WHY (OR WHY NOT) COMBINATION THERAPY MAY BE BEST FOR MY KIDNEY CANCER

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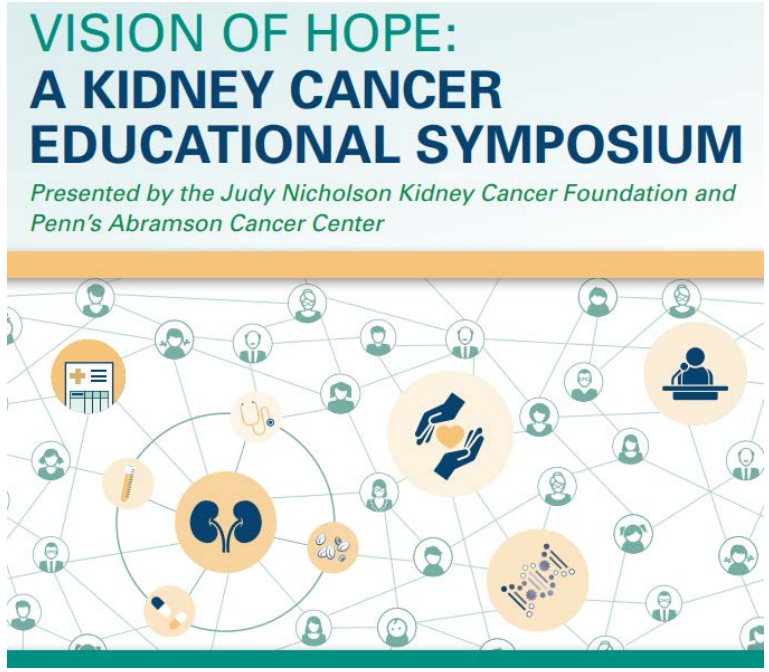
FOX CHASE CANCER CENTER



Relevant Disclosures

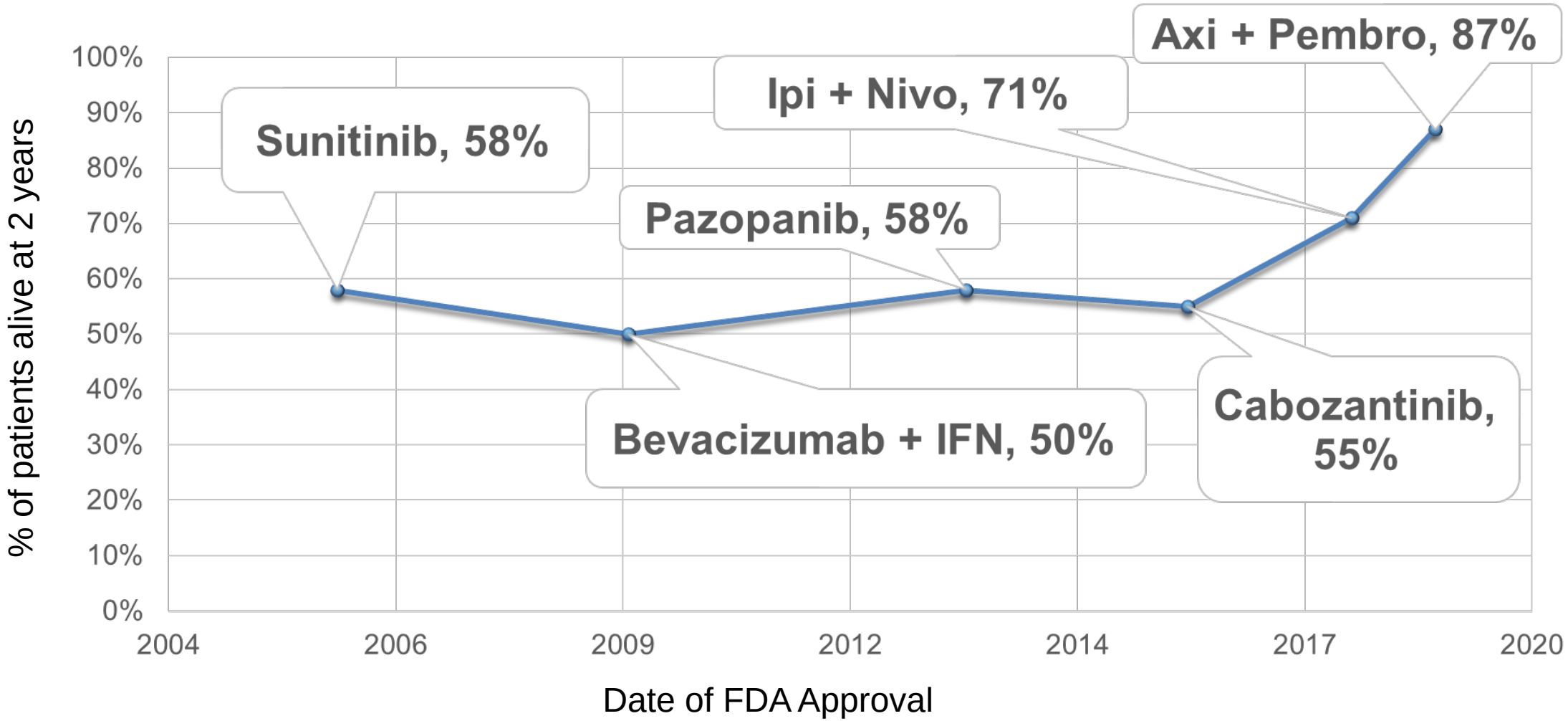
Scientific Advisor: BMS, Flatiron, Genentech, Janssen, Merck, Seattle Genetics

