VIGO NORTE INTERNATIONAL GU DEBATES

First line mRCC: IO-IO vs IO-TKI: Is the eternal debate over?

Limpias; October 2026

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Royal Marsden, London.



COI Disclosures

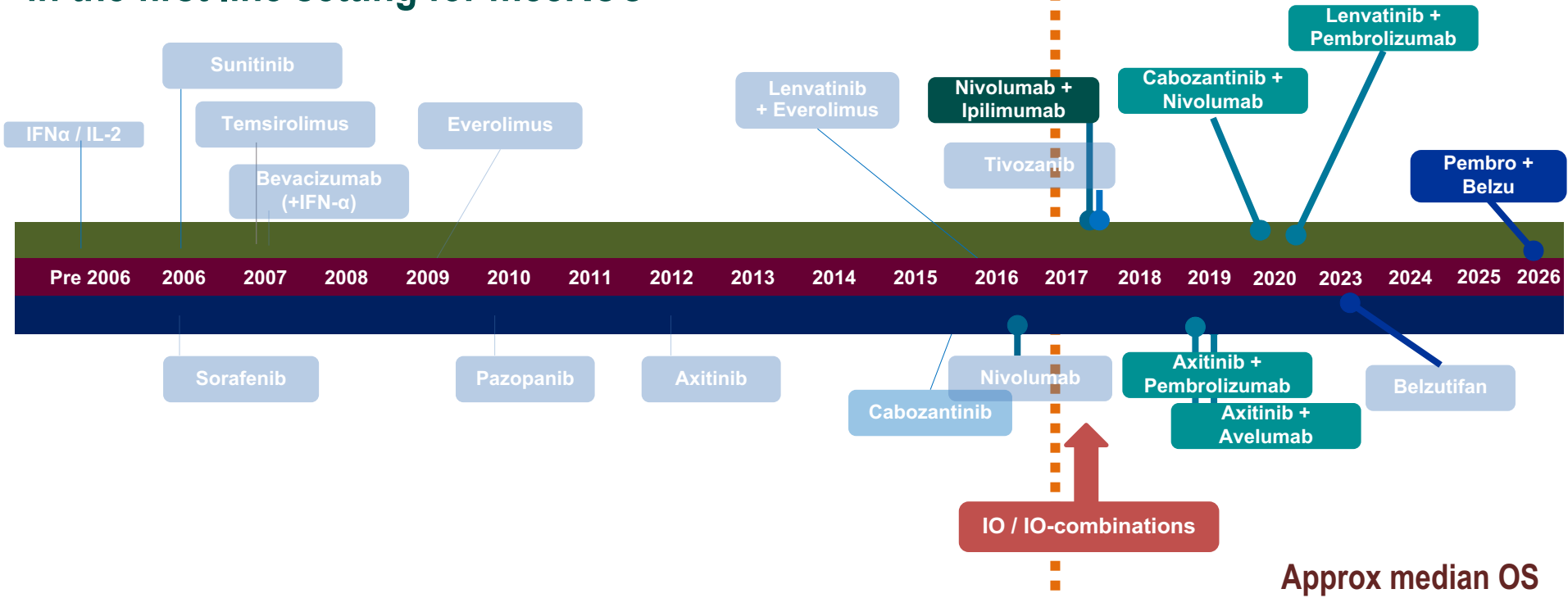
Nature of Relationship	Name of commercial interest
Advisory Bureau	Eisai, Ipsen, MSD,
Speaker fees	BMS, Eisai, Ipsen, MSD

And I have taken part in a debate on this topic three times (that I remember)

Why might we be having this debate?

Look on this side of the dotted line

Since 2017 IO-based combinations have become standard of care for most patients in the first line setting for mccRCC

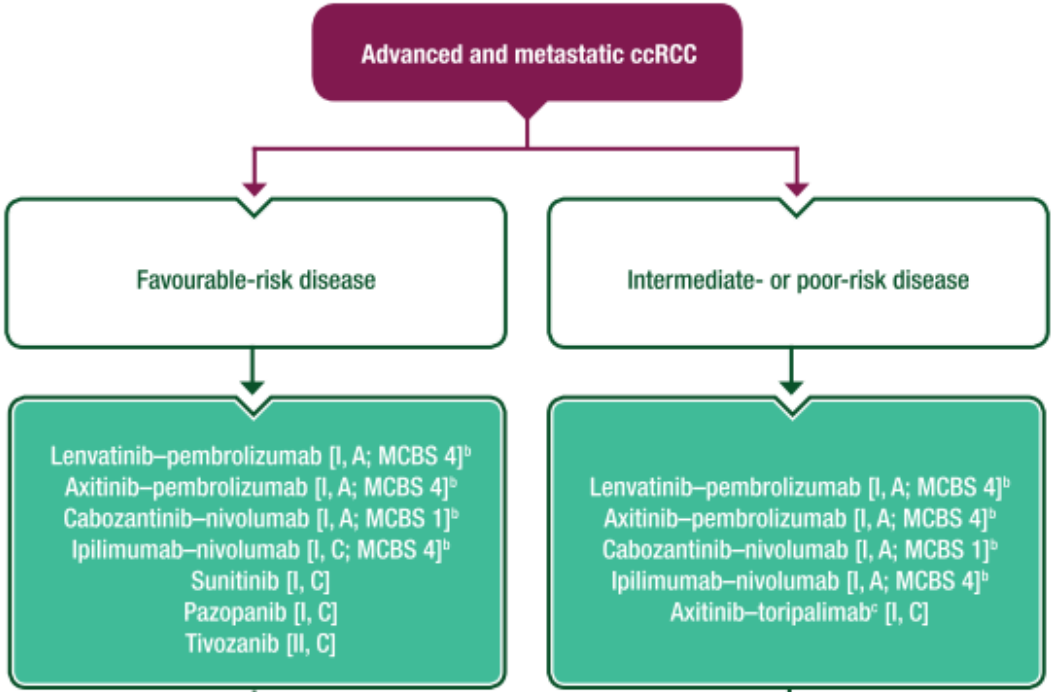


Approx median OS

12-15 months	24 months	36 months	45-55 months

ESMO guidelines

First line treatment of advanced clear cell renal cell carcinoma



i.e. there are options, which is good, but means a choice has to be made.

How to select?
Does it matter?
Guidelines alone don't answer this.

Let's quickly consider who we are not talking about today

- **Checkpoint inhibitors are contra-indicated**
  - Absolute contra-indication is rare but 'relative' contra-indication may be relevant
- **VEGF-directed therapies are contra-indicated**
  - Less common but may happen
- **Patient is of borderline PS and together you have decided against combination**
- **Any other reason you have decided against combination therapy**
- **Not currently to have systemic therapy (metastasis-directed therapy / surveillance)**

I am focussing on patients who are expected to receive IO-based combination therapy

For situations in which you have access to an IOIO and IOTKI option

For these patients who are to have IO-based combination therapy, let's think about goals when selecting 1st line treatment in mRCC?

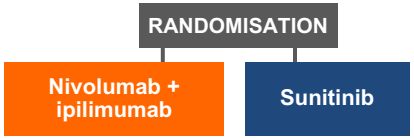
- Control or maximal shrinkage of cancer for as long as possible
- Extending life expectancy
- Limiting symptoms of cancer
- Whilst having the fewest side effects from treatment
- Therefore delivering the best quality of life for the longest time possible
- And achieving all of this for the majority of patients
- Without reliable predictive markers to select therapy at an individual level (yet)

We have plenty of data to consider: >5000 pts in 1st line RCTs
These are the key trials to help us examine the question

As well as JAVELIN Renal 101

IO-IO

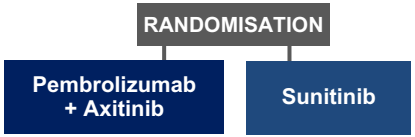
CHECKMATE 214
IO-IO
Phase III N=1070
Co-primary endpoints:
PFS, OS, ORR



