# Therapeutic 1st line options in advanced Renal Cell Carcinoma

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Interdisciplinary GU Oncology

*Bildnachweis: istockphoto*

# Conflicts of interest

## 1. Appointment

University Hospital Essen

## 2. Consultant

BMS, MSD, Roche, Ipsen, Novartis, Roche, Merck KGa, Nanobiotix, Janssen, EUSA Pharma, Pfizer. Lilly

## 3. Stocks

Astra Zeneca, BMS, MSD

## 4. Patent

none

## 5. Honoraria

Astra Zeneca, Bayer, BMS, MSD, Merck KGa, Eisai, Roche, Ipsen, Novartis, Janssen, Pfizer, Novartis, Lilly

## 6. Financial research support

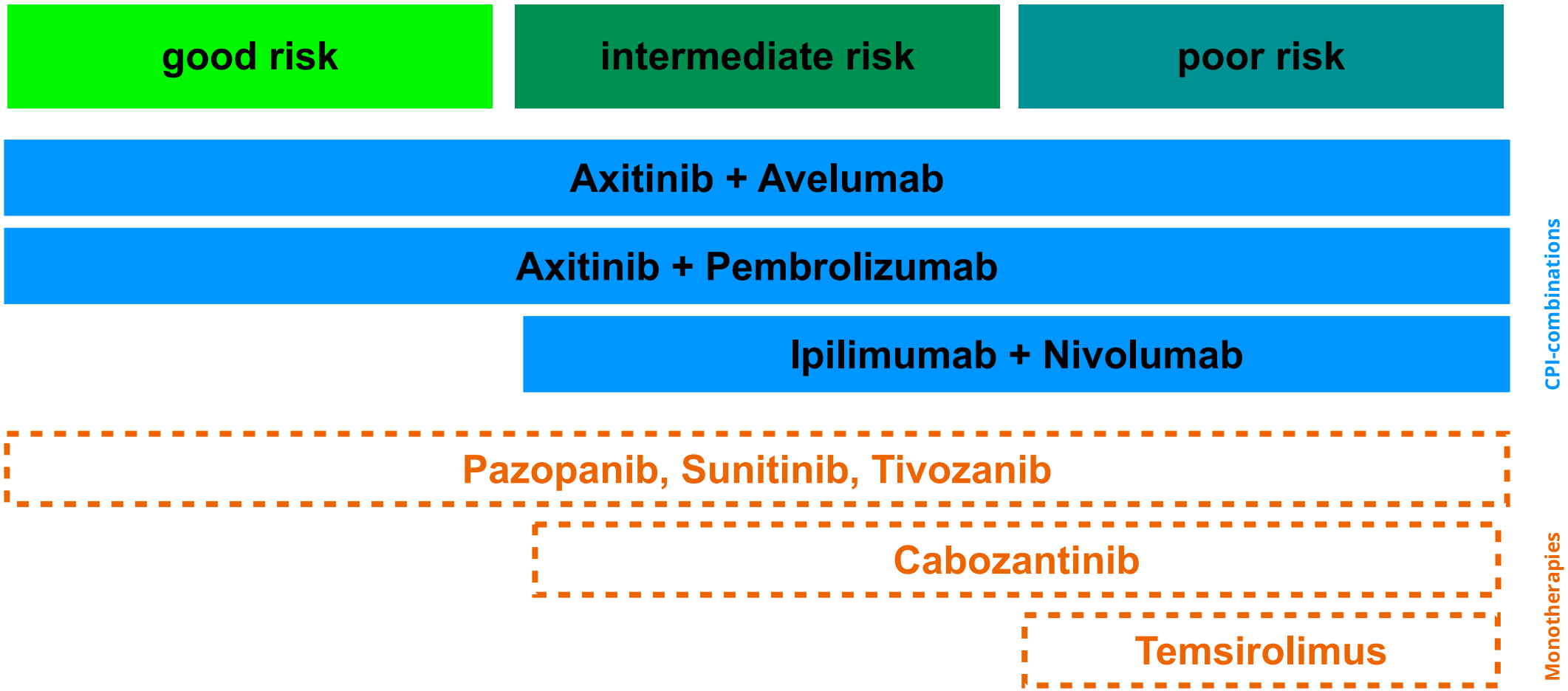
Pfizer (Wyeth), BMS, MSD, Novartis, Astra Zeneca

## 7. Other financial support

BMS, Ipsen, Pfizer, AstraZeneca, Bayer

# Efficacy

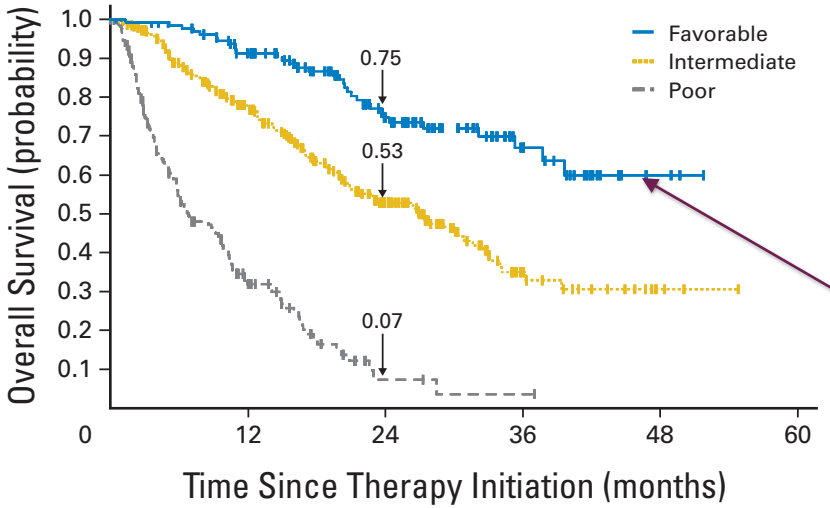
# Licensed 1st line therapies in advanced RCC



# Risk stratification is the basis of therapy selection in 1st line mRCC

**IMDC**

- time to medical treatment
- Hyper-calcaemia
- Anemia
- Performance status
- Thrombo-cytophilia
- Neutrophilia



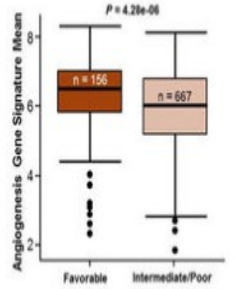

No. of events/No. at risk

| | | | | | |
|---|---|---|---|---|---|
| Favorable | 11/133 | 16/110 | 4/62 | 2/22 | 0/3 |
| Intermediate | 61/301 | 50/182 | 17/82 | 2/18 | 0/3 |
| Poor | 94/152 | 19/36 | 1/3 | 0/1 | 0/0 |

| | Δ good vs. interm./poor risk (%) | P-value |
|---|---|---|
| HIF2a | +57 | 0.03 |
| VEGFA | +67 | 0.07 |
| VEGFR-1 | +100 | 0.02 |
| VEGFR-2 | +128 | 0.009 |
| VEGFR-3 | +52 | 0.03 |

Beuselinck et al. ESMO 2018: 869PD

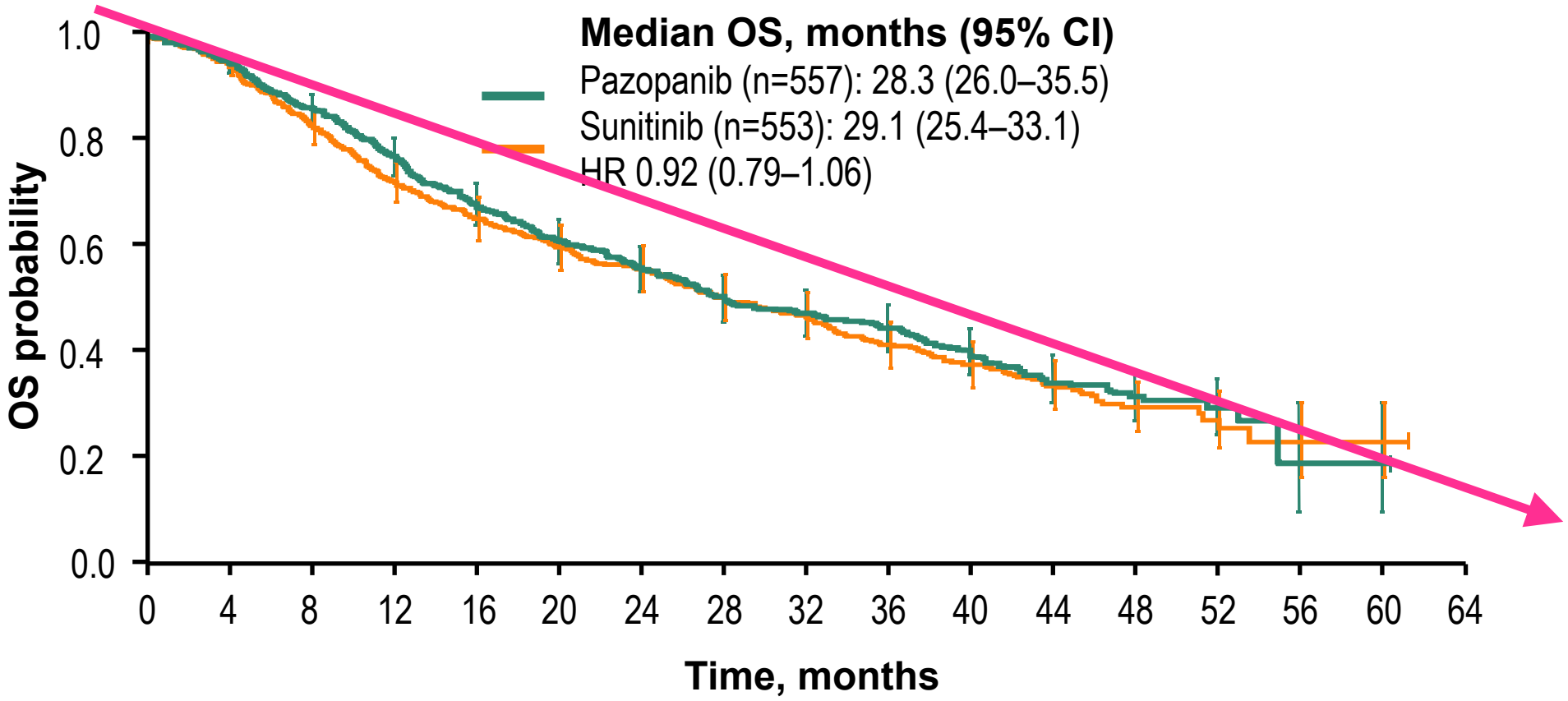
Favorable MSKCC Risk Patients are Characterized by Higher Angiogenesis Gene Signature Expression




Rini et al. ESMO 2018: LBA31

Heng et al. (2009). Journal of Clinical Oncology, 27(34), 5794–5799. http://doi.org/10.1200/JCO.2008.21.4809

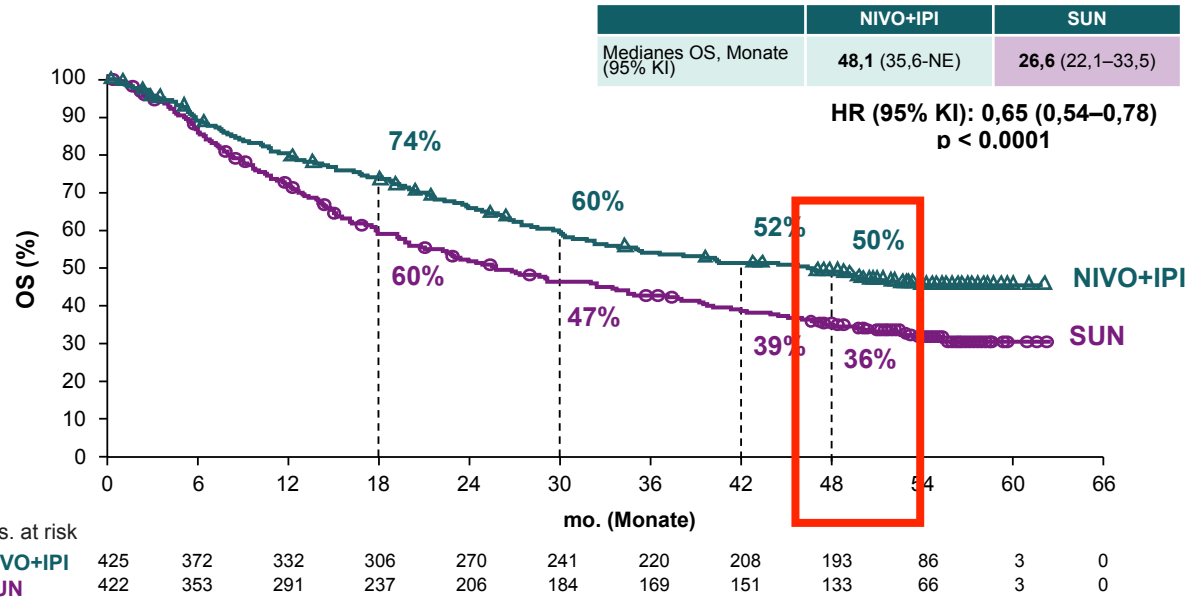
# 1st generation TKIs achieve similar OS




Motzer RJ et al. *N Engl J Med* 2014;370:1769–1770.

# IPI-NIVO - sets the bar for long-term results (4 yrs. FU)

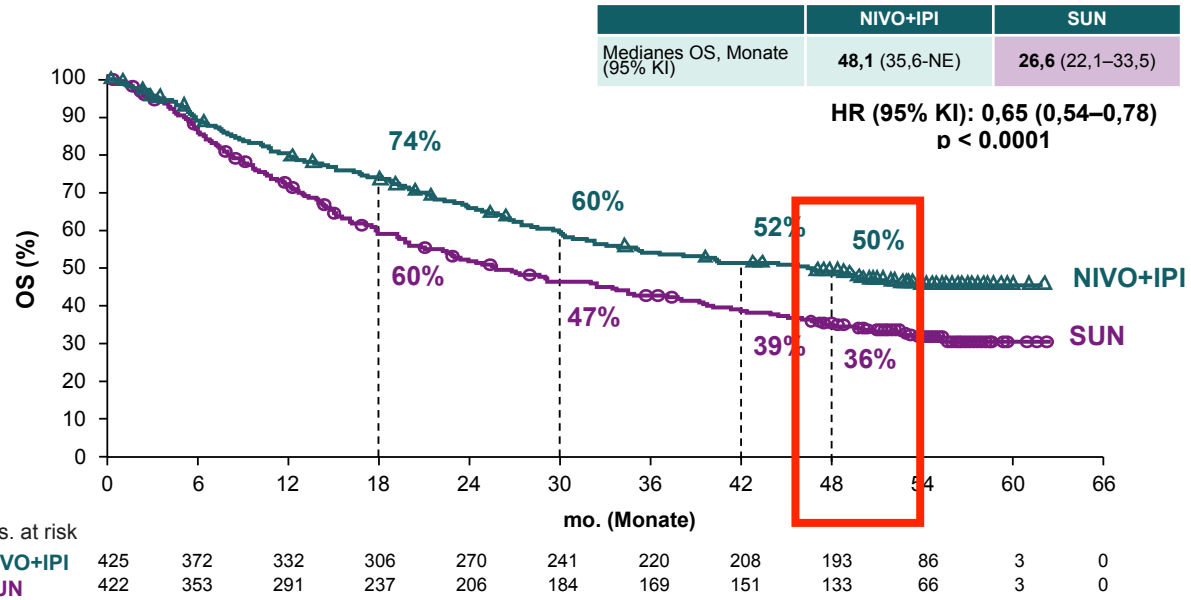
## CM214 - RCC



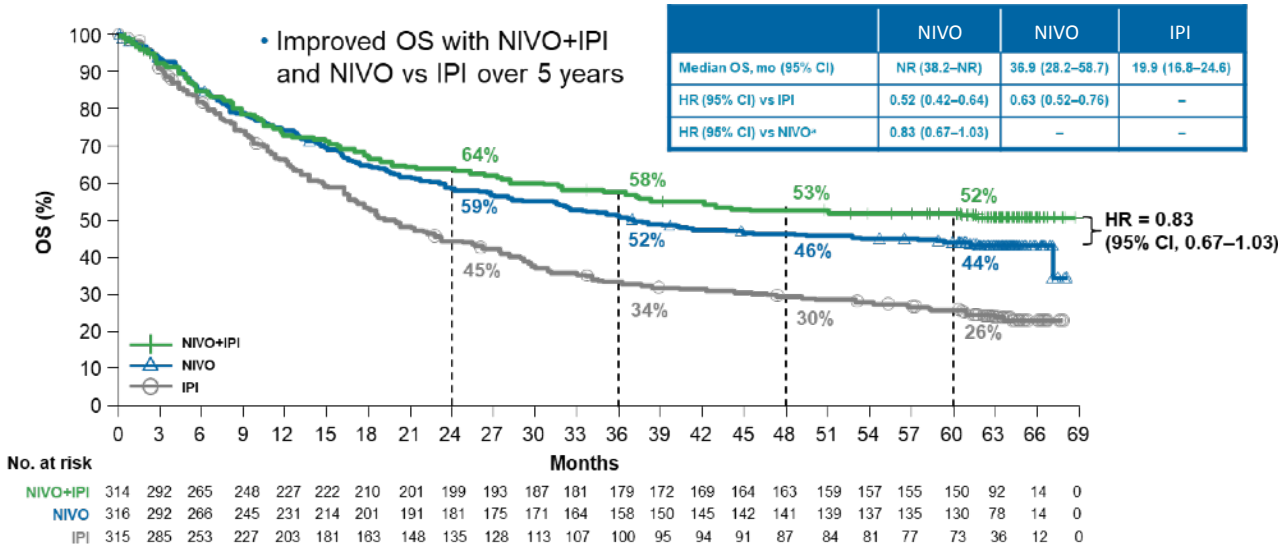

NE = not estimable
Albiges L et. al ESMO Virtual Congress, 2020; Presentation, Abstract #711P