Data Safety Monitoring: AstraZeneca, Pfizer.

Grants for clinical research: Astellas, , BMS, Genentech, Merck, Peloton

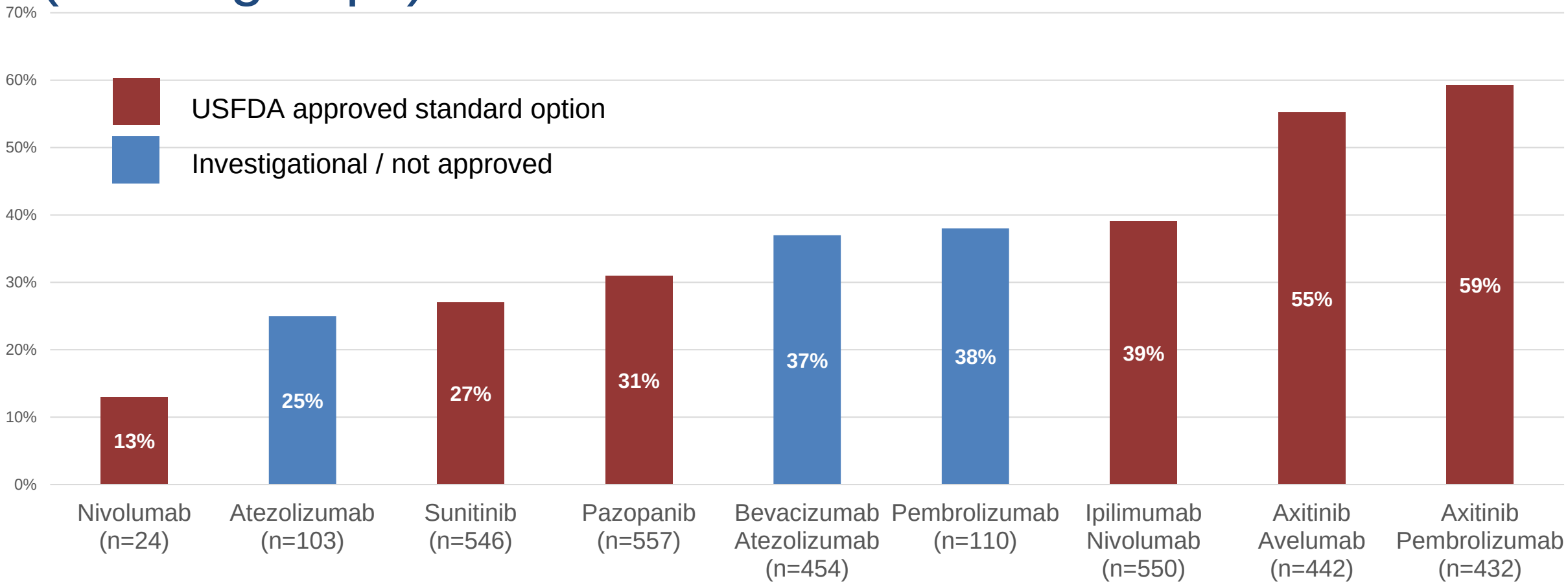
CME presentations: AUA, Clinical Care Options, Fox Chase Cancer Center, Georgetown, Medscape, NCCN, PER, PriME Oncology, Research to Practice

Improved 2 year overall survival in first line RCC



Motzer NEJM (COMPARZ) 2013, Escudier (AVOREN) JCO 2010,Tannir (CM214) GU ASCO 2019, Choueiri (CABOSUN) JCO 2017, Atkins (Phase I/II) Lancet Onc 2018

Response Rates in Front Line Metastatic ccRCC (all risk groups)