Motzer et al. NEJM; 2018. Albiges; 2020

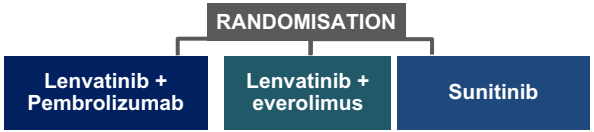
IO-TKI

KEYNOTE 426
IO-TKI
Phase III N=840
Co-primary endpoint: PFS, OS



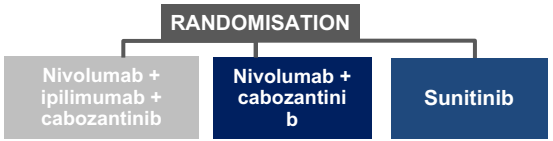
Rini et al. NEJM; 2019

CLEAR
IO-TKI
Phase III N=735
Primary endpoint: PFS



Motzer et al. NEJM; 2021

CHECKMATE 9ER
IO-TKI
Phase III N=1014
Primary endpoint: PFS



Choueiri et al. NEJM; 2021

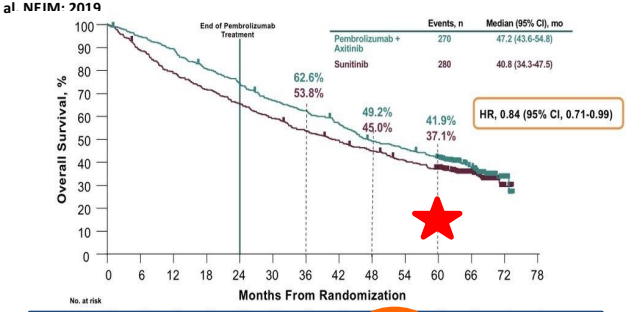
What do the data show us for the key efficacy endpoints?

1. www.clinicaltrials.gov (NCT02231749);
2. www.clinicaltrials.gov (NCT02853331);
3. www.clinicaltrials.gov (NCT02811861);
4. https://clinicaltrials.gov (NCT03141177)

These four combinations all also show significant Overall Survival benefit over sunitinib that is durable at 4 or 5+ years

KN 426. Axi + Pembro @ 5 years

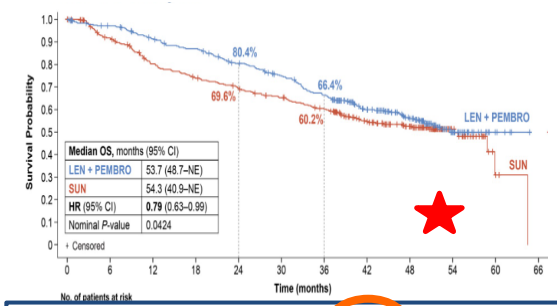
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HR for OS at 5 years: 0.84 (0.71-0.96)

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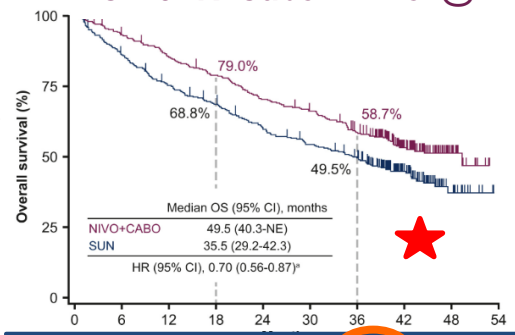
Motzer et al. ASCO; 2023



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CM 9ER. Cabo + Nivo. @ 44 mths

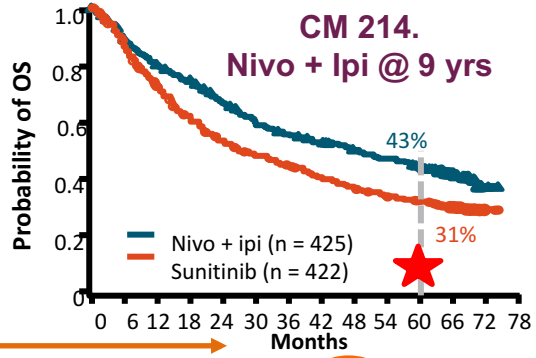
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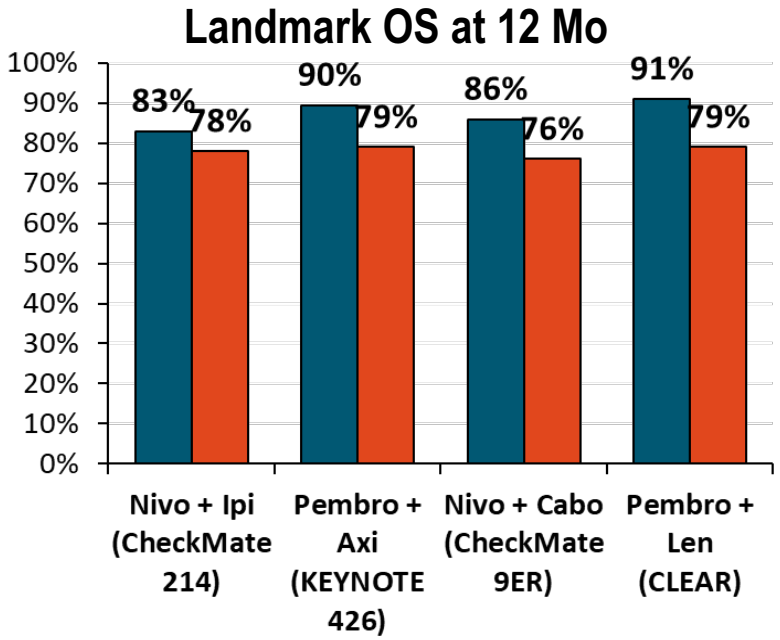
CM 214. Nivo + Ipi @ 9 yrs

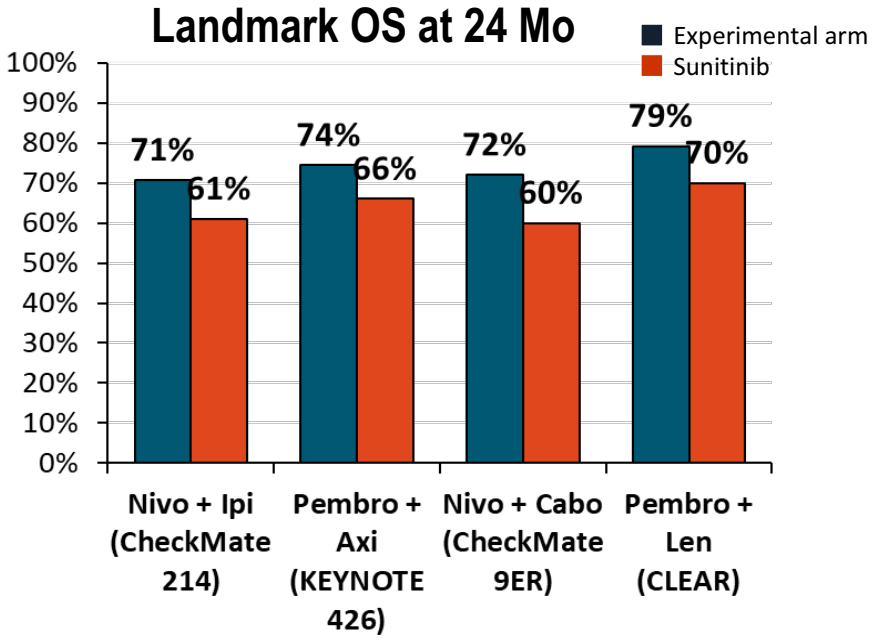
Motzer et al. NEJM; 2018. Albiges; 2020



HR for OS at 9 years: 0.71 (0.62-0.82)

Comparison of Landmark Overall Survival at 12 & 24 months with IOIO and IOTKI regimens. (*Cross trial caveats*)





Motzer. ESMO 2021. Abstr 661P. Rini. ASCO 2021. Abstr 4500. Motzer. ASCO GU 2022. Abstr 350. Motzer. ASCO GU 2021. Abstr 269.

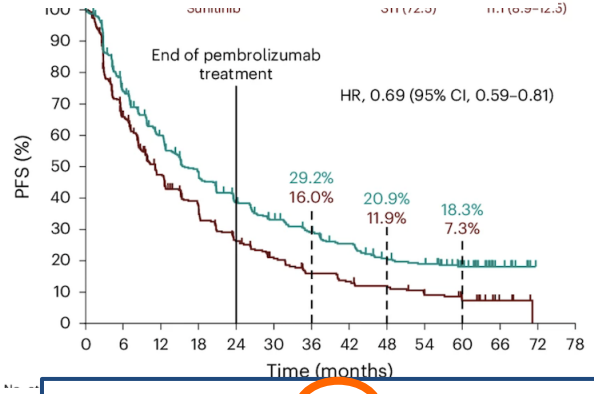
Albiges. ESMO Open. 2020;5:epub001079. Rini. ASCO 2021. Abstr 4500. Motzer ASCO GU 2021. Abstr 308. Motzer. NEJM. 2021;384:1289

These look pretty similar to me. At least to 24 months.