# IPI-NIVO - sets the bar for long-term results (4 yrs. FU)

## CM214 - RCC




## CM67 - melanoma

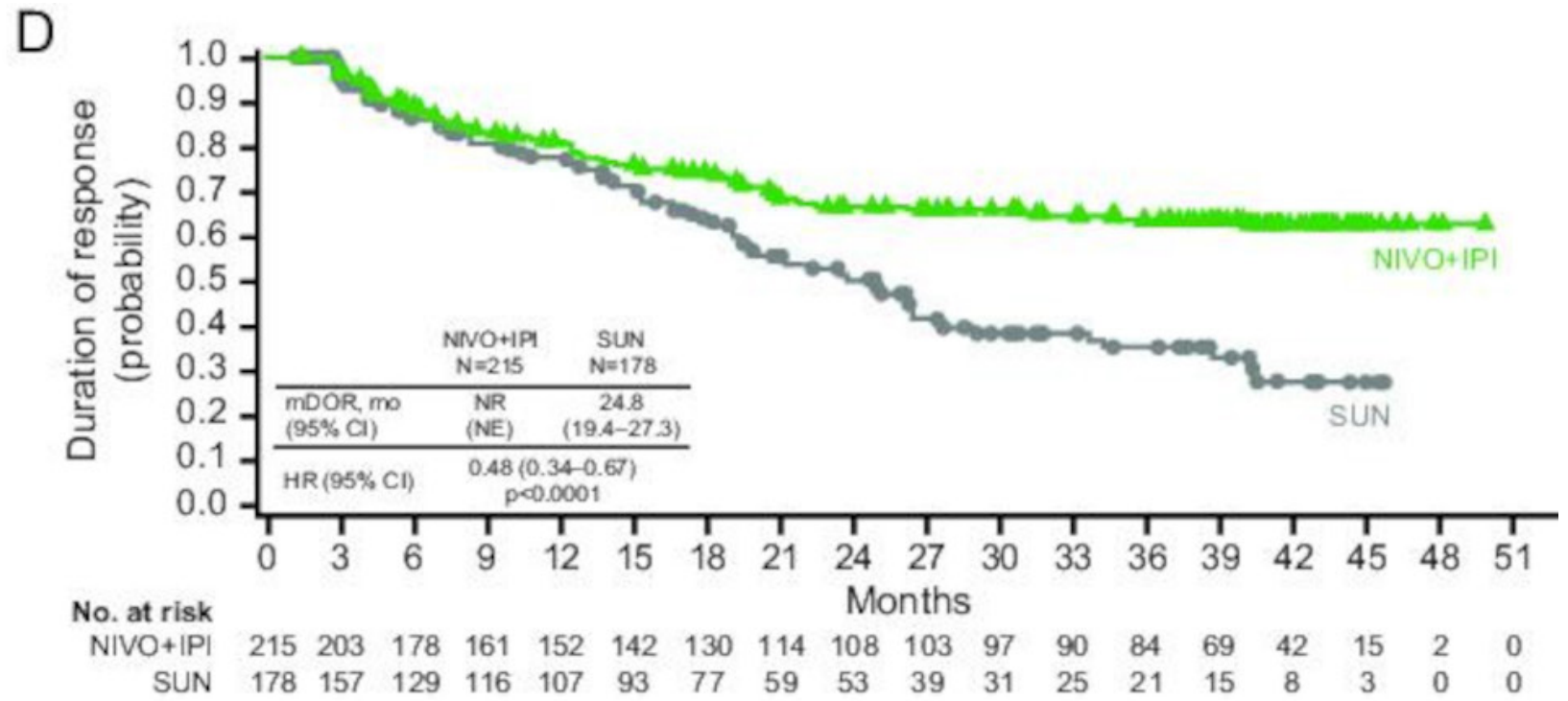



NE = not estimable
Albiges L et. al ESMO Virtual Congress, 2020; Presentation, Abstract #711P

Larkin J et al., N Engl J Med 2019; 381:1535-46

# Better quality for CPI-induced responses (DoR)

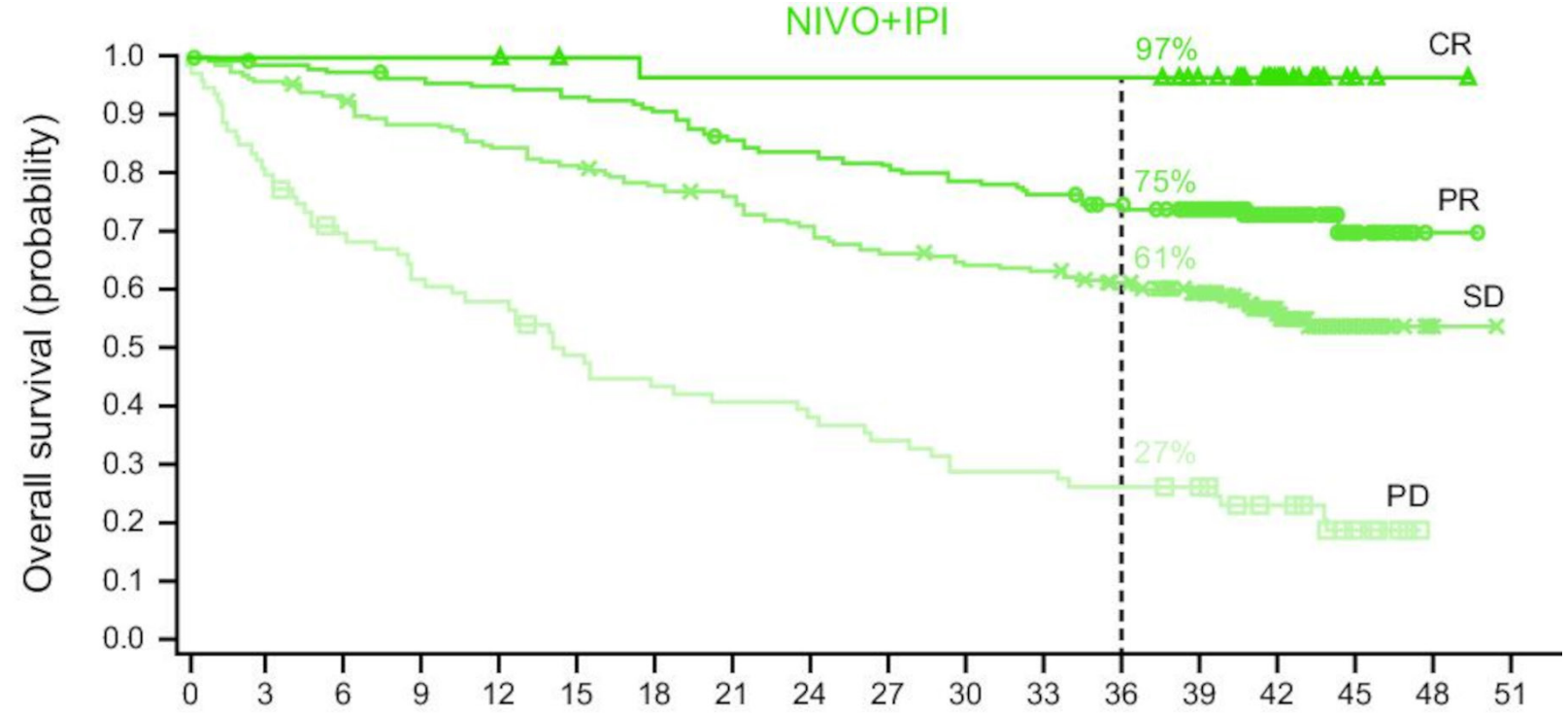
CR rate:
11%




Follow-up: ≧ 42 Mo. - ITT

*Motzer, R. et al.*(2020). Journal for ImmunoTherapy of Cancer 8(2), e000891. https://dx.doi.org/10.1136/jitc-2020-000891

# Type of response is associated with prognosis




No. at risk

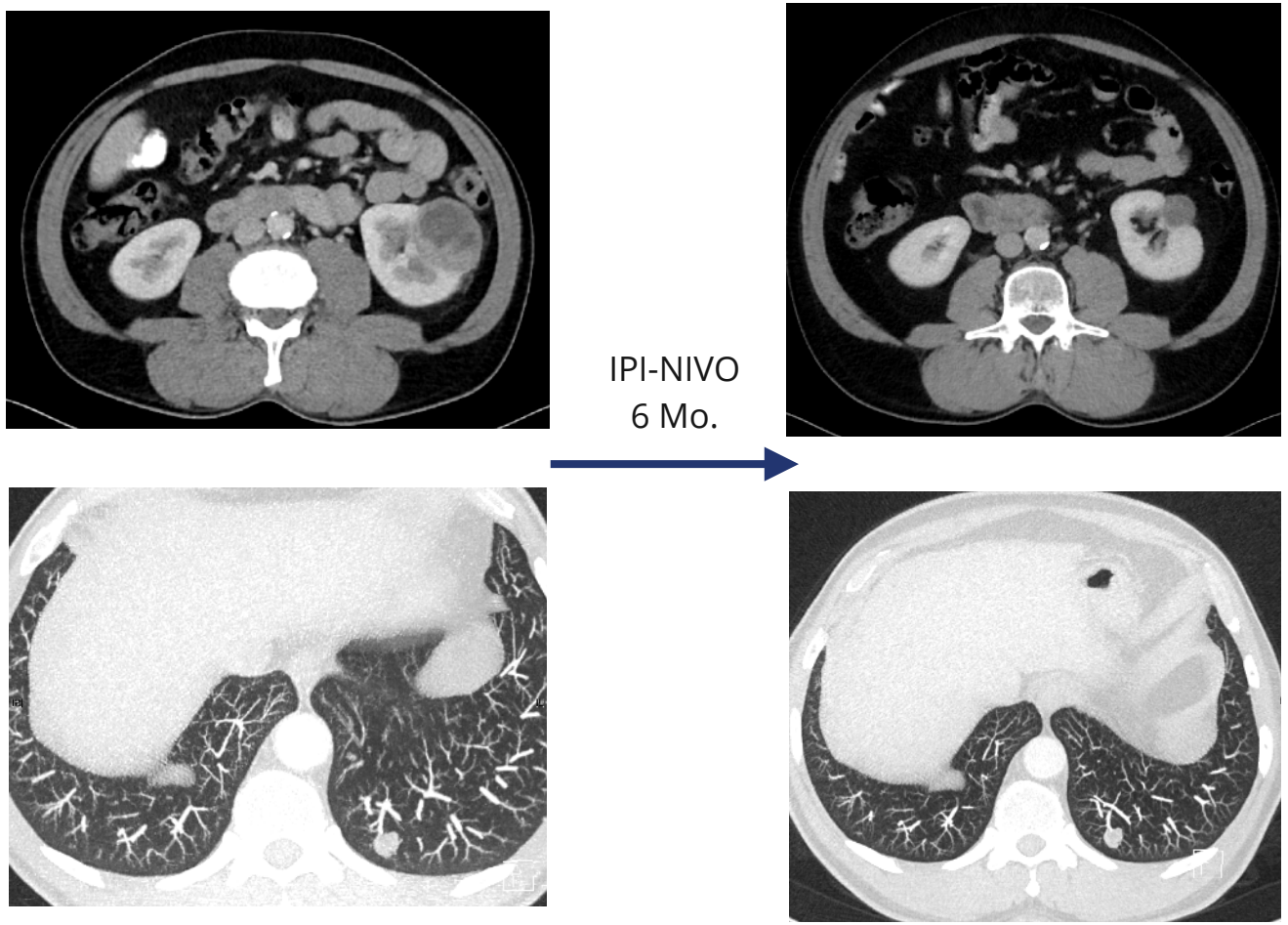
| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CR | 32 | 32 | 32 | 32 | 32 | 30 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 25 | 12 | 2 | 1 | 0 |
| PR | 166 | 162 | 160 | 157 | 155 | 152 | 148 | 139 | 135 | 132 | 128 | 124 | 118 | 100 | 49 | 18 | 1 | 0 |
| SD | 203 | 195 | 187 | 178 | 170 | 164 | 156 | 149 | 140 | 132 | 127 | 125 | 117 | 97 | 61 | 24 | 1 | 0 |
| PD | 80 | 64 | 54 | 48 | 45 | 37 | 33 | 31 | 29 | 26 | 22 | 22 | 20 | 18 | 13 | 5 | 0 | 0 |



*Motzer, R. et al.*(2020). Journal for ImmunoTherapy of Cancer 8(2), e000891. https://dx.doi.org/10.1136/jitc-2020-000891

# 56-year-old with synchronous lung metastases

## IMDC: intermediate risk



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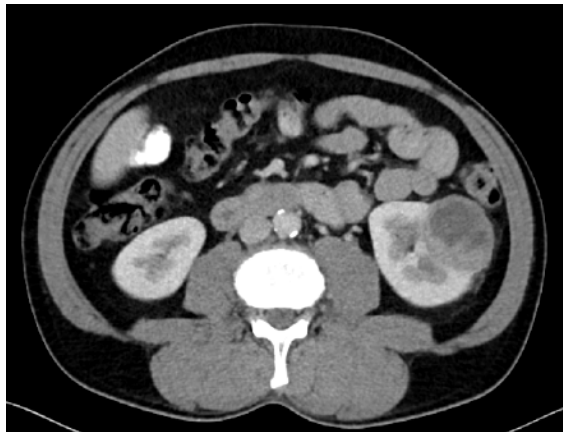
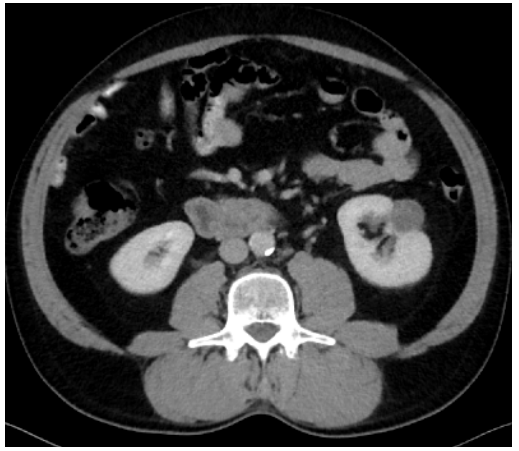
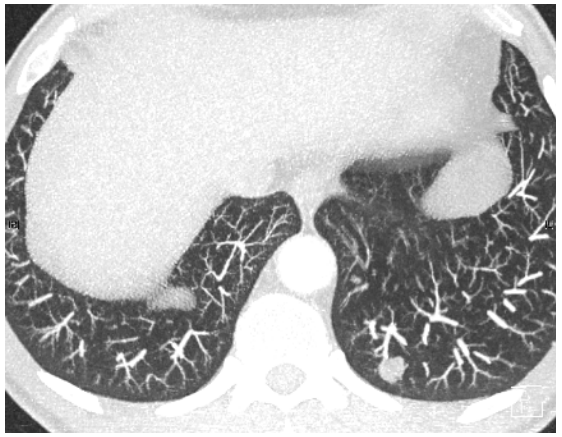
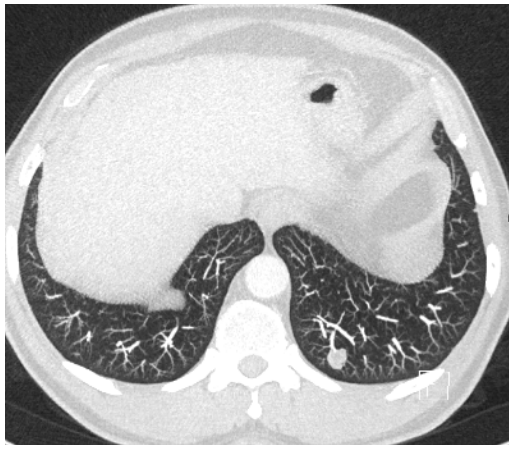


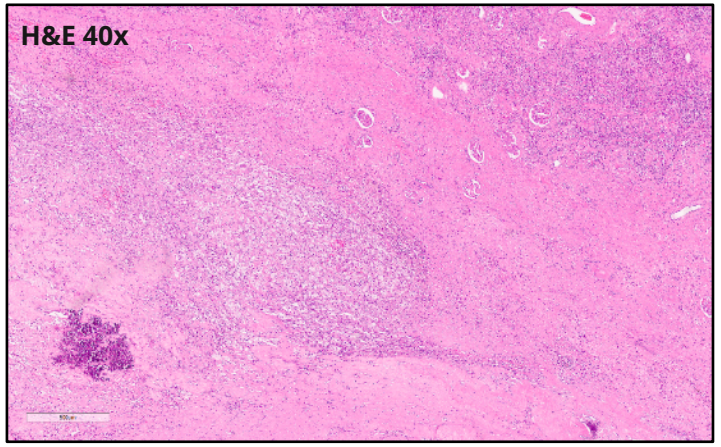


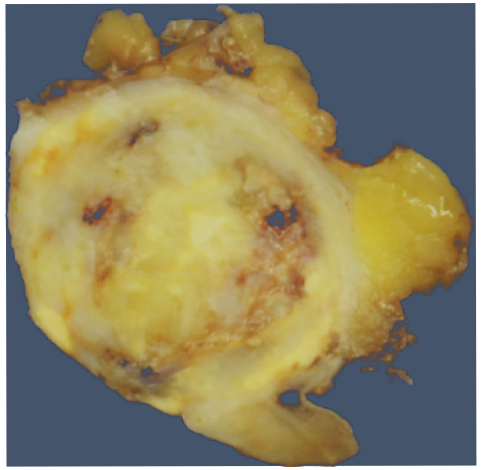
IPI-NIVO
6 Mo.



