

Outcome Response	irRECIST*
PR %	64
SD %	30
Ne %	6
ORR% (95%CI)	64 (45-80(
DOR median, months (95%CI)	9.1 (6.1-ne)

Figure 4. Kaplan–Meier Plot of PFS Using irRECIST and mRECIST v1.1 by Investigator Assessment



CI, confidence interval; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; mRECIST v1.1, modified Response Evaluation Criteria In Solid Tumors version 1.1; NE, not evaluable; PFS, progression-free survival.

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Manuela Schmidinger, MD
Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Centre

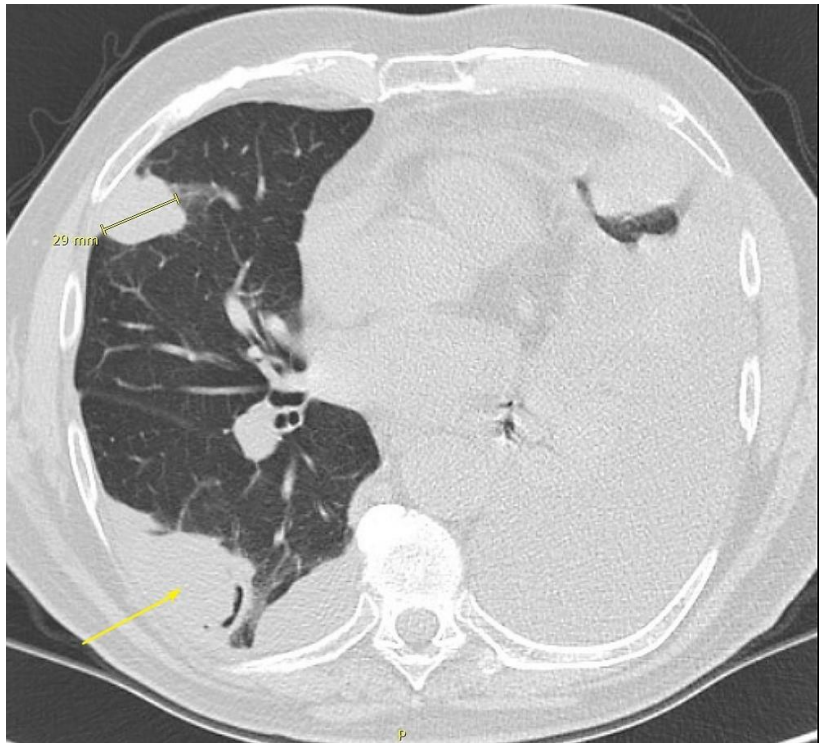
What about next, next, next… line?

- **Don‘t adhere too strictly to guidelines: consider that some patients can‘t wait for new data…**
- Guidelines are retrospective
- And they don‘t take into account that the biology of resistance to IO is completely different to targeted agents

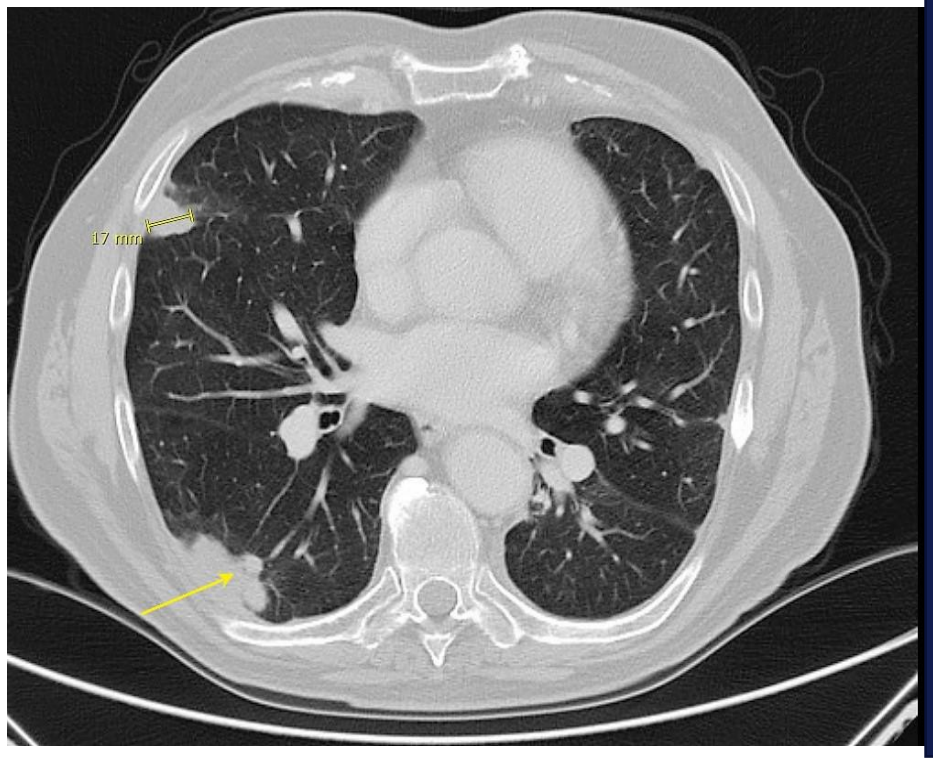
Manuela Schmidinger, MD
Department of Medicine I, Medical University of Vienna

Patient EZ, 75 years
Nivo+Ipi 5th-line after
Sunitinib>Nivolumab>Cabozantinib>Lenvatinib+Everolimus

- January 2018



- September 2018



- Strategy LATER confirmed in the TITAN-study:
- Ipi boost in patients with SD or PD with Nivo mono in 1st- and 2nd-line
- Ipi-boost: 1st line **29.8%** (12.8 % with PR) 2nd Line **35.1%** (10.5% with CR/PR)[1]

Conclusions

- In 2020, former „lost cases“ can survive due highly efficacious agents
- In the absence of H2H studies among new players, patient-disease and tumor related factors may help to guide our treatment decisions between IO+IO or IO+TKI
- Many „me too“ studies underway: may identify other great combinations but ressources should be kept for extensive biomarker research
- In the era of immune check point inhibitors, we should not be glued to guidelines:
  - They do not take into account that the biology of resistance to IO is completely different to targeted agents