And all four show Progression Free Survival benefit for IO combo over sunitinib

KN 426. Axi + Pembro @ 5 years

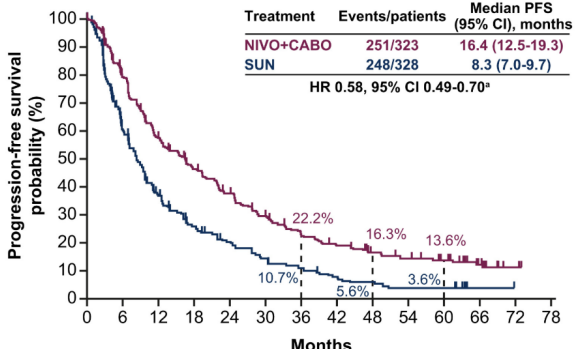
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HR for PFS: 0.69 (0.59-0.81)

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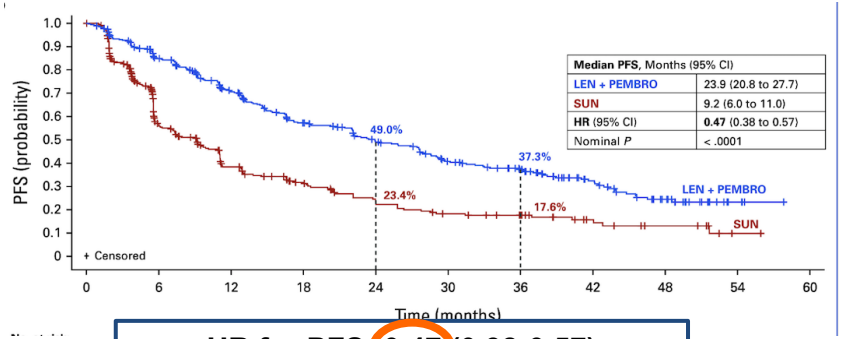
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HR for PFS: 0.58 (0.49-0.70)

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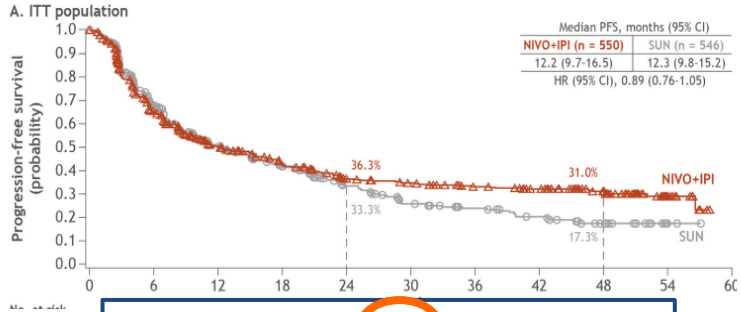
Motzer et al. ASCO; 2023



HR for PFS: 0.47 (0.38-0.57)

CM 214. Nivo + Ipi @ 9 yrs

Motzer et al. NEJM; 2018. Albiges; 2020



HR for PFS: 0.88 (0.76-1.04)

Toxicity and Tolerability:

Does differ but maybe not enough always to drive choice

	Keynote-426 Axi+Pembro	Checkmate 9-ER Cabo+Nivo	CLEAR Lenva+Pembro	Checkmate 214 Nivo+Ipi
AE any grade (%)	**98.4** v 99.5	**99.7** v 99.1	**99.7** v 98.4	**94.0** v 97.4
G3+ AE (%)	**75.8** v 70.6	**75.3** v 70.6	**82.4** v 71.8	**47.9** v 64.1
Treatment discontinuation (%)	**30.5** v 13.9	**19.7** v 16.9	**37.2** v 14.4	**22.7** v 13.1

Motzer. ESMO 2021. Abstr 661P. Rini. ASCO 2021. Abstr 4500. Motzer. ASCO GU 2022. Abstr 350. Motzer. ASCO GU 2021. Abstr 269.

- Treatment-related toxicity is common and unpredictable but with care is manageable in most
- They are different of course, but in truth not too much to pick between them (*in my opinion*)

So maybe the debate is over and these regimens are similar.

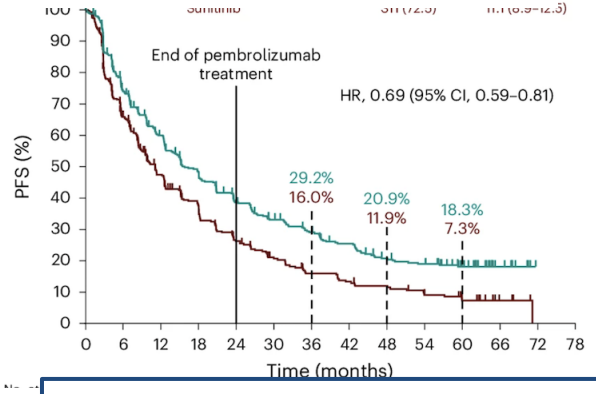
Are there differences that might be important for patients?

Let’s look again at some data

The PFS curve separation takes much longer to appear with nivo+ipi

KN 426. Axi + Pembro @ 5 years

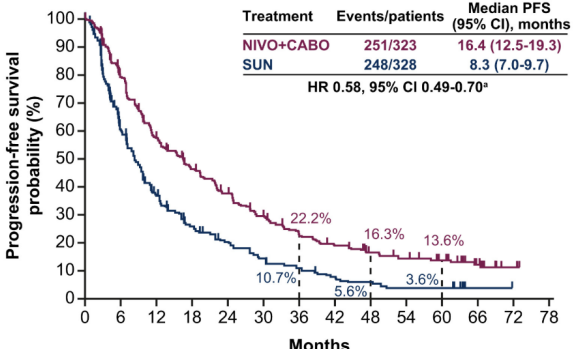
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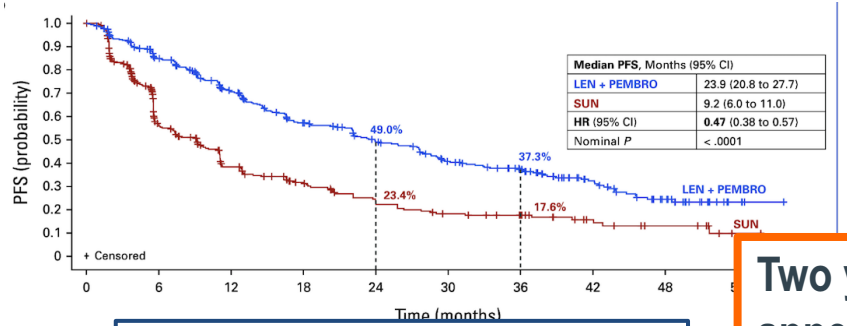
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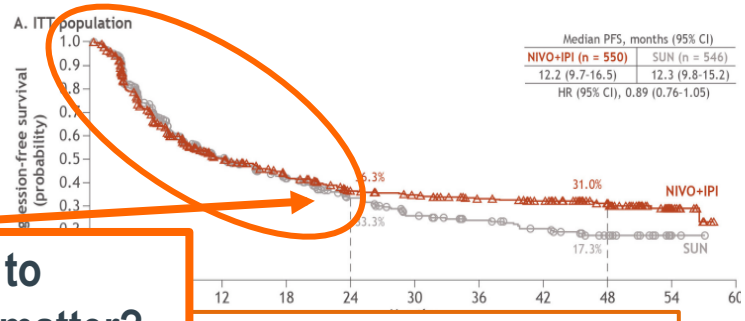
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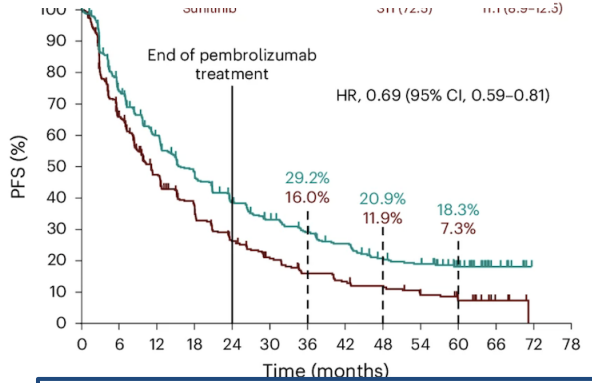
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Two years for this to appear. Does that matter?