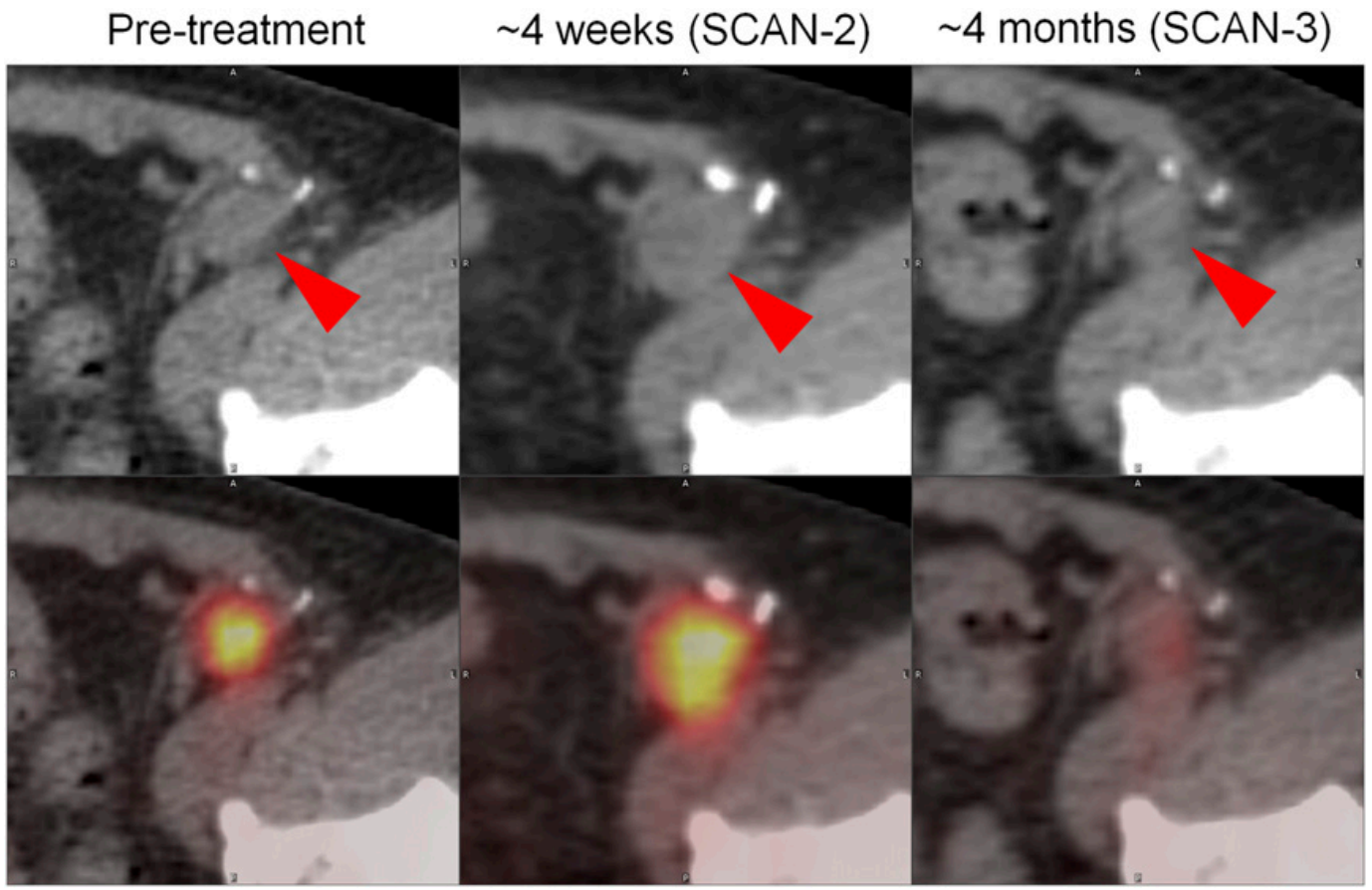


**ypT0, ypM0**



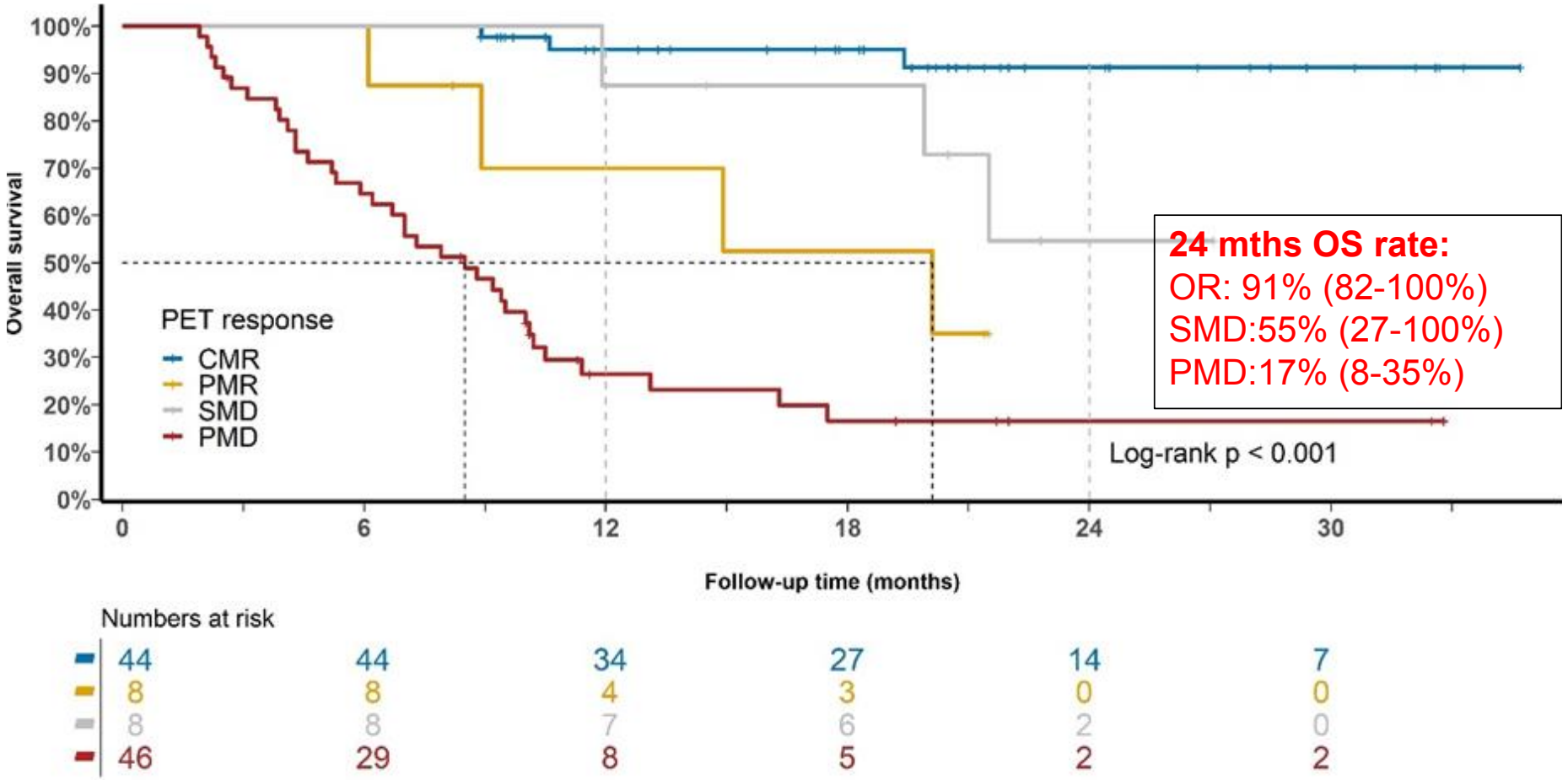



# Metabolic response - a clinical tool for residual disease




1. Cho, S. Y. *et al.* Prediction of Response to Immune Checkpoint Inhibitor Therapy Using Early-Time-Point 18F-FDG PET/CT Imaging in Patients with Advanced Melanoma. *J Nucl Med* **58,** 1421–1428 (2017).

# FDG-PET response to IPI-NIVO is prognostic in Melanoma




**24 mths OS rate:**
OR: 91% (82-100%)
SMD:55% (27-100%)
PMD:17% (8-35%)

10041 Iravani et al. ASCO 2020

# DISCO

## PET-based therapy DISContinuation in Melanoma & RCC

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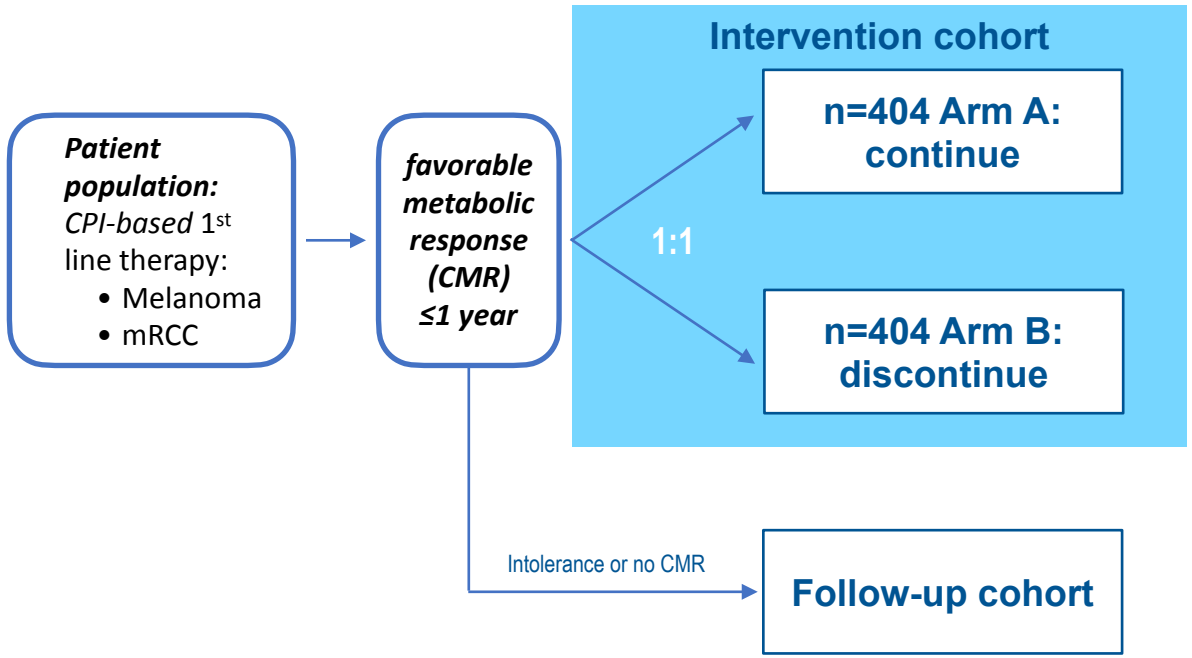
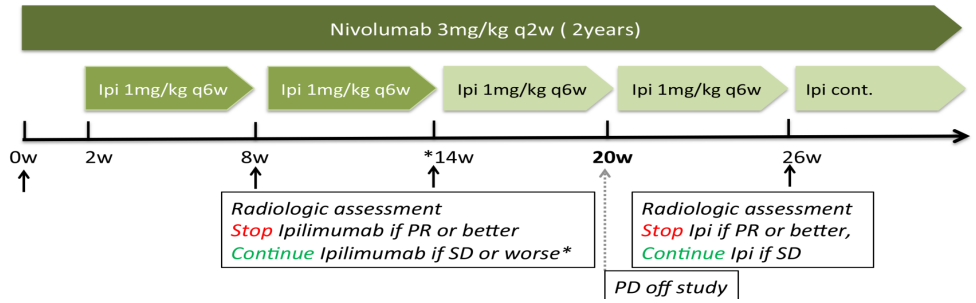
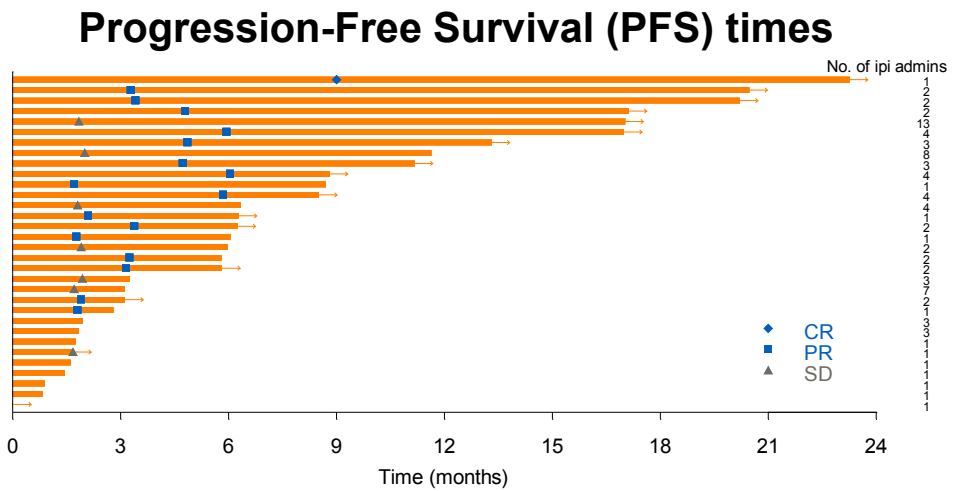
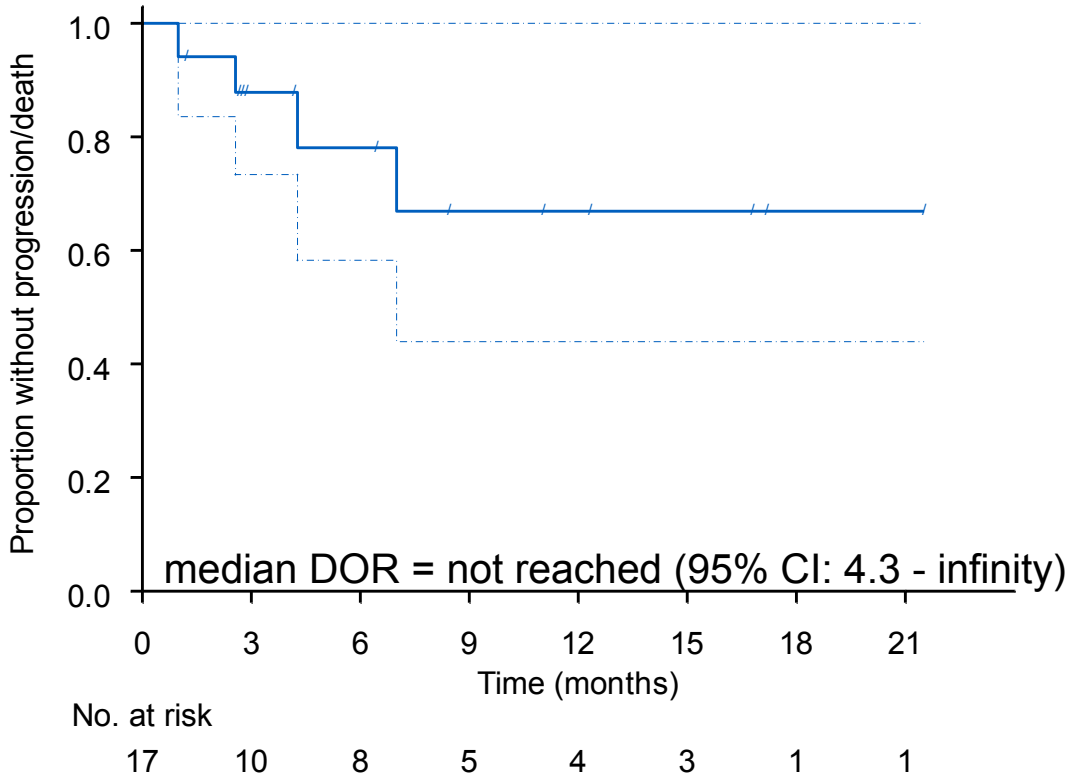


# Response-triggered therapy is an option for de-escalation




Pts. are ordered by progression-free survival times. 16/32 pts. continue treatment.