The PFS curve separation takes much longer to appear with nivo+ipi

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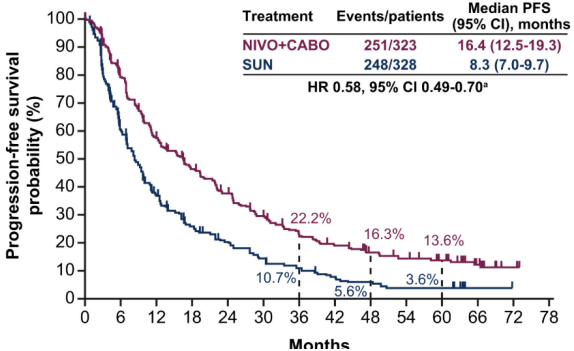
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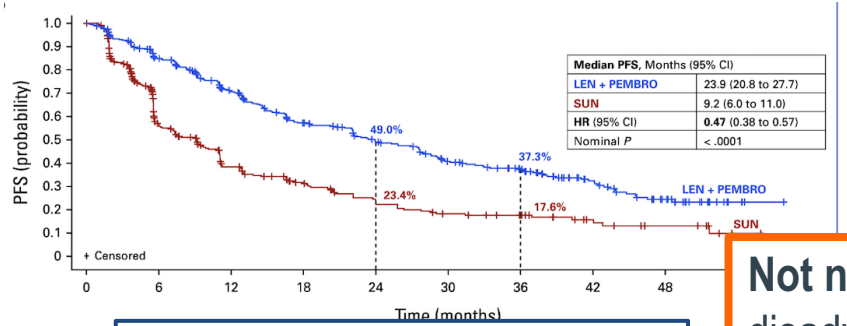
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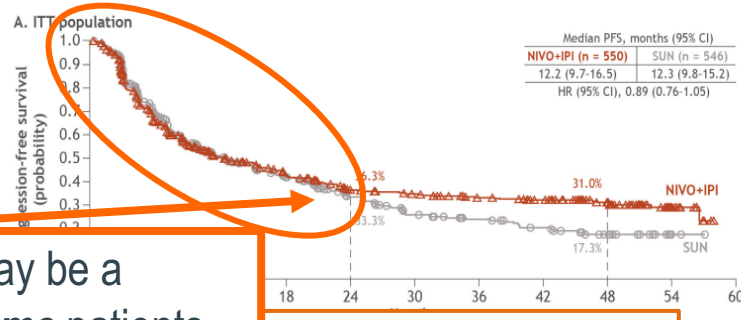
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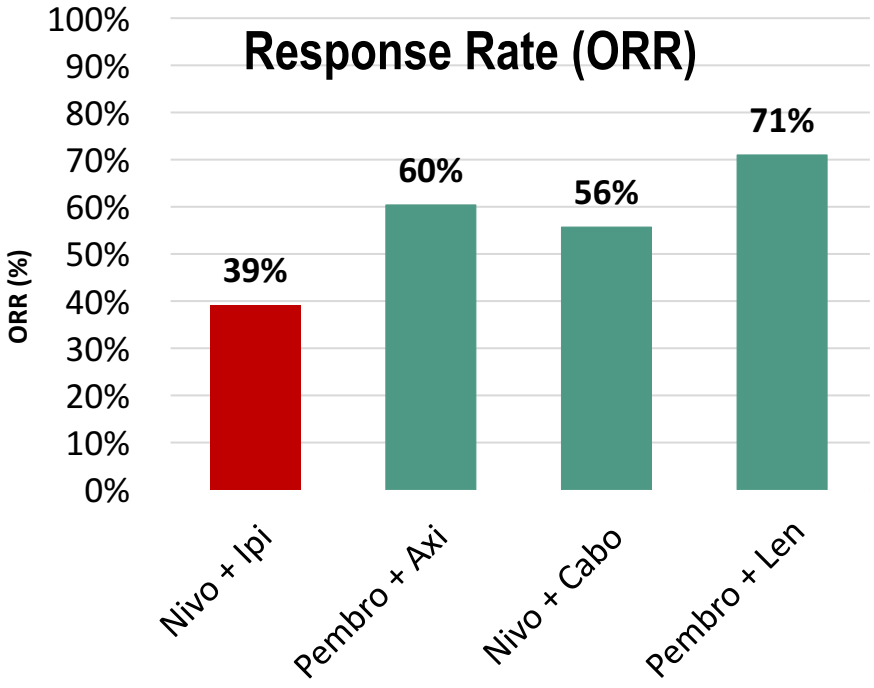


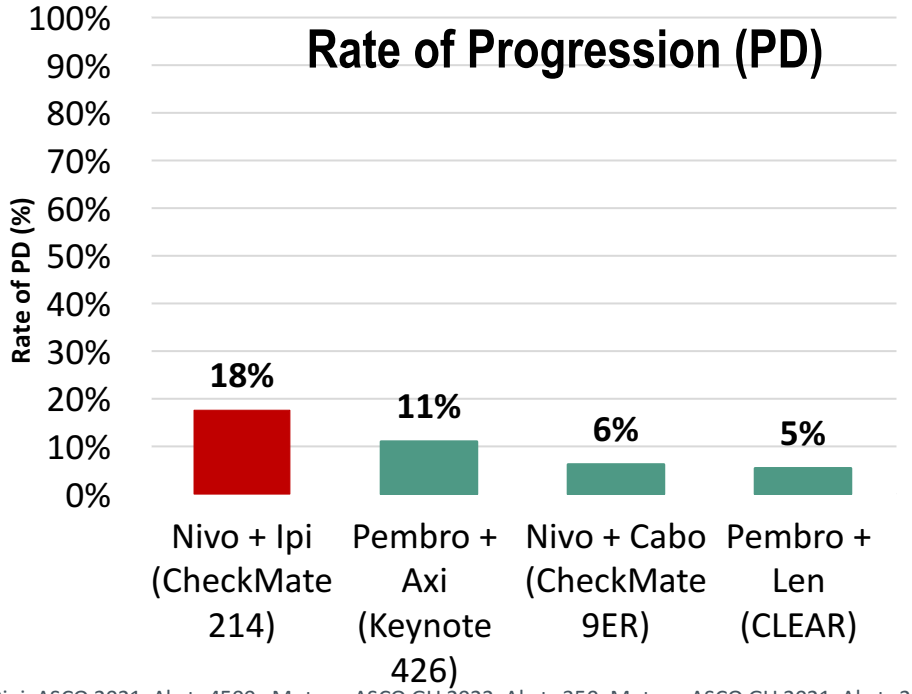
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Not necessarily. May be a disadvantage for ***some*** patients

Comparison of Response: Can be important for symptom control

Lower response rate & higher primary progression rate with Nivo+Ipi (IO-IO)

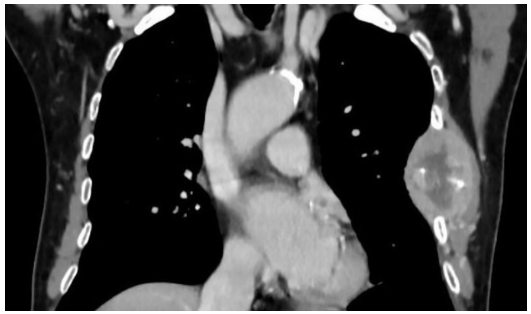


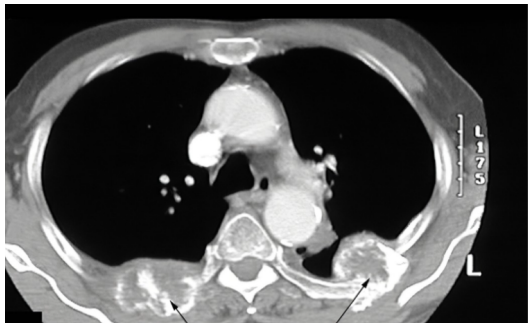


Motzer. ESMO 2021. Abstr 661P. Rini. ASCO 2021. Abstr 4500. Motzer. ASCO GU 2022. Abstr 350. Motzer. ASCO GU 2021. Abstr 269.