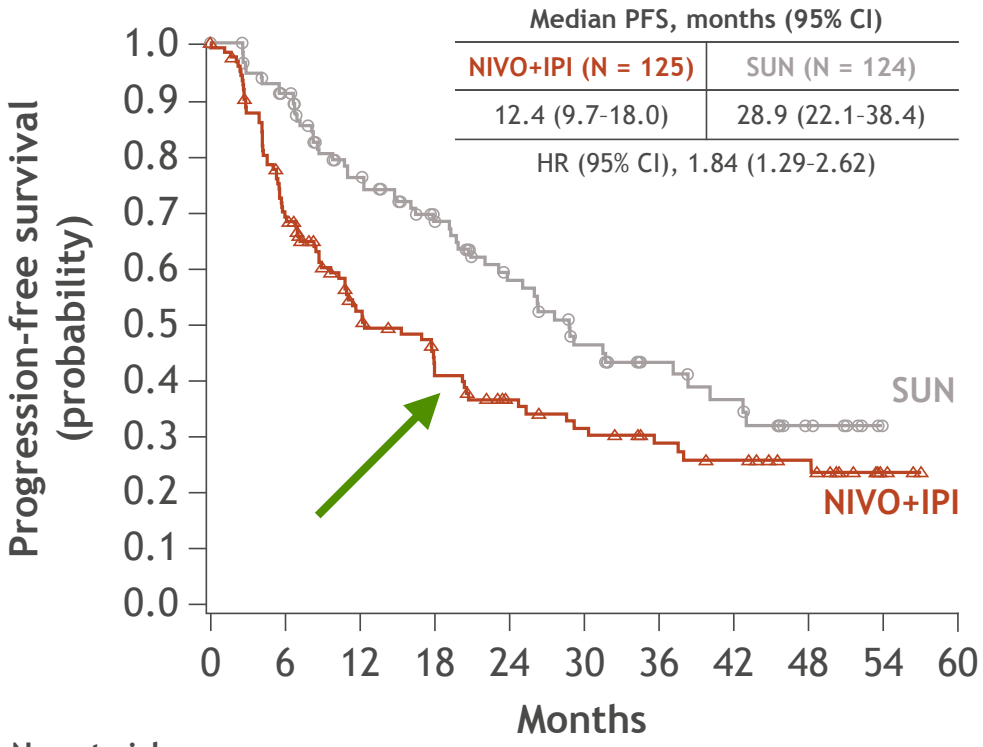




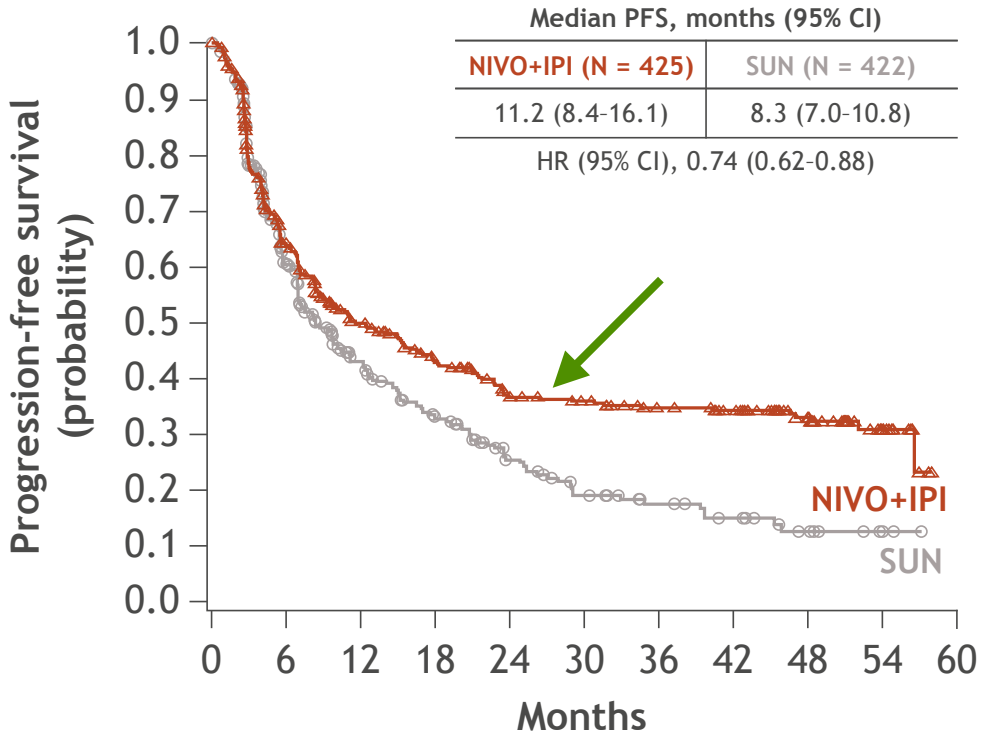

Stenner et al ESMO 2020: 716P

# IPI-NIVO - not a one-size-fits-all approach

## favorable risk




## intermediate/poor risk





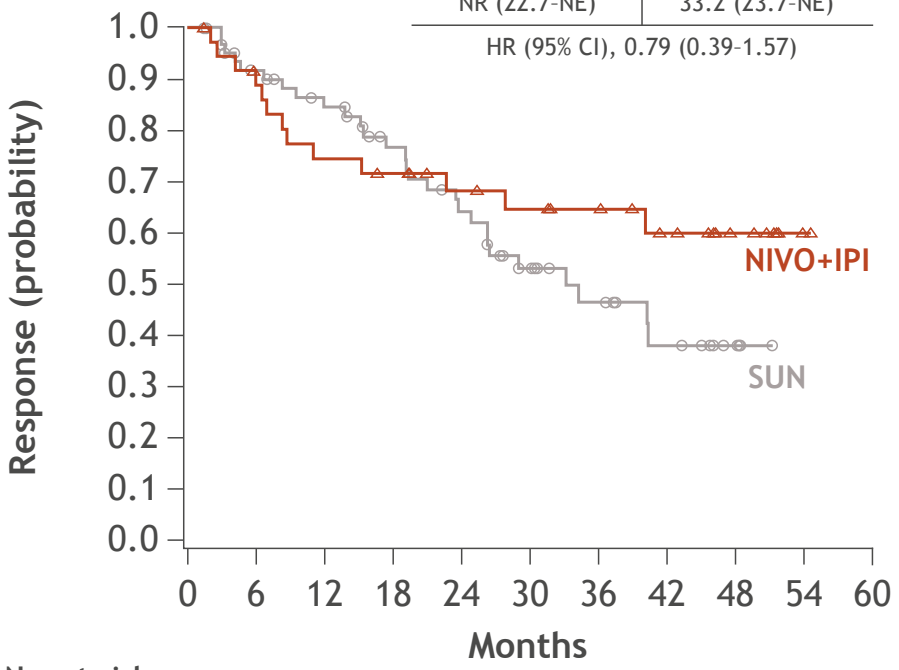

Albiges et al. ESMO 2020: 711P

# Durability of CPI-induced responses is steady

**favorable risk**

| Median DOR, months (95% CI) | |
|---|---|
| NIVO+IPI (N = 37) | SUN (N = 64) |
| NR (22.7-NE) | 33.2 (23.7-NE) |

HR (95% CI), 0.79 (0.39-1.57)



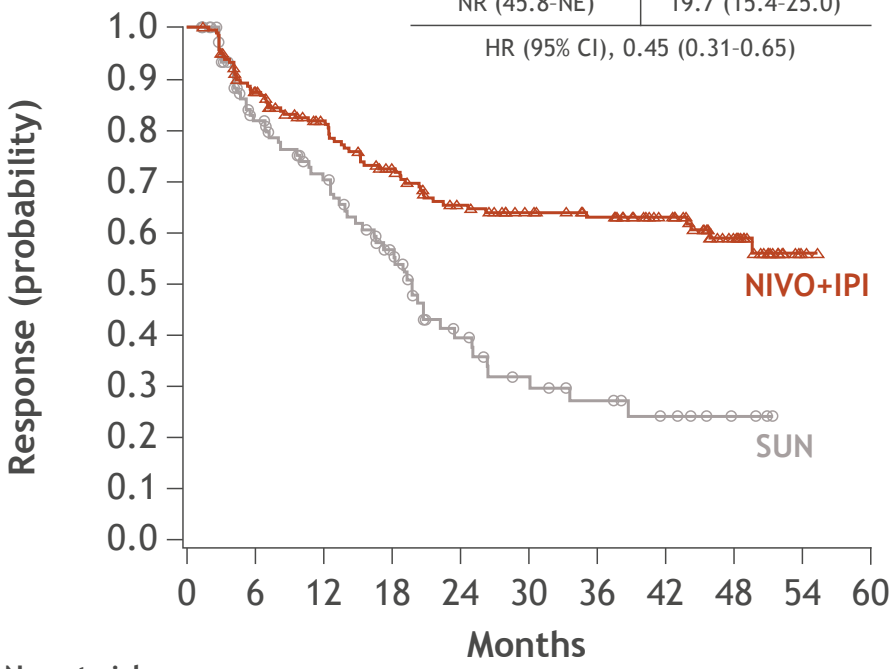

No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+IPI | 37 | 31 | 26 | 24 | 20 | 18 | 16 | 12 | 7 | 1 | 0 |
| SUN | 64 | 53 | 46 | 37 | 30 | 21 | 14 | 9 | 4 | 0 | 0 |

**intermediate/poor risk**

| Median DOR, months (95% CI) | |
|---|---|
| NIVO+IPI (N = 178) | SUN (N = 113) |
| NR (45.8-NE) | 19.7 (15.4-25.0) |

HR (95% CI), 0.45 (0.31-0.65)



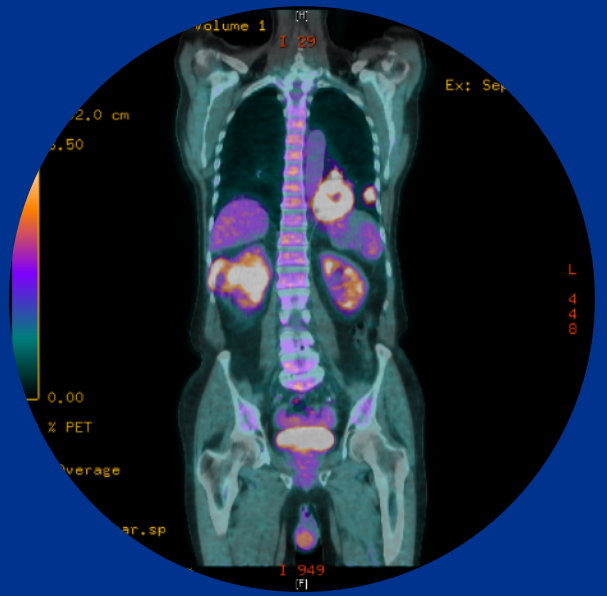

No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+IPI | 178 | 145 | 123 | 104 | 88 | 78 | 71 | 57 | 31 | 2 | 0 |
| SUN | 113 | 75 | 59 | 40 | 22 | 15 | 11 | 7 | 3 | 0 | 0 |



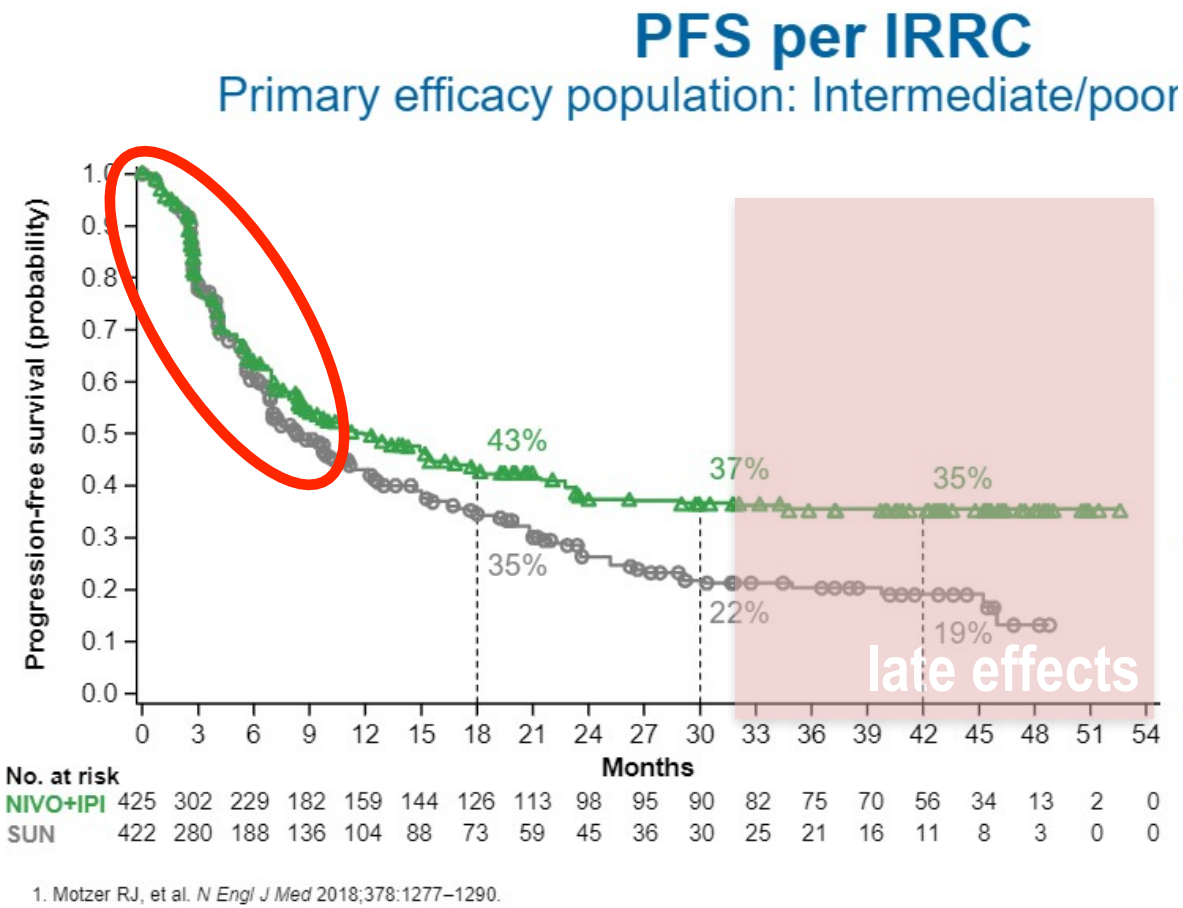
Albiges et al. ESMO 2020: 711P

# Can we do any better by combining TKI-CPI?




*Bildnachweis: istockphoto*

# Ipilimumab + Nivolumab (CM214, 42 mo FU): late separation of the curves with long-term effects



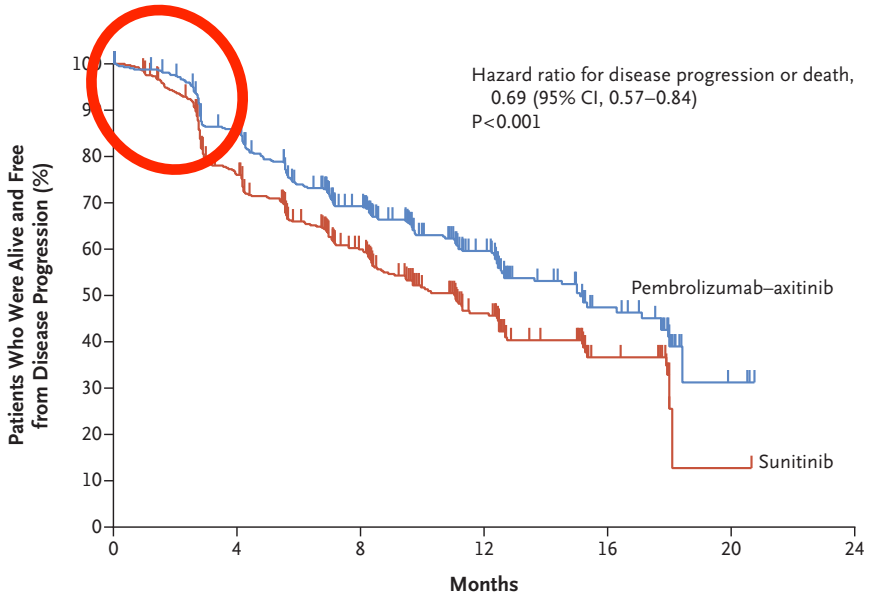

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277–1290.



*Motzer, R. et al.*(2020). Journal for ImmunoTherapy of Cancer 8(2), e000891. https://dx.doi.org/10.1136/jitc-2020-000891

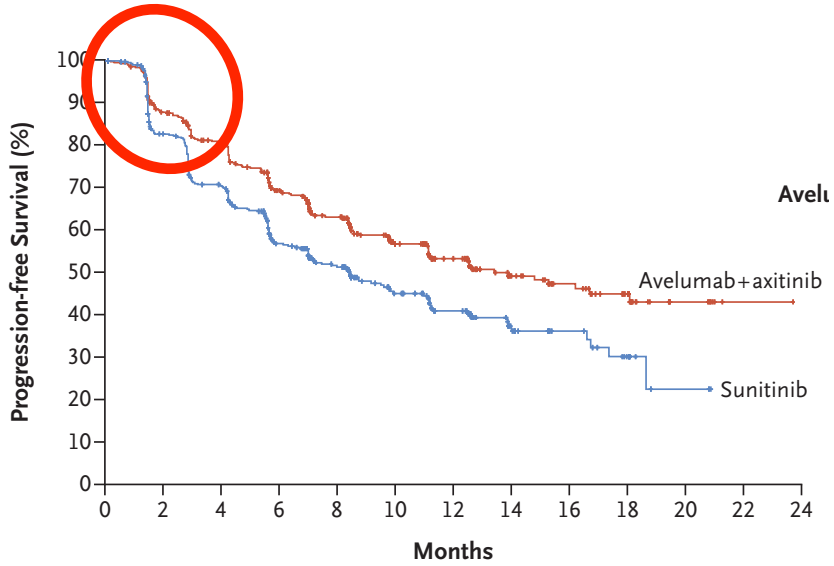
# Axitinib-based CPI-combinations impact early on PFS

**KN426**
**med. FU: 12,8 Mo. (ITT)**




Rini, B. I. *et al. N Engl J Med* NEJMoa1816714–12 (2019).

**JAVELIN101**
**med. FU 11,6 Mo. (ITT)**




Motzer et al. N Engl J Med NEJMoa1816047 (2019).
doi:10.1056/NEJMoa1816047

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**KN426**
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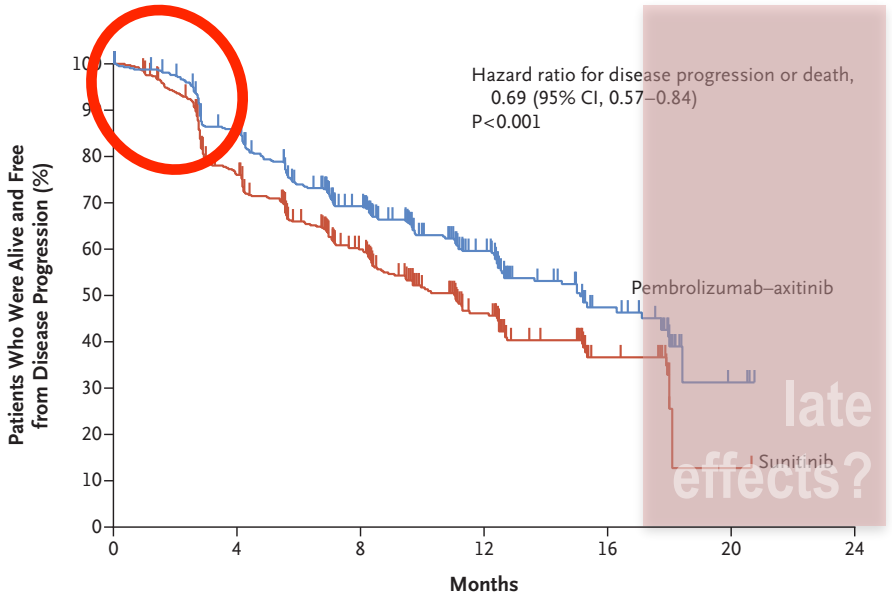


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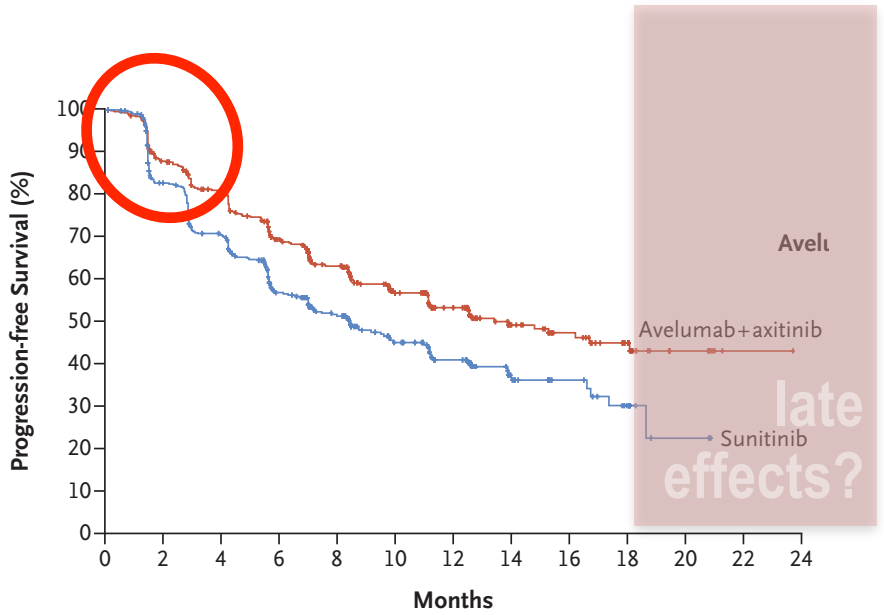
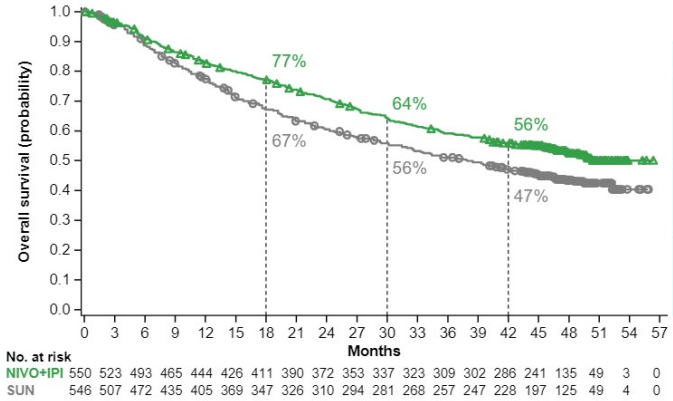
**JAVELIN101**
**med. FU 11,6 Mo. (ITT)**




Motzer et al. N Engl J Med NEJMoa1816047 (2019).
doi:10.1056/NEJMoa1816047

# OS for current standard 1st line combinations

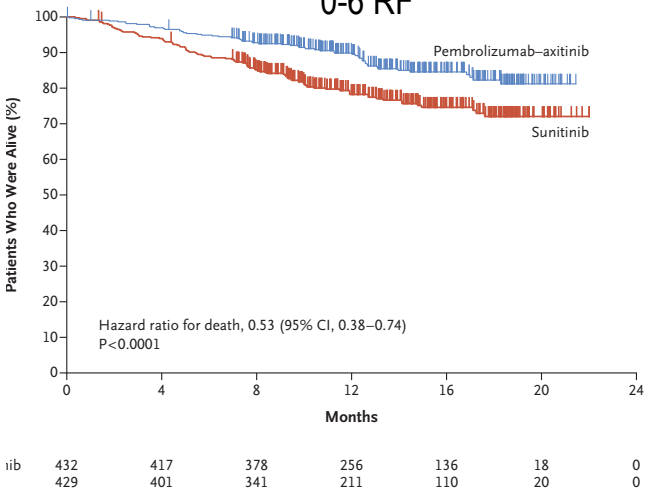
## CM214
0-6 RF




| Minimum follow-up | OS | NIVO+IPI N = 550 | SUN N = 546 |
|---|---|---|---|
| 17.5 mo[1] | Median, mo (95% CI) | NR (NE) | 32.9 (NE) |
| | HR (99.8% CI) | 0.68 (0.49–0.95) P < 0.001 | |
| 30 mo[2] | Median, mo (95% CI) | NR (NE) | 37.9 (32.2–NE) |
| | HR (95% CI) | 0.71 (0.59–0.86) P = 0.0003 | |
| 42 mo | Median, mo (95% CI) | NR (46.3–NE) | 38.4 (32.0–44.7) |
| | HR (95% CI) | 0.72 (0.61–0.86) P = 0.0002 | |

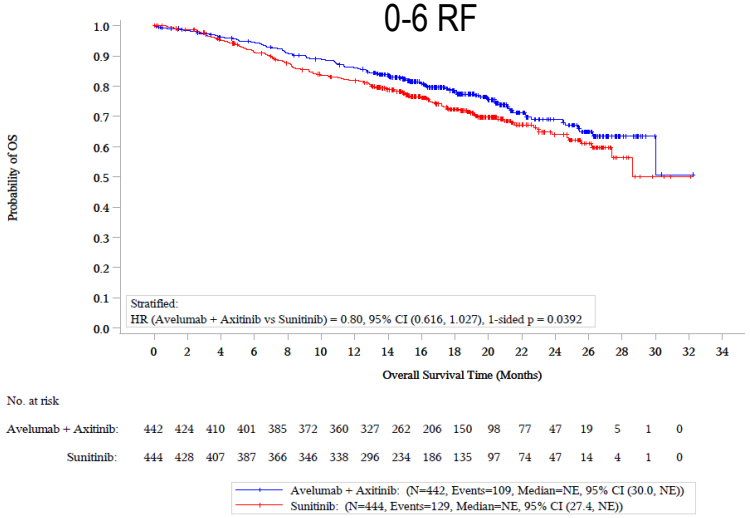
Tannir et al . ASCO GU 2020: 609

## KN426
0-6 RF




Rini, B. I. *et al. N Engl J Med* NEJMoa1816714–12 (2019).

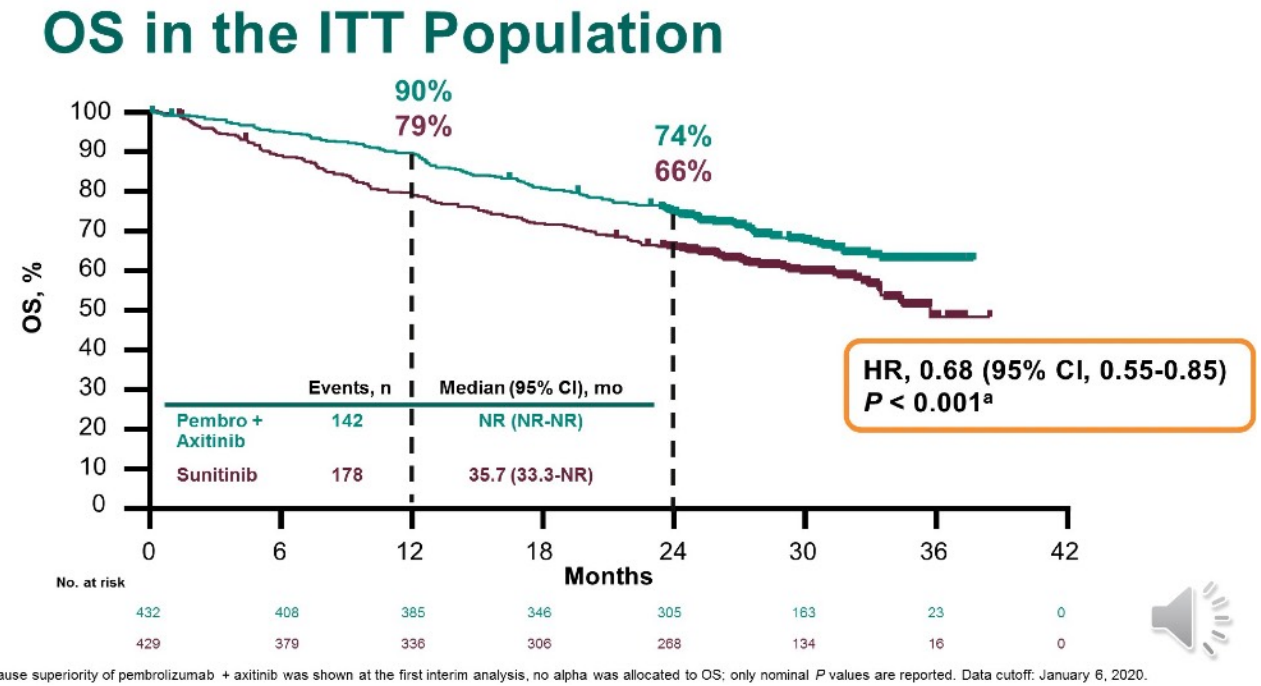
## JAVELIN101
0-6 RF




EPAR Avelumab SEP 2019

| | CM214 | KN426 | JAVELIN101 RCC |
|---|---|---|---|
| FU (mo.) | 42 | 12,8 | 19 |
| CR (%) | 11 | 5,8 | 3,4 |
| ORR (%) | 42 | 59,3 | 51,4 |

# KN426: longer FU (≧ 23 Mo.) has impact on outcome parameter

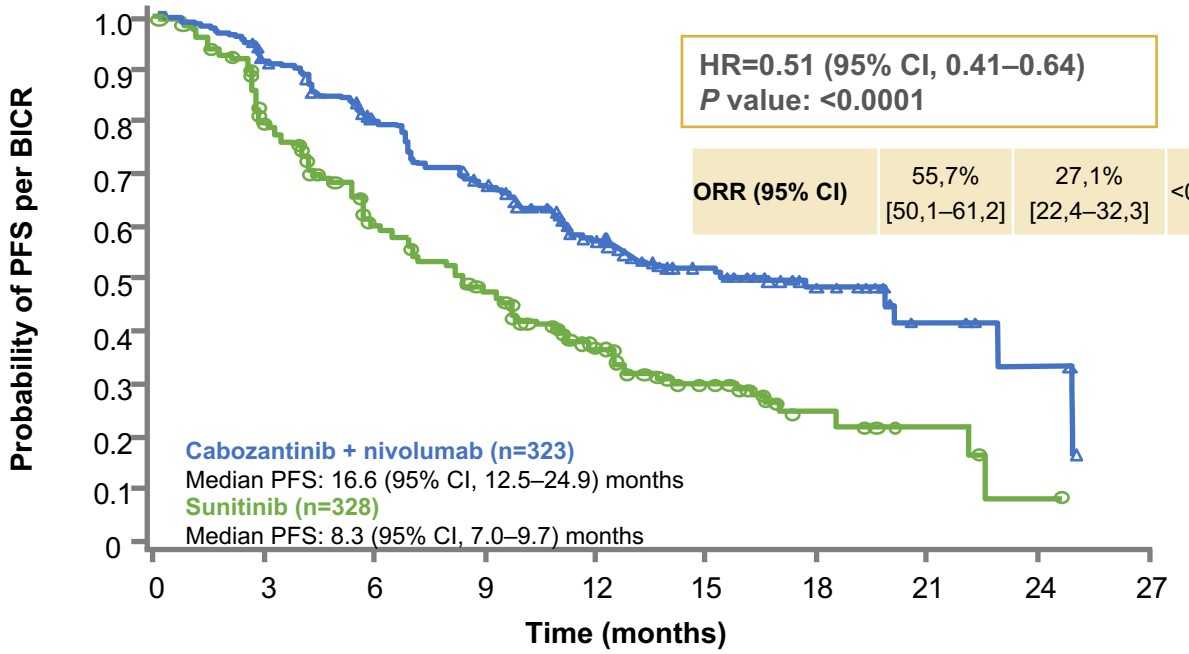


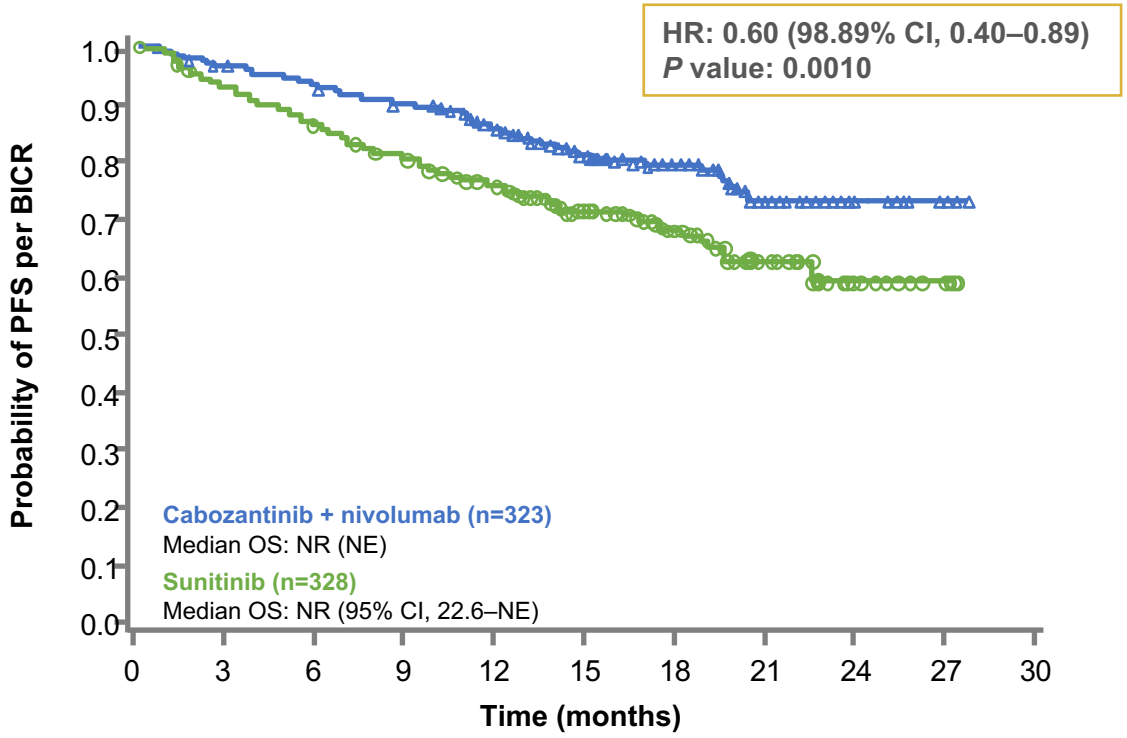

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

| | Pembro + Axitinib n = 432 | Sunitinib n = 429 |
|---|---|---|
| Best response, n (%) | | |
| CR | 38 (8.8) | 13 (3.0) |
| PR | 222 (51.4) | 158 (36.8) |
| SD | 100 (23.1) | 150 (35.0) |
| PD | 49 (11.3) | 74 (17.2) |
| NE[b] | 16 (3.7) | 28 (6.5) |
| NA[c] | 7 (1.6) | 6 (1.4) |
| Duration of response, median (range), mo | 23.5 (1.4+ to 34.5+) | 15.9 (2.3 to 31.8+) |

5001 Plimack et al. ASCO 2020

# Cabozantinib + Nivolumab (CM9ER) - a future option in 1st line




- Choueiri TK, et al. ESMO 2020; oral presentation (#696O).