Again, this will matter for some but not all patients

Consider this patient…





I think early response is likely to be helpful in managing this patient's symptoms.

There are other examples – any metastasis that is symptomatic or is threatening a major structure: brain, spine, pancreas, bones, LN

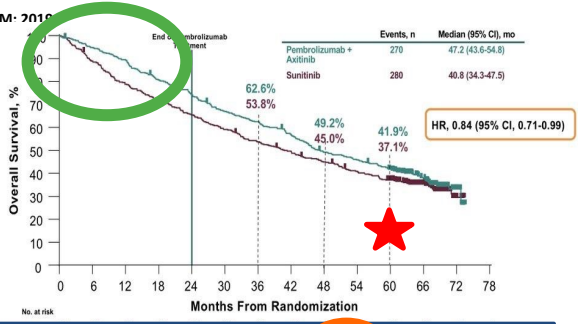
But there are many more patients without a critical site of disease

Let's also re-examine the 'similar' Overall Survival curves

With IO-TKI you get rapid onset of benefit which matters for pts who may get only one line of Rx

KN 426. Axi + Pembro @ 5 years

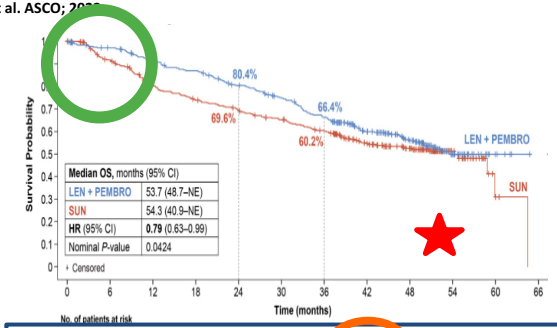
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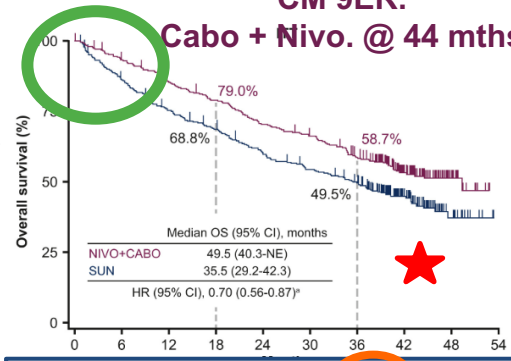
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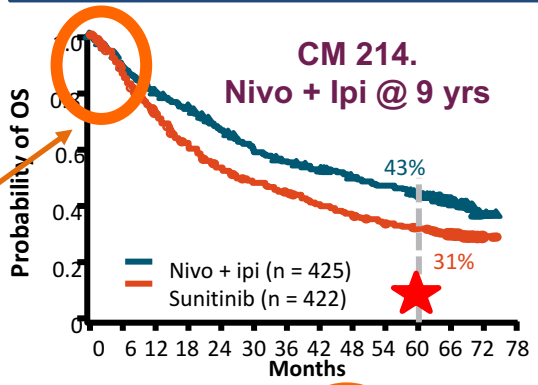
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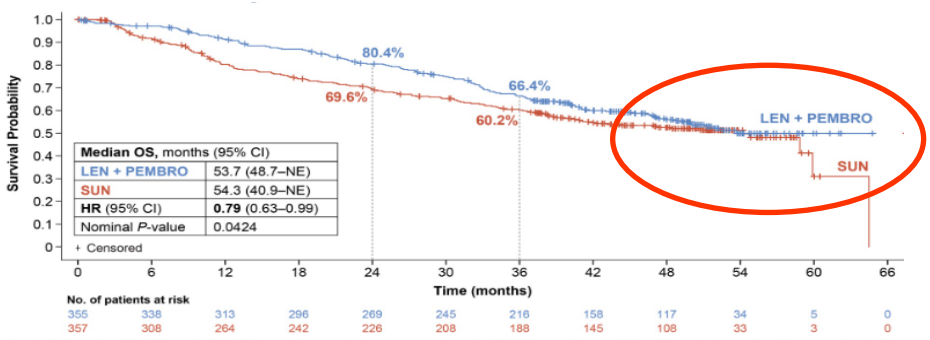
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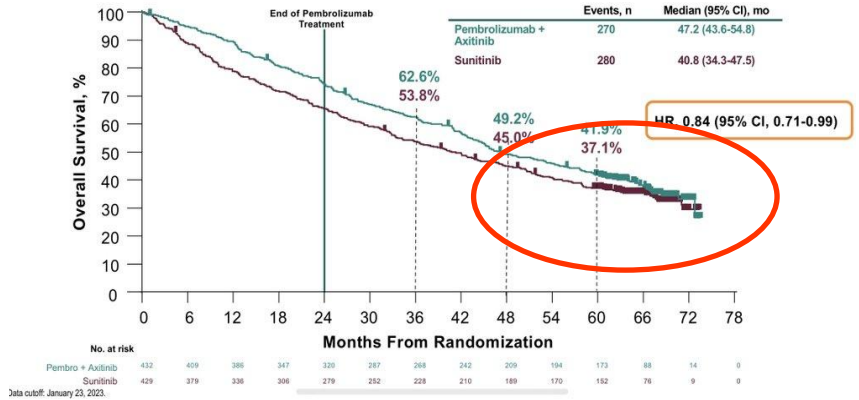


Separation only clear at approx. 6 mths

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But are the IO+TKI Overall Survival curves coming together? Lots of discussion at / following ASCO 2023

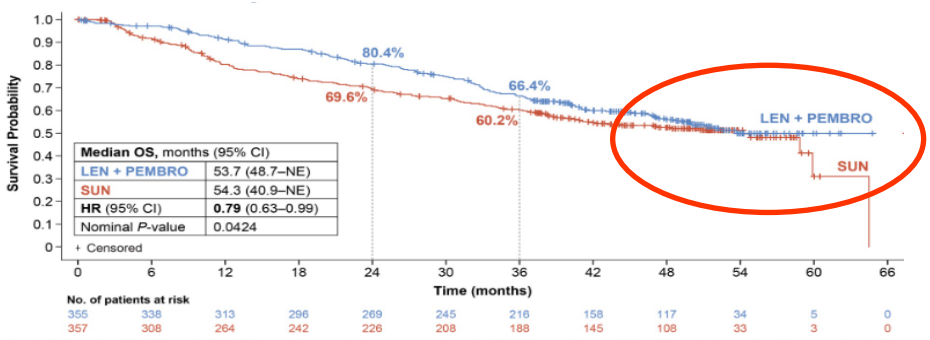


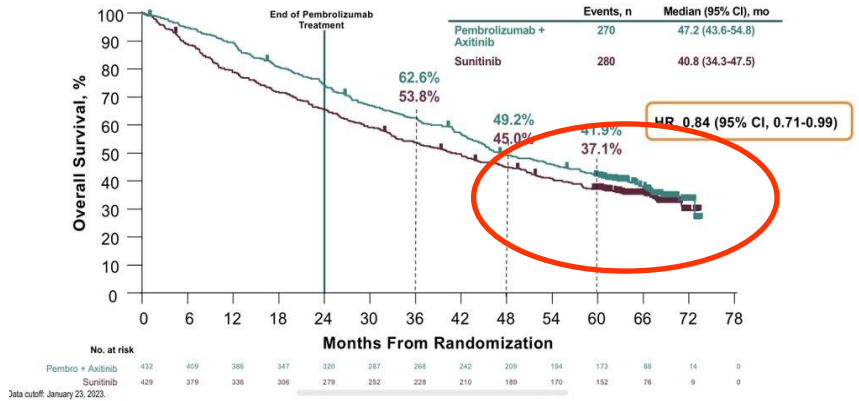




‘Should anyone be getting IO+TKI?’

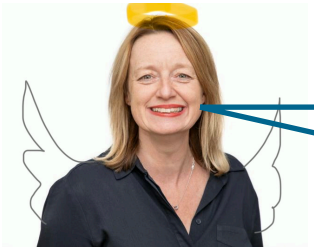
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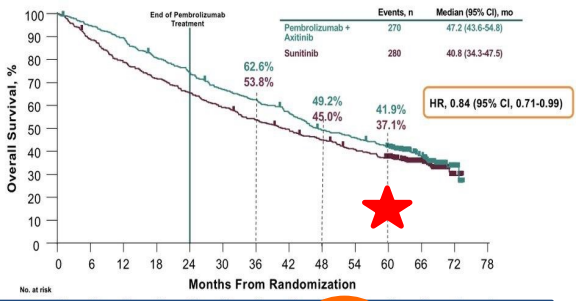
‘Of course some should!’