Eisai U.S.

**to be presented at ASCO GU Symposium 2021**



# KEYTRUDA® (PEMBROLIZUMAB) PLUS LENVIMA® (LENVATINIB) DEMONSTRATED STATISTICALLY SIGNIFICANT IMPROVEMENT IN PROGRESSION-FREE SURVIVAL (PFS), OVERALL SURVIVAL (OS) AND OBJECTIVE RESPONSE RATE (ORR) VERSUS SUNITINIB AS FIRST-LINE TREATMENT FOR PATIENTS WITH ADVANCED RENAL CELL CARCINOMA

## LENVIMA Plus Everolimus Also Showed Statistically Significant Improvement in PFS and ORR Endpoints Versus Sunitinib

## Results of Investigational Phase 3 KEYNOTE-581/CLEAR Trial (Study 307) to be Presented at Upcoming Medical Meeting

# Efficacy parameter of TKI-CPI combinations

| | COSMIC-021 CABO 40 mg + ATEZO (N=34) | COSMIC-021 CABO 60mg + ATEZO (N=36) | 9-ER CABO 40mg + NIVO (N=323) | KEYNOTE426 AXITINIB + PEMBRO (n=432) | JAVELIN AXITINIB + AVELUM (n=442) | LENVATINIB + PEMBRO (n=104) | TINIVO TIVOZANIB + NIVO (n=25) |
|---|---|---|---|---|---|---|---|
| **Median Follow up , mo** | 25.8 | 15.3 | 18.1 | 12.8 | 11.6 | - | 19.0 |
| **ORR - BICR**<br>**ORR - Investigator** | -<br>53 | -<br>58 | 55.7<br>59.4 | 59.3 | 51.4 | 52 (pretreated population) | 56% |
| **Progressive disease, n(%) - BICR** | 2 (6%) | 2 (6%) | 5.6% | 11% | 11.5% | 6% | 4% |
| **Disease control rate, % - BICR** | 94% | 92% | 88% | 83.3% | 81% | 93% | 96% |
| **PFS, Median (95% CI), months** | 19.5 (11.0–NR) | 15.1 (8.2–22.3) | 16.6 (12.5–24.9) | 15.4 (12.7-18.9) | 13.8 | 11.3 | 18.9 |
| **OS, Median(95% CI), months** | - | - | NR (HR 0.6) | NR (HR 0.53) | NR ( HR | NR | NE |

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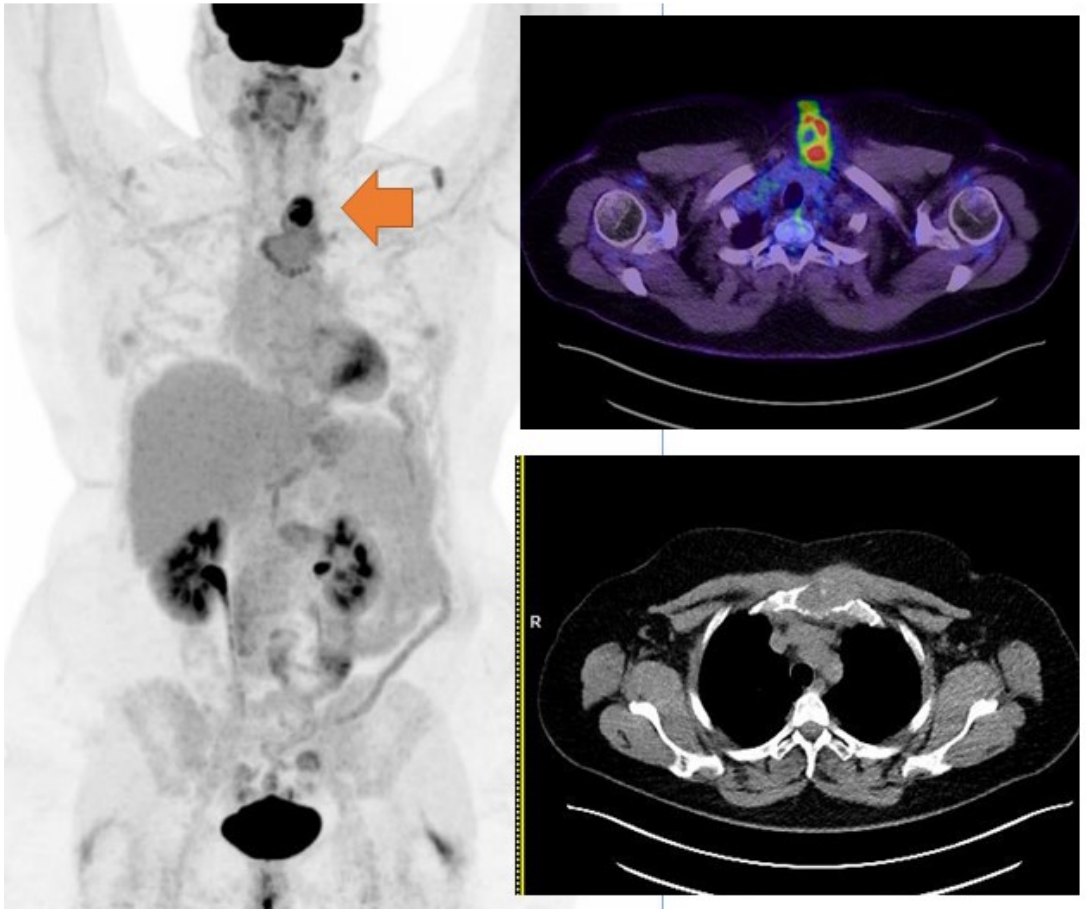
Choueiri et al. ESMO 2020 presidential session; Rini et al. NEJM 2019; Motzer et al. 2019; Lee et al. ASCO 2020. Albiges et al. *in press* 2020
modified from Albiges ESMO 2020

# 47-year-old pts. with oligometastatic mRCC on axitinib + pembrolizumab

## IMDC risk: intermediate

**Baseline, symptomatic**



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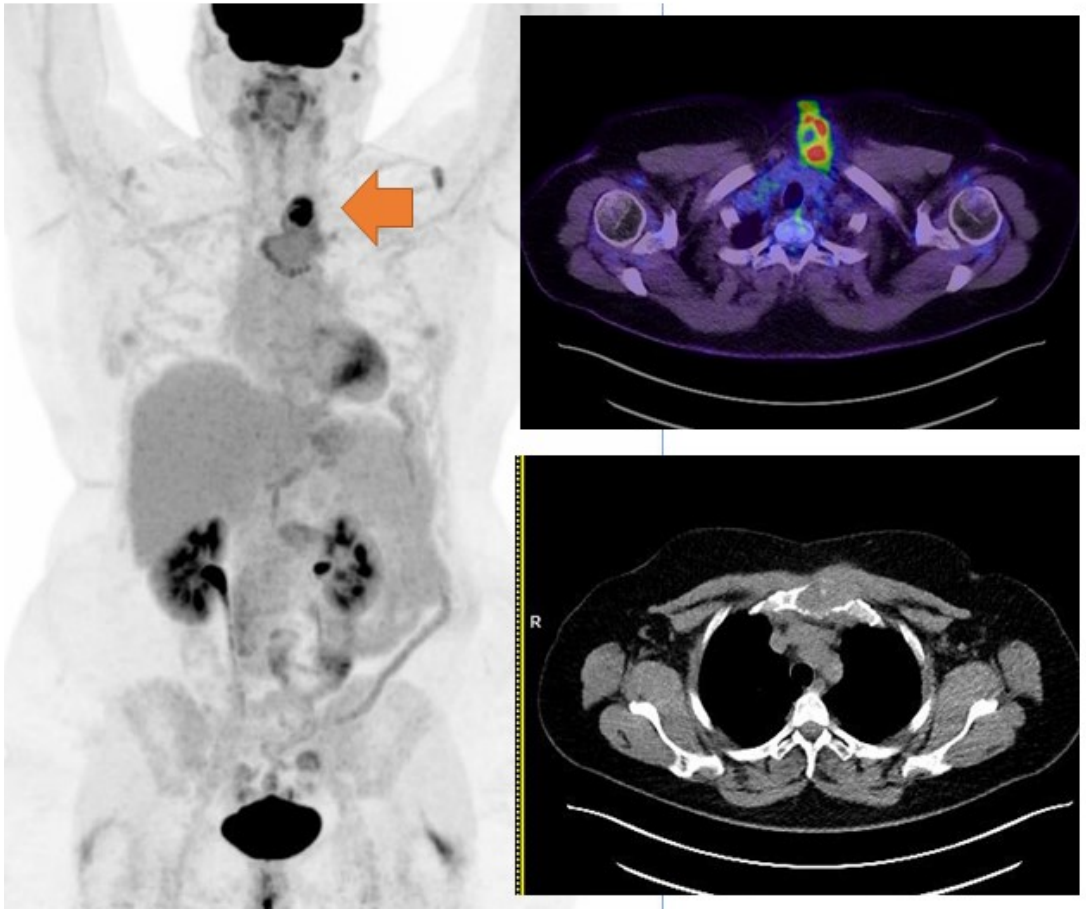
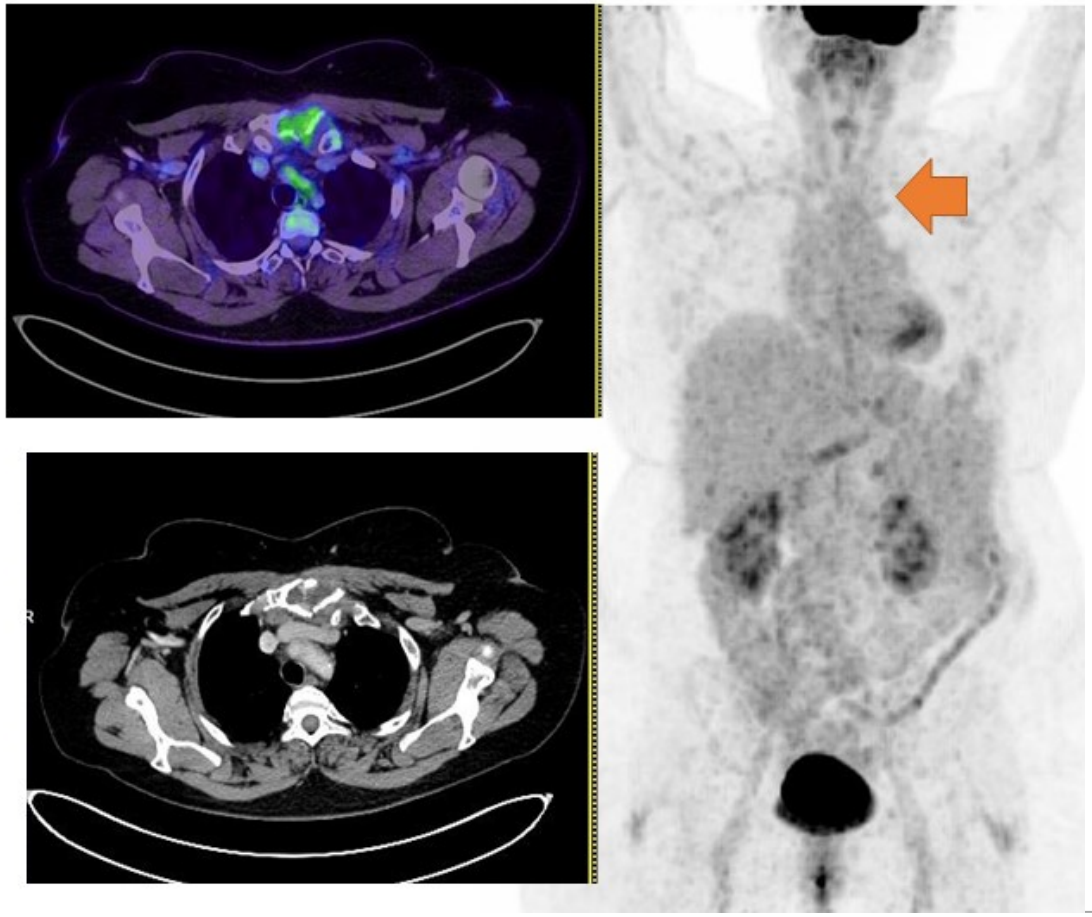
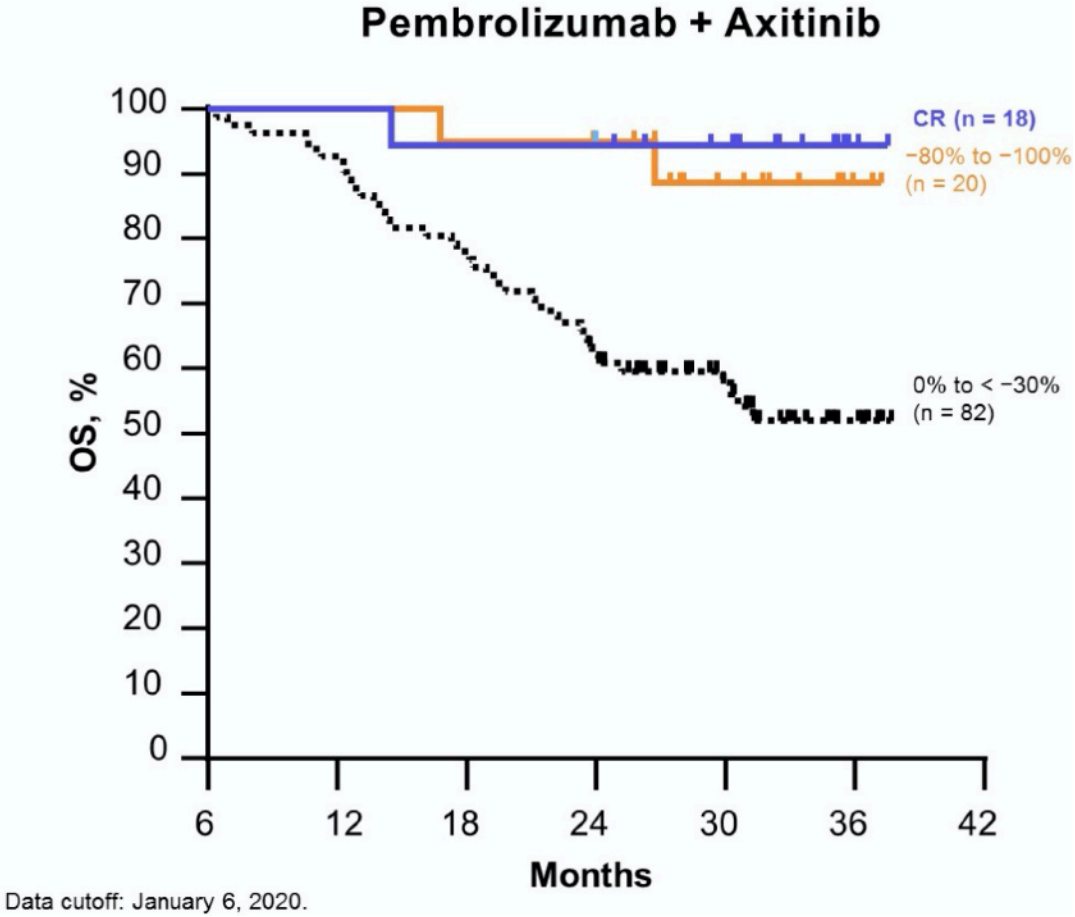
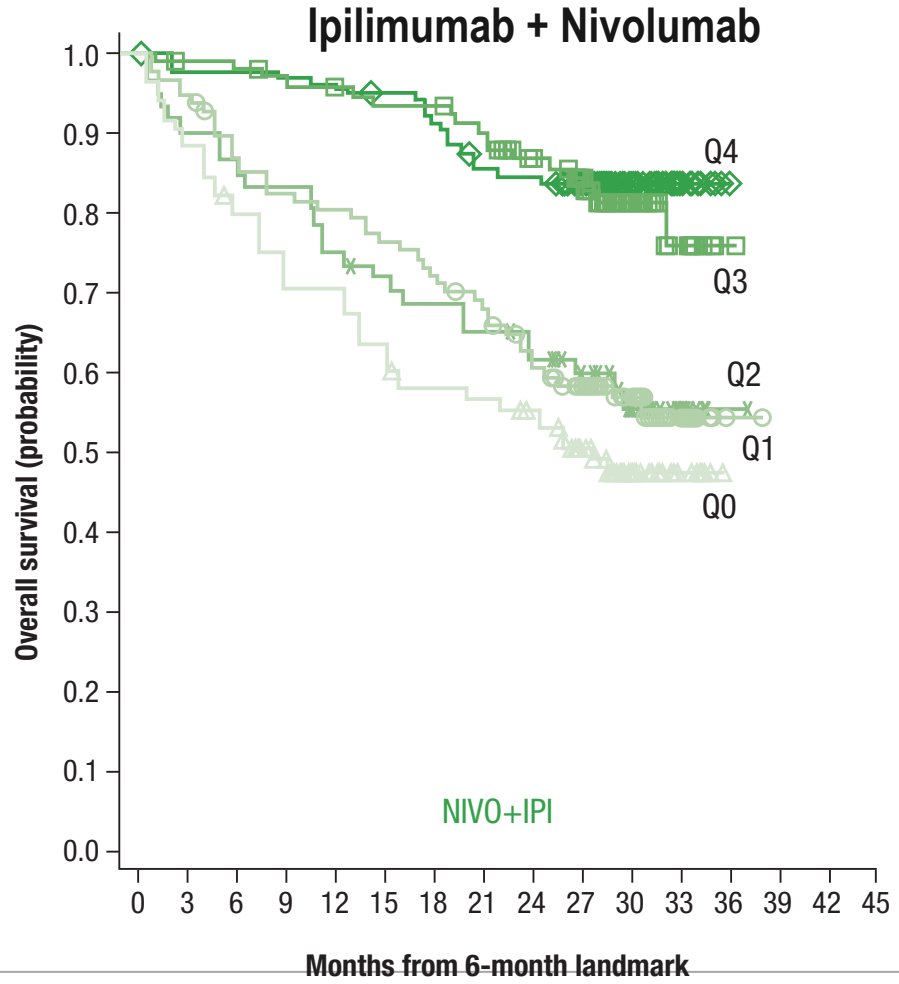