But let's look at the 'tail' – noting with CM 214 (Nivo+Ipi) now 9 yrs FUp

Not clear that there is the same opportunity for durable benefit with IO+TKI seen with Nivo+Ipi

KN 426. Axi + Pembro @ 5 years

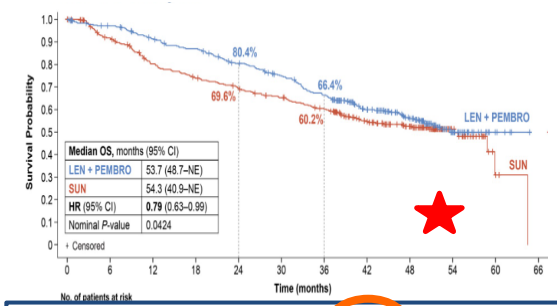
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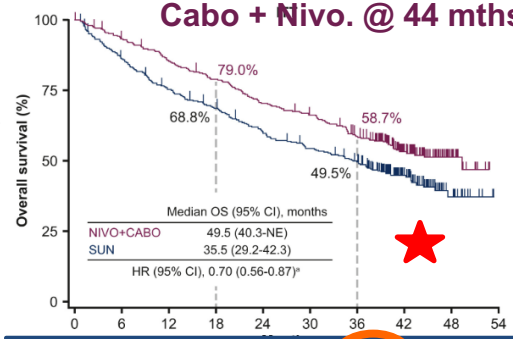
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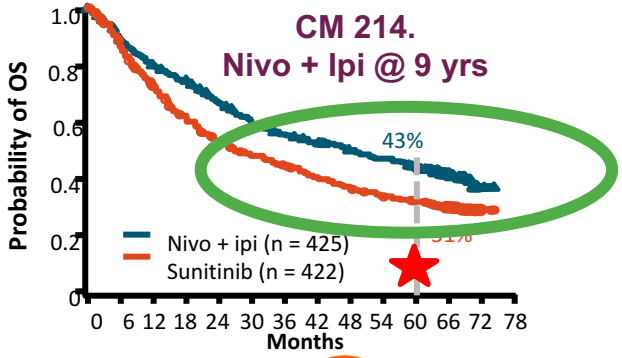
Choueiri et al. NEJM; 2021



HR for OS at 44 mths: 0.70 (0.56-0.87)

CM 214. Nivo + Ipi @ 9 yrs

Motzer et al. NEJM; 2018. Albiges; 2020



HR for OS at 9 years: 0.71 (0.62-0.82)

But let's look at the 'tail' – noting with CM 214 (Nivo+Ipi) now 9 yrs FUp

Not clear the same opportunity for durable benefit seen with Nivo+Ipi occurs with IO+TKI

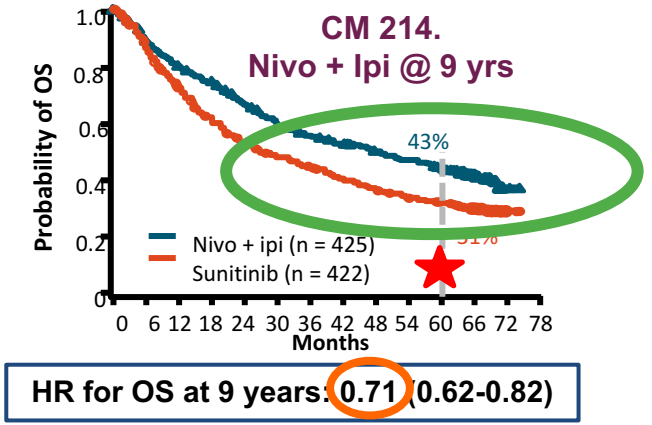
There is an impressive, durable response in *some* (not all) patients on Nivo+Ipi.

Not seen to the same extent with IO-TKI
Although we probably all have a few long responders.

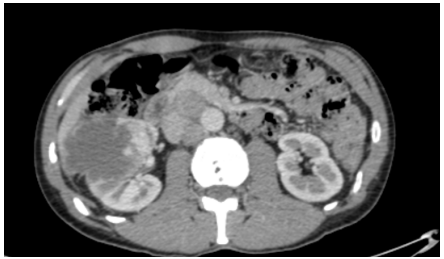
But whilst 20-30% of patients on Nivo + Ipi achieve this plateau or tail, the majority do not.

So it is a balance of goals, risks and individual preferences.

Motzer et al. NEJM; 2018. Albiges; 2020

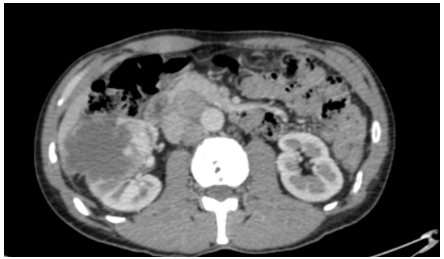


So now let's consider this patient

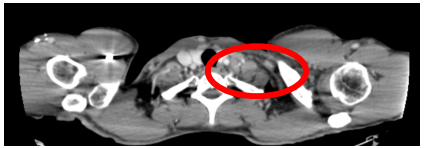


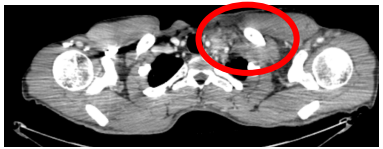
- 46yo man; no PMHx; PS 0
- Nephrectomy for G4 pT3a N1 M0 clear cell RCC
- 1 month later: Unwell. Deteriorating PS.

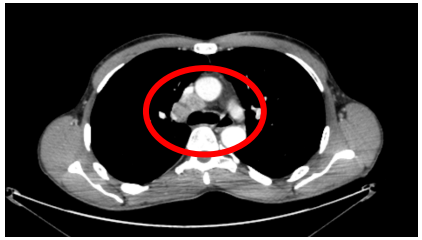
So now let's consider this patient



- 46yo man; no PMHx; PS 0
- Nephrectomy for G4 pT3a N1 M0 clear cell RCC
- 1 month later: Unwell. Deteriorating PS.









- Clustered SCF & mediastinal LN up to 25mm
- Two small liver metastases max 15mm
- Bloods OK - Intermediate risk

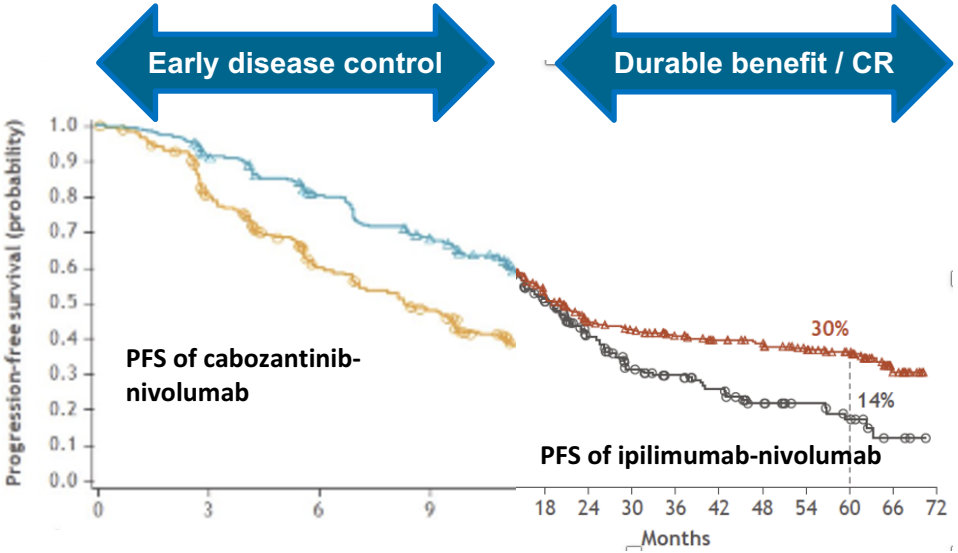
Rapid, high-grade disease in a fit young patient

But currently small volume & no threatening sites.

I would try to give the chance of durable CR here.

So in some situations perhaps there is not too much debate.

Should we deal with these relative strengths by giving triplet therapy?
Can we get early response from IO+TKI & prolonged benefit from IOIO?



Slide adapted from Dr Tian Zhang, UT South Western

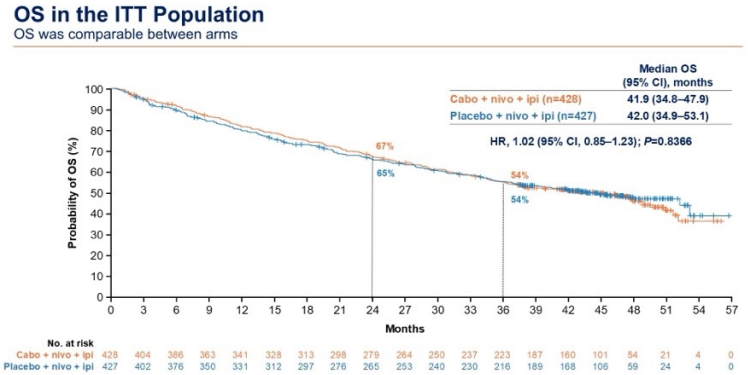
Attractive in theory!

And therefore avoid having to choose between the options?

Should we deal with these relative strengths by giving triplet therapy?

COSMIC 313: Nivo+Ipi ±Cabo

Met its primary endpoint for PFS, but not OS



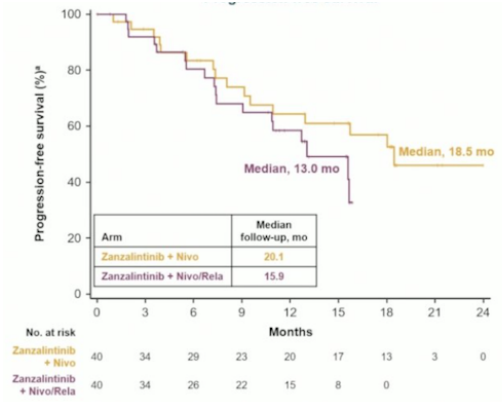
Reduced exposure to Cabo

Higher toxicity rates & treatment discontinuations

Not easily deliverable in clinical practice

STELLAR-002: Zanzalitinib+Nivo±Rela

Triplet with anti-LAG3 -no improved efficacy



Similar exposure to all drugs

Slightly higher toxicity

Deliverable but efficacy no better

LITESPARK 012 *press release*. Lenva+Belzu+Pembro – negative for OS & PFS vs with Len+Pem

Three trials. Answer = NO!! ***Still no clear role for IOIOTKI triplets in 1st line treatment of ccRCC***

Are there settings where there is not equipoise?

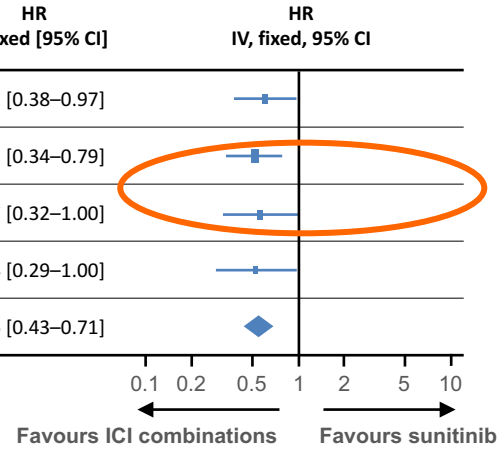
ie where it may matter which you pick?

Sarcomatoid renal cell carcinoma?

Sarcomatoid renal cell carcinoma: Comparative PFS from ICIs

Meta-analysis of PFS from ICI-containing combos in sRCC

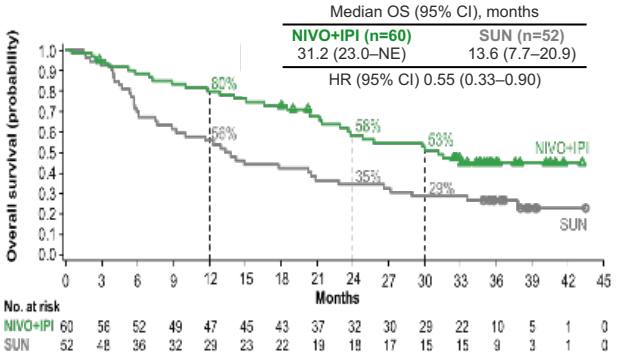
Study or subgroup	Log (HR)	SE	Weight	HR IV, fixed [95% CI]
CheckMate 214	–0.499	0.2391	28.7%	0.61 [0.38–0.97]
IMmotion 151	–0.6573	0.2151	35.5%	0.52 [0.34–0.79]
JAVELIN Renal 101	–0.5697	0.2907	19.4%	0.57 [0.32–1.00]
KEYNOTE-426	–0.6189	0.3158	16.4%	0.54 [0.29–1.00]
TOTAL (95% CI)			100.0%	0.56 [0.43–0.71]



Heterogeneity: Chi²=0.26, df=3 (p=0.97); I²=0%
Test for overall effect: Z=4.60 (p<0.00001)

Iacovelli R, *et al. Eur J Cancer* 2020;136:195–203.

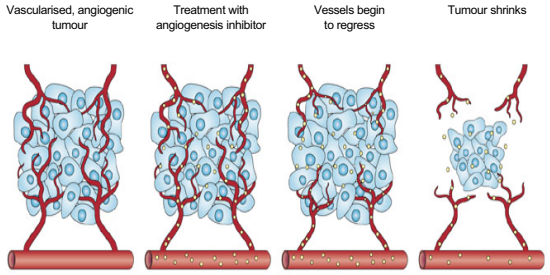
Overall survival in intermediate-/ poor-risk sarcomatoid in CM214



In sarcomatoid RCC all ICI (IO) combinations perform better than sunitinib for PFS

- And so are justifiable although admittedly I usually use Nivo+Ipi

Favourable risk patients with mRCC?



From Zetter B. *Nat Rev Cancer* 2008

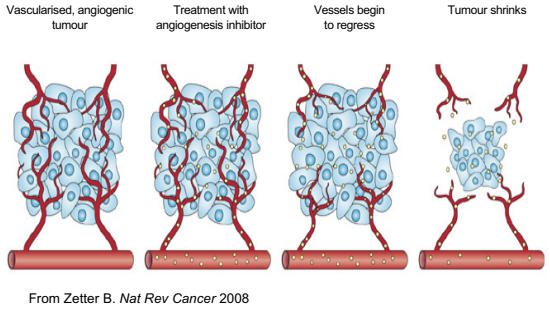
Inhibiting VEGF leads to tumour regression

It is biologically attractive to target VEGF - the most ubiquitous driver in RCC.

Especially in 'Favourable risk' which is highly VEGF dependent.

Should you always include a VEGF inhibitor?

Favourable risk patients with mRCC?



From Zetter B. *Nat Rev Cancer* 2008

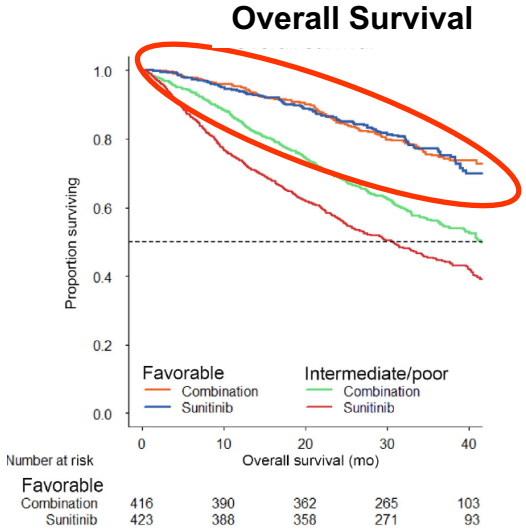
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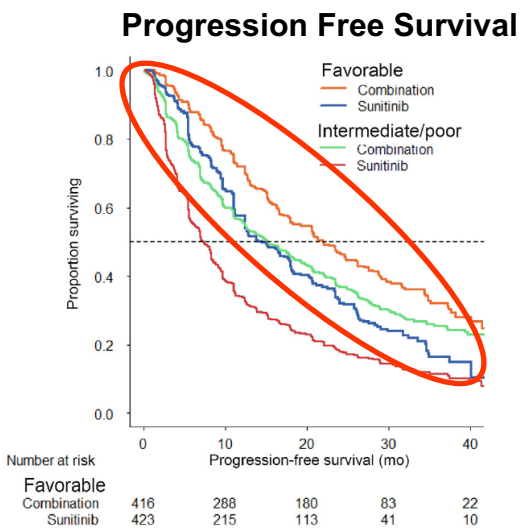
It is biologically attractive to target VEGF - the most ubiquitous driver in RCC.