**6 mo. later, very good PR**



# Depth of response informs on prognosis in mRCC






5001 Plimack et al. ASCO 2020

Grünwald ESMO 2019 :2368P

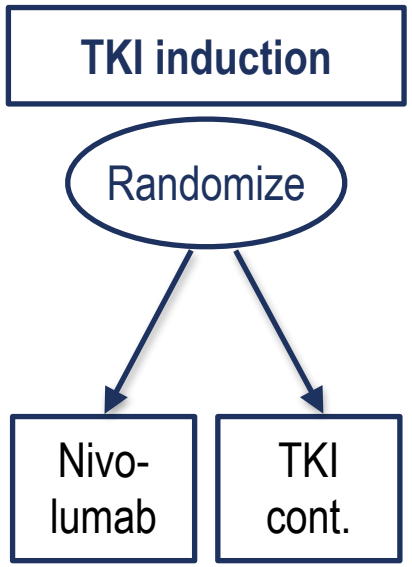
# Resection of metastasis

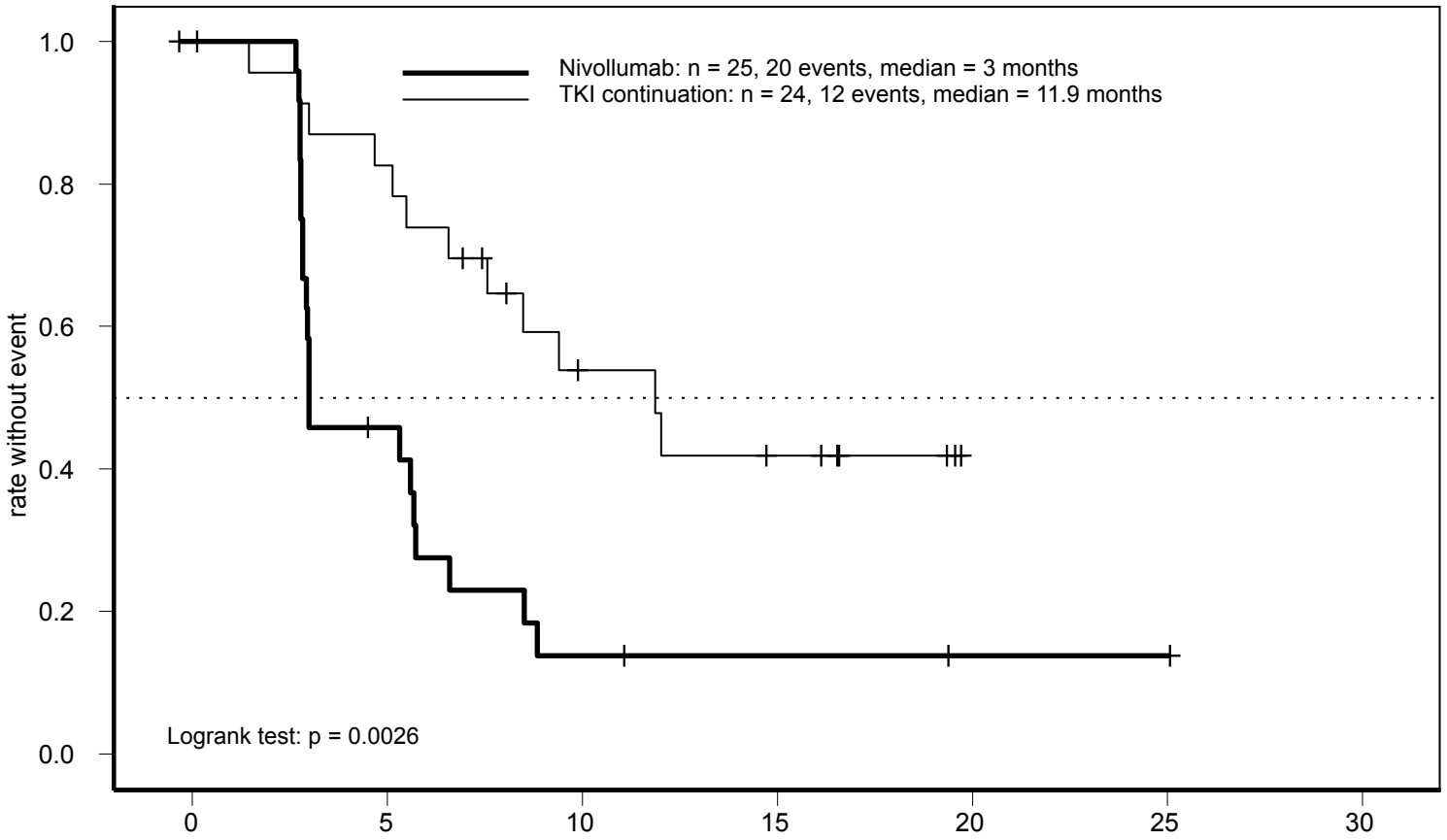
**R0-resection**
**20 % vital cells**

→

1. Stop therapy
2. Continue both agents
3. Continue one agent

# Switch-Maintenance - not an option in mRCC



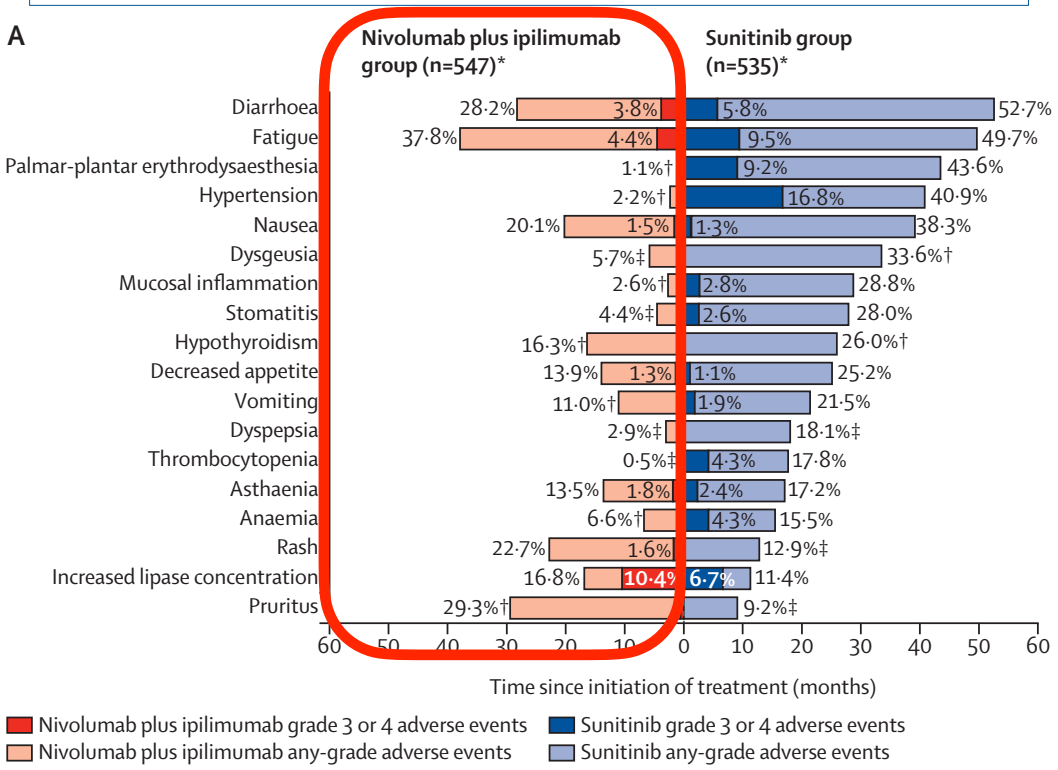




Grünwald et al. ESMO 2019: 959P

# Tolerability

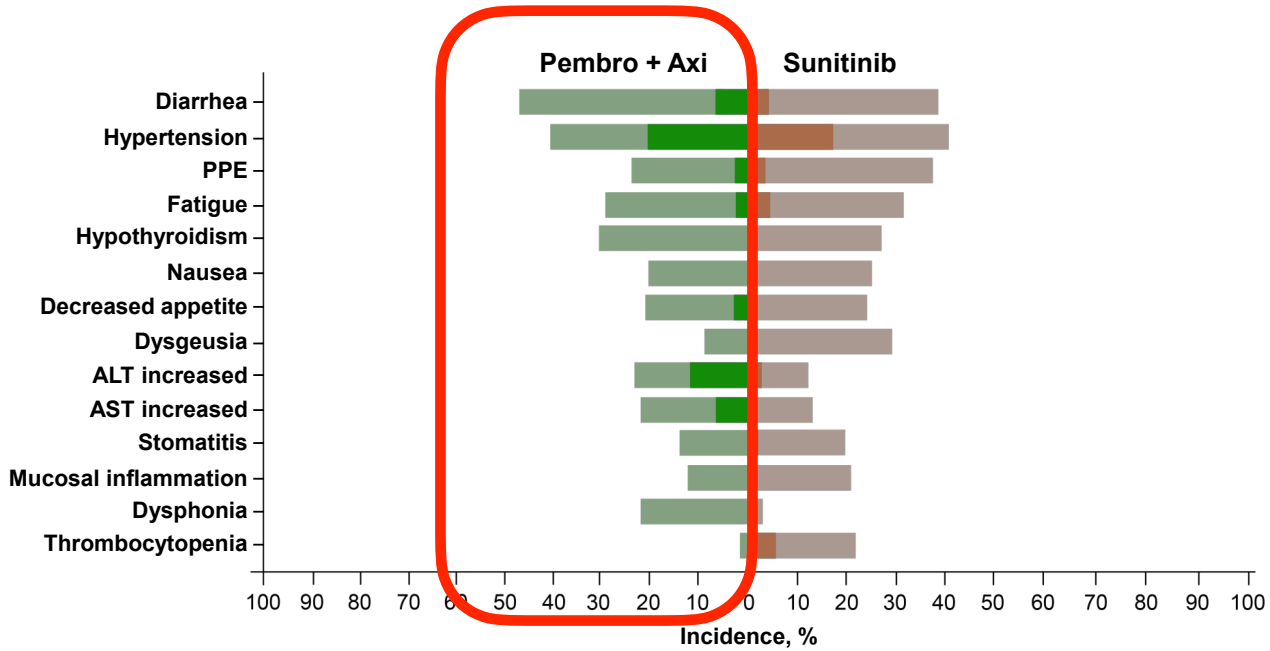
# TKI toxicity dominates the AE profile of axitinib-combination

**Grade 3-4 TRAE:**
46,6% 63,9%



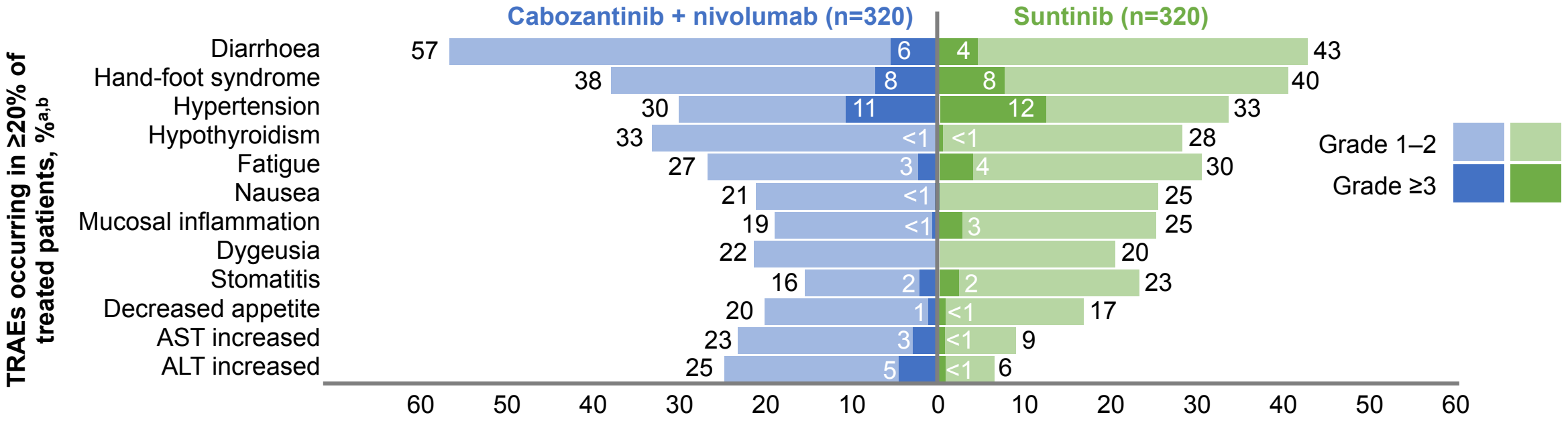

Motzer, R. J. *et al. Lancet Oncol* (2019). doi:10.1016/S1470-2045(19)30413-9

**Grade 3-4 TRAE:**
63% 58%




Powles T et al., J Clin Oncol 37, 2019 (suppl 7S; abstr 543) – ASCO GU 2019

# Similar pattern for Cabo-Nivo combination



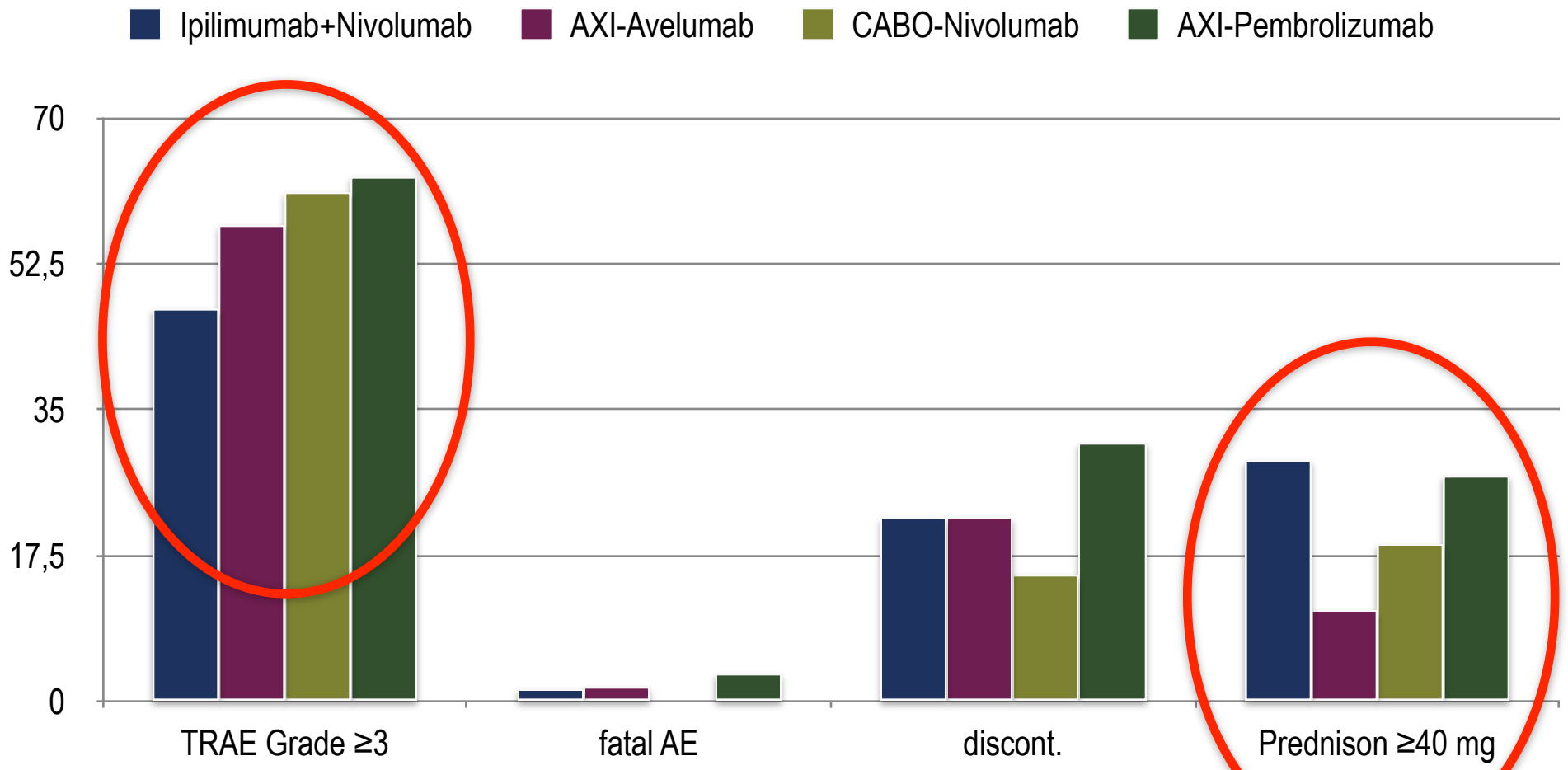

| Events, % | Cabozantinib + nivolumab (n=320) | | Sunitinib (n=320) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| All cause AEs | 100 | 75 | 99 | 71 |
| Treatment-related AEs | 97 | 61 | 93 | 51 |

The observed safety profiles of cabozantinib plus nivolumab, and of sunitinib, were as expected on the basis of the known profiles of these three drugs

[a]Total bar represents treatment-related AEs of any grade ≥20% in either treatment arm; of these events, none were Grade 5. [b]Grade ≥3 treatment-related AEs were reported in ≤3.0% unless otherwise indicated. [c]Included events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. One death was considered by investigators to be treatment related with cabozantinib + nivolumab (small intestine perforation), and 2 deaths were considered treatment-related with sunitinib (pneumonia and respiratory distress).

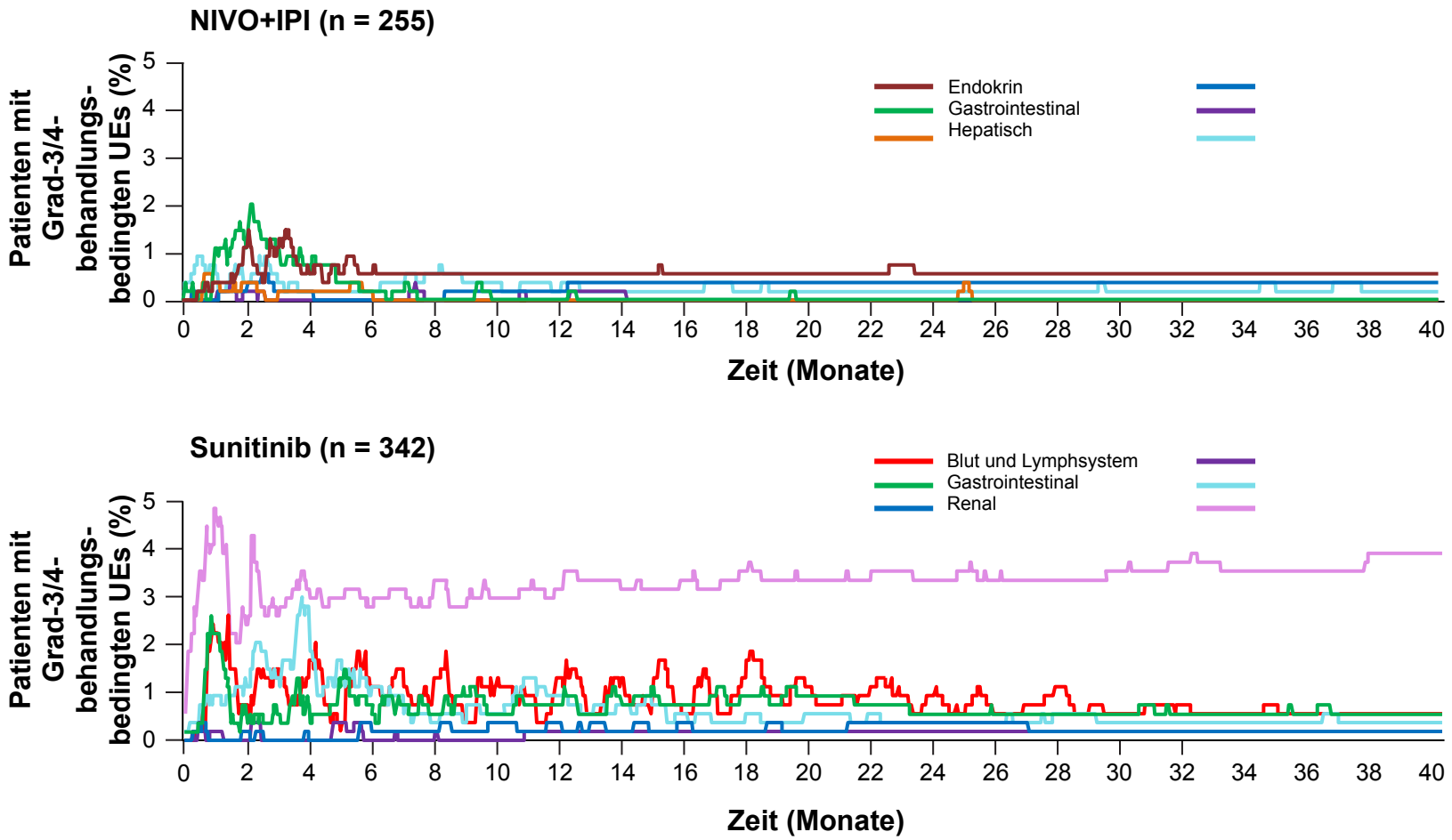
Choueiri TK, et al. ESMO 2020; oral presentation (#696O).

# Adverse Events of current 1st line options




Motzer et al. Lancer Oncol 2019 http://dx.doi.org/10.1016/S1470-2045(19)30413-9. Motzer et al. N Engl J Med NEJMoa1816047 (2019). doi:10.1056/NEJMoa1816047. Rini, B. I. *et al. N Engl J Med* NEJMoa1816714–12 (2019).

# TKI is a driver of chronic toxicity

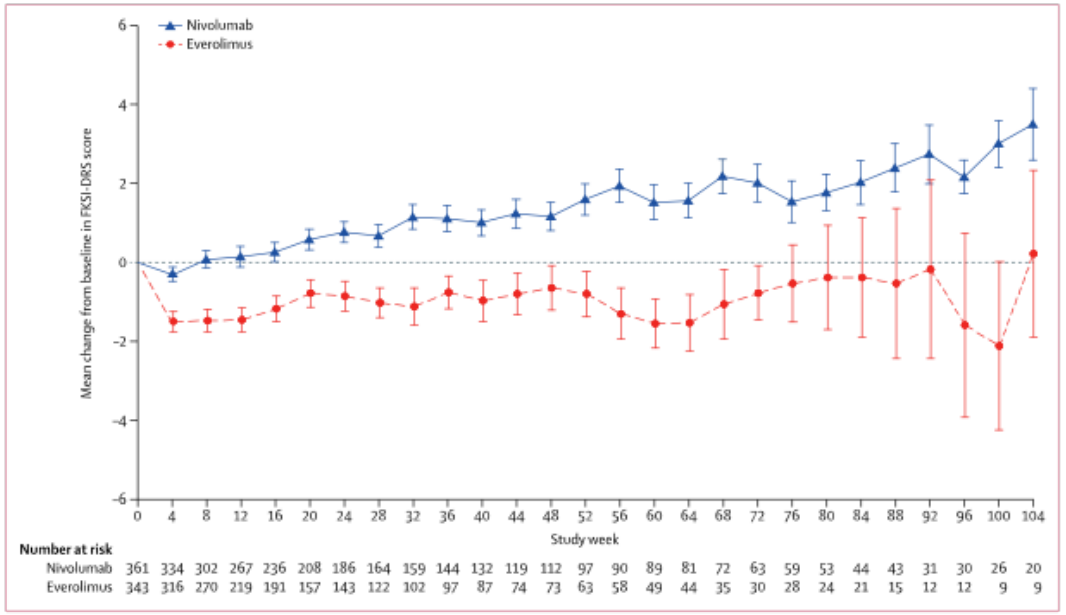



* selected AEs in all treated patients shown

Tannir NM et al. Genitourinary Cancers Symposium San Francisco, 2019; Poster Presentation #547

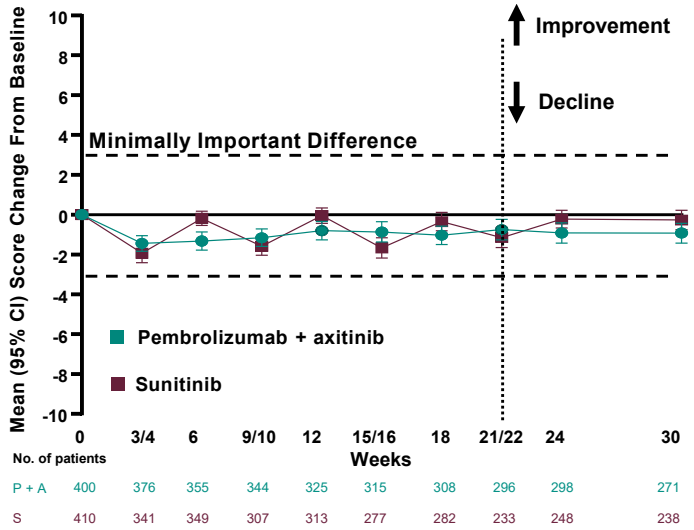
# Impact on HR-QoL varies among combinations

## Nivolumab + Ipilimumab



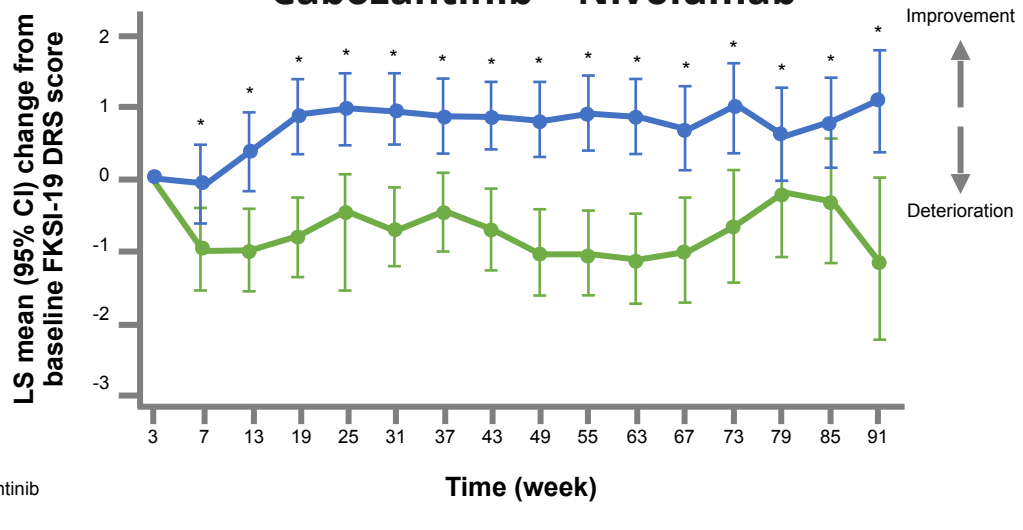

Cella, D., Grünwald, V., Nathan, P., Doan, J., Dastani, H., Taylor, F., et al. (2016). Lancet Oncology, 17(7), 994–1003. http://doi.org/10.1016/S1470-2045(16)30125-5

## Axitinib + Pembrolizumab




*Bedke et al. EAU* 2020

## Cabozantinib + Nivolumab




Choueiri TK, et al. ESMO 2020; oral presentation (#696O); 2. Rao D, et al. J Pain Symptom Manage 2009;38:291–298.

# Pharmacological background for 1st line components

| Avelumab | Ipilimumab | Nivolumab | Pembrolizumab | Axitinib | Cabozantinib |
|---|---|---|---|---|---|
| Half-life: 6 days | Half-life: 15 days | Half-life: 25 days | Half-life: 22 days | Half-life: 3-6h | Half-life: 110h |
| 5x $t_{1/2}$: 1.0 mo. | 5x $t_{1/2}$: 2.5 mo. | 5x $t_{1/2}$: 4.1 mo. | 5x $t_{1/2}$: 3.6 mo. | 5x $t_{1/2}$: approx. 1 day | 5x $t_{1/2}$: approx. 23 days |

PK information accessed at https://www.ema.europa.eu/ on 05.10.2020

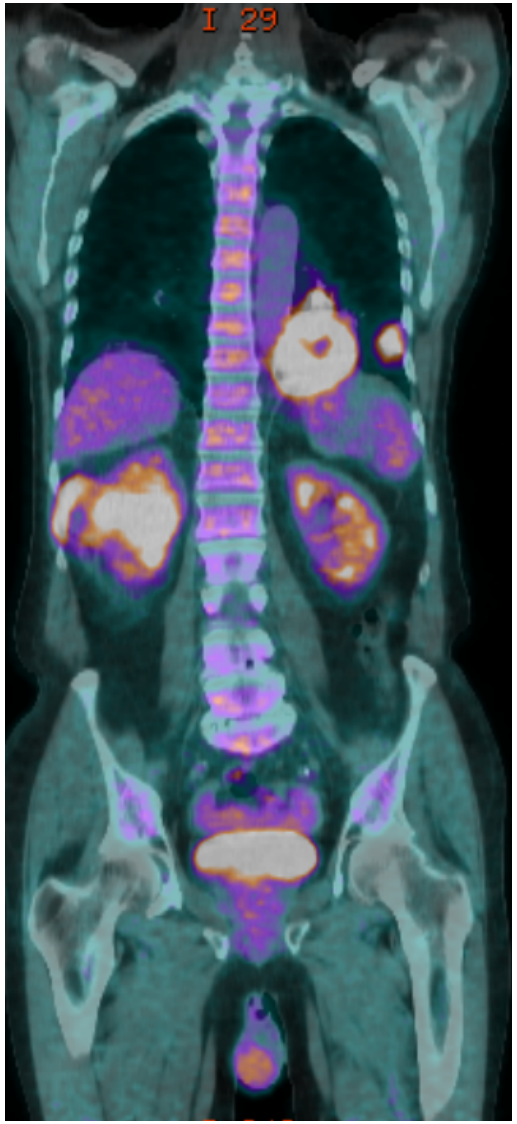
# 64-year old male patient

- Presents with renal mass and lung lesions
- Biopsy reveals: ccRCC, G2 in lung and renal lesions
- TNM: cT3b, cN0, cM1 (lung)
- Stage: IV

***medical history:***

restrictive pulmonary disease (FVC 50%)

replicative chronic Hepatitis B



# Hepatic toxicities of combinations vary

**AXI-AVELU:**
ir-Hepatitis:
alle Grade 6,3%
Grad ≧3: 4,3%
EPAR Avelumab (https://www.ema.europa.eu)

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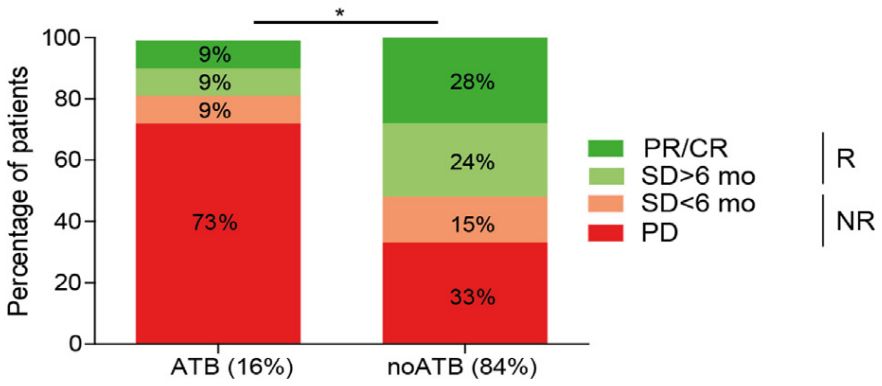
**Therapy choice: Axitinib + Avelumab**

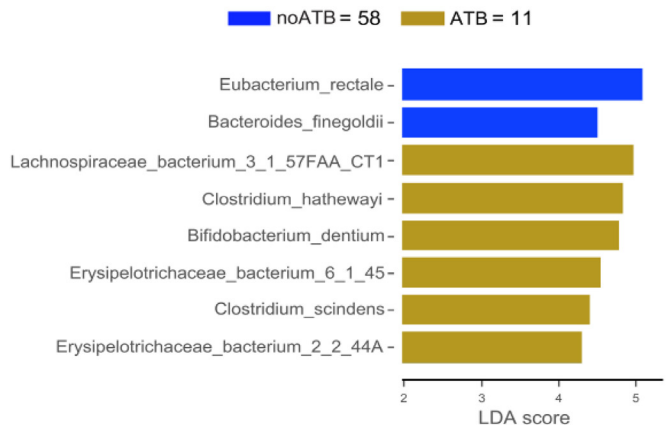
**monthly HBV PCR monitoring**

# Antibiotics and TKIs alter the microbiom

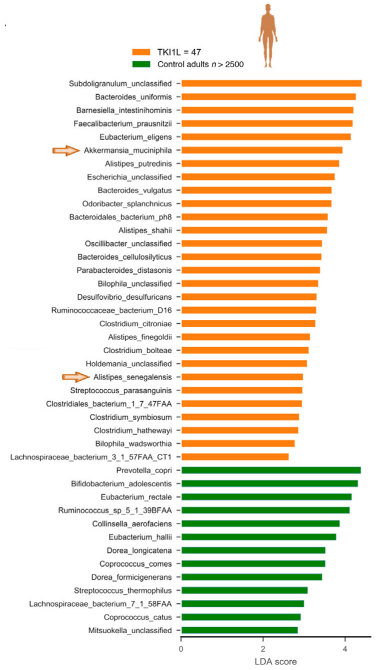
9% ORR bei Pts. mit Antibiose




Diskriminierende Bakterien




TKI Vorbehandlung verändert das Mikrobiom




*Derosa, L. et al.* (2020). **Gut Bacteria Composition Drives Primary Resistance to Cancer Immunotherapy in Renal Cell Carcinoma Patients** European Urology 78(2), 195-206. https://dx.doi.org/10.1016/j.eururo.2020.04.044

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- Use each combination in the indication, where it offers the best benefit