Especially in 'Favourable risk' which is highly VEGF dependent.

Should you always include a VEGF inhibitor?

FDA pooled analysis of 3098 pts; 839 favourable risk (Orange v Blue)





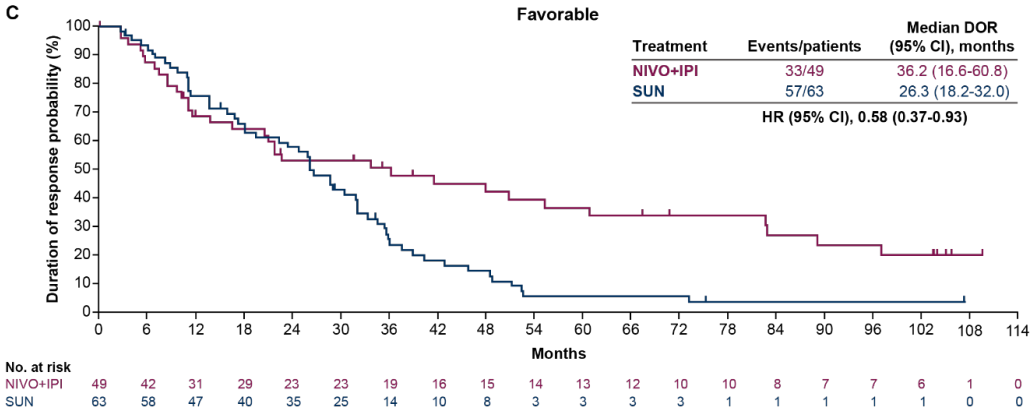
Figures from Lee D *et al. Eur J Oncol* 2023.

In this analysis, IO-TKI show an improvement over sunitinib for PFS but not for OS

But all these include a VEGF TKI as well. How about IO+IO?

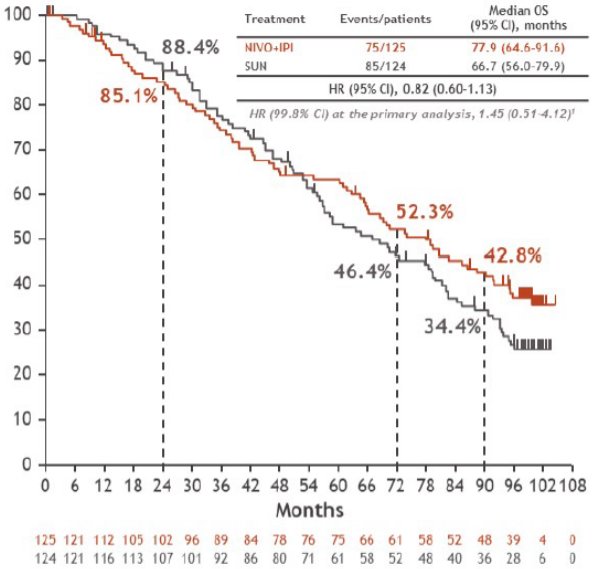
CM 214 update: Duration of Response & Overall Survival in Favourable Risk

Duration of Response in Favourable Risk Cohort



Separation of these curves at about 30 months

Overall Survival in Favourable Risk Cohort



The HR for OS has improved over time in favourable-risk patients

So maybe IO+IO is reasonable in some favourable risk. But who? *I don't think I know…*

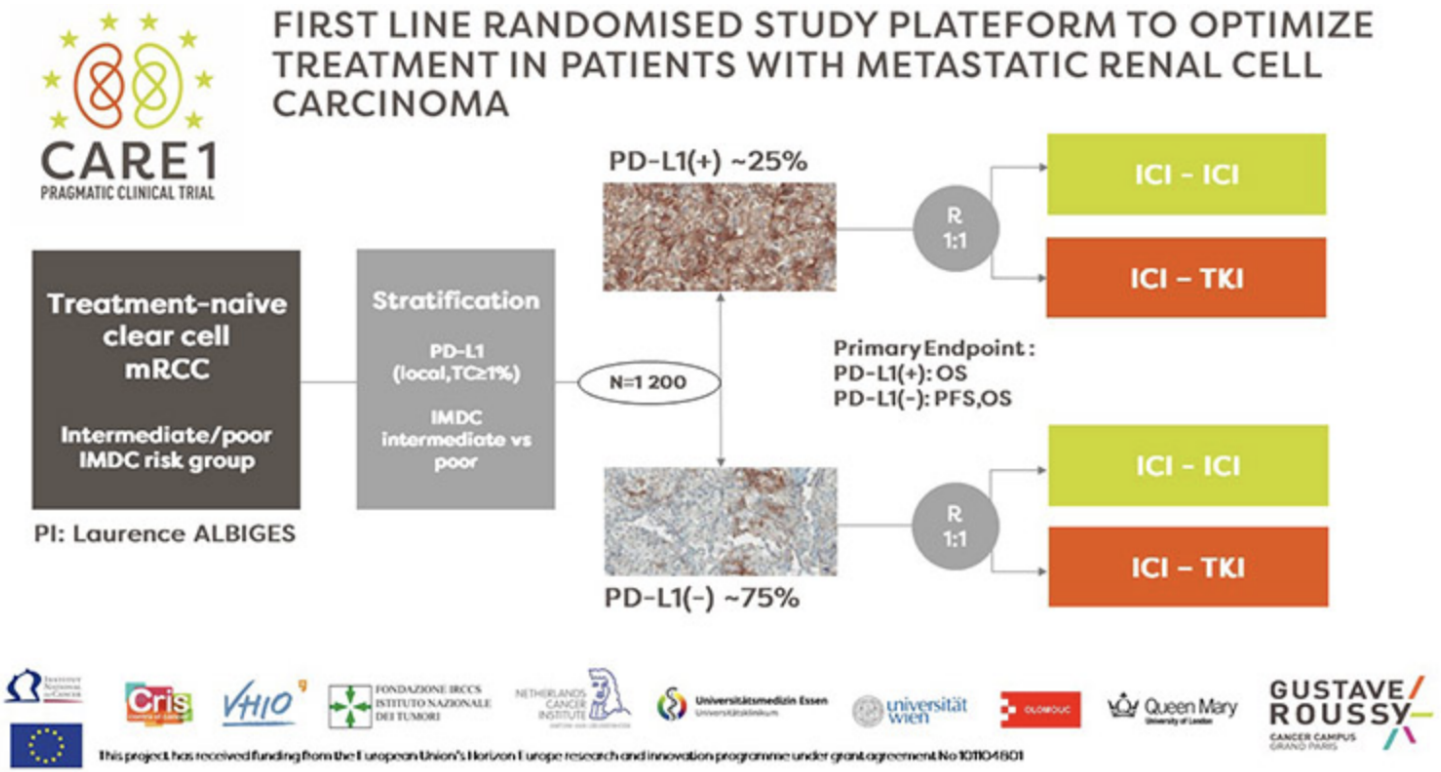
What do we hope for when selecting 1st line treatment in mRCC?

- Control or maximal shrinkage of cancer for as long as possible
- Extending life expectancy
- Limiting symptoms of cancer
- Whilst having the fewest side effects from treatment
- Therefore delivering the best quality of life for the longest time possible
- And achieving all of this for the majority of patients
- Without reliable predictive markers to select therapy at an individual level (yet)

We have seen that both IOIO and IOTKI regimens can achieve this
But if this debate was completely over…

Would we need this trial? *I think we do…*





So is the eternal debate over? My thoughts…

1. **Know the strengths of each approach**

   - Response rate, Progression free and Overall survival, Durability of response

1. **And the limitations**

   - Primary progression rate, toxicity profiles

1. **So when you and your patient have worked out the priorities you can decide whether there is a preferred or better option for them**

2. **If it seems either option may be appropriate, it probably is**

   - The patient may have unpredictable toxicity or may not benefit. That does not mean the initial choice was wrong

1. **And in these situations, follow the mantra ‘pick one and use it well’**

VIGO NORTE INTERNATIONAL GU DEBATES

Thank you