Choueiri CCR. 2016 PubMed: 27169994

McDermott GU ASCO 2017 Abstract # 431

Motzer NEJM 2018 PubMed: 29562145

Motzer NEJM 2013 PubMed: 23964934

Escudier ASCO 2018 Abstract #4511

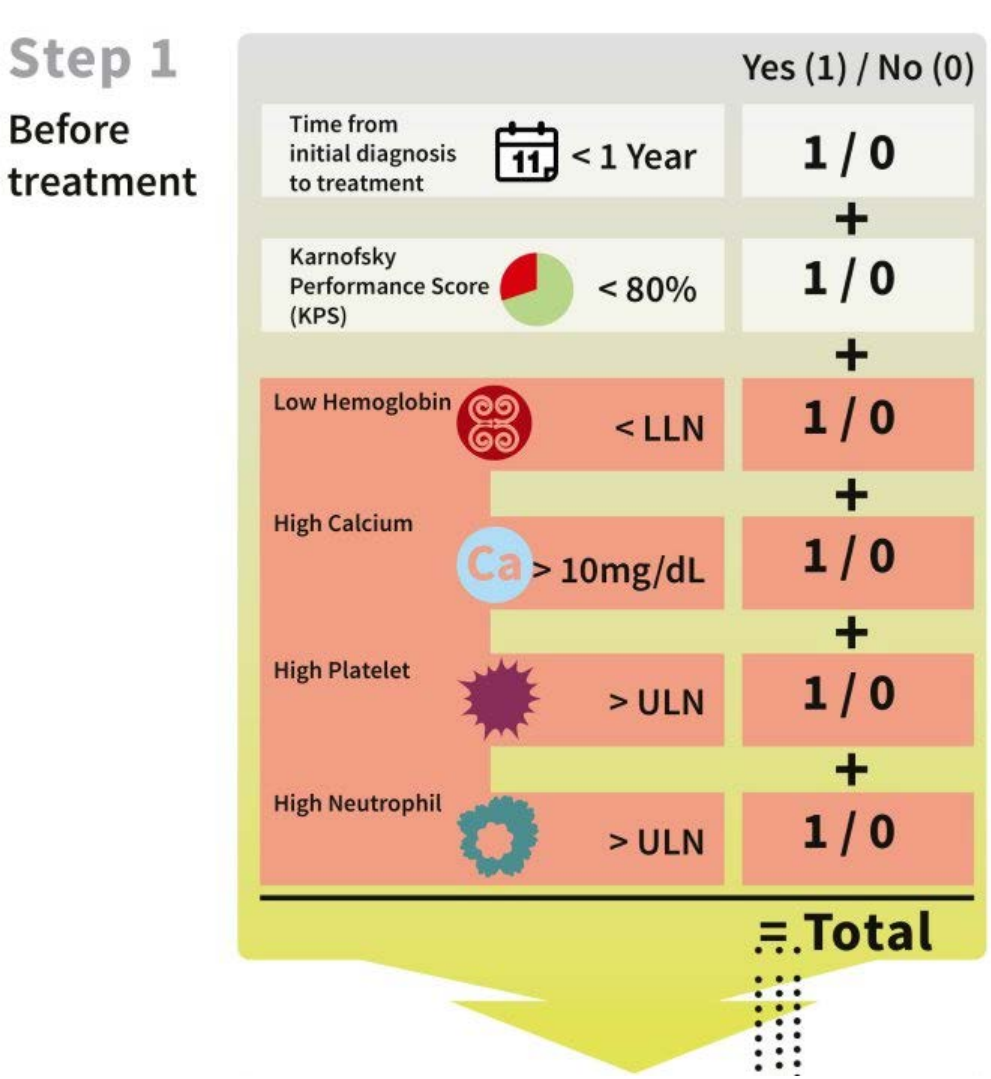
McDermott ASCO 2018 Abstract #4500

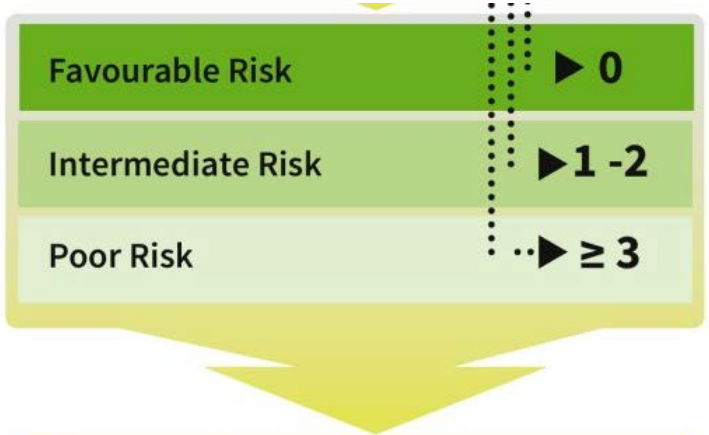
Motzer NEJM 2018 PubMed: 29562145

Motzer NEJM 2019 PubMed: 30779531

Rini NEJM 2019 PubMed: 30779529

IMDC (Heng) Criteria for Metastatic RCC





About IMDC Risk Categories

75 – 80% of patients selecting 1st line mRCC treatment options have at least 1 of these risk factors, therefore classifying their mRCC as intermediate/poor risk. Risk classification may change over time and may help in selecting treatments such as immunotherapy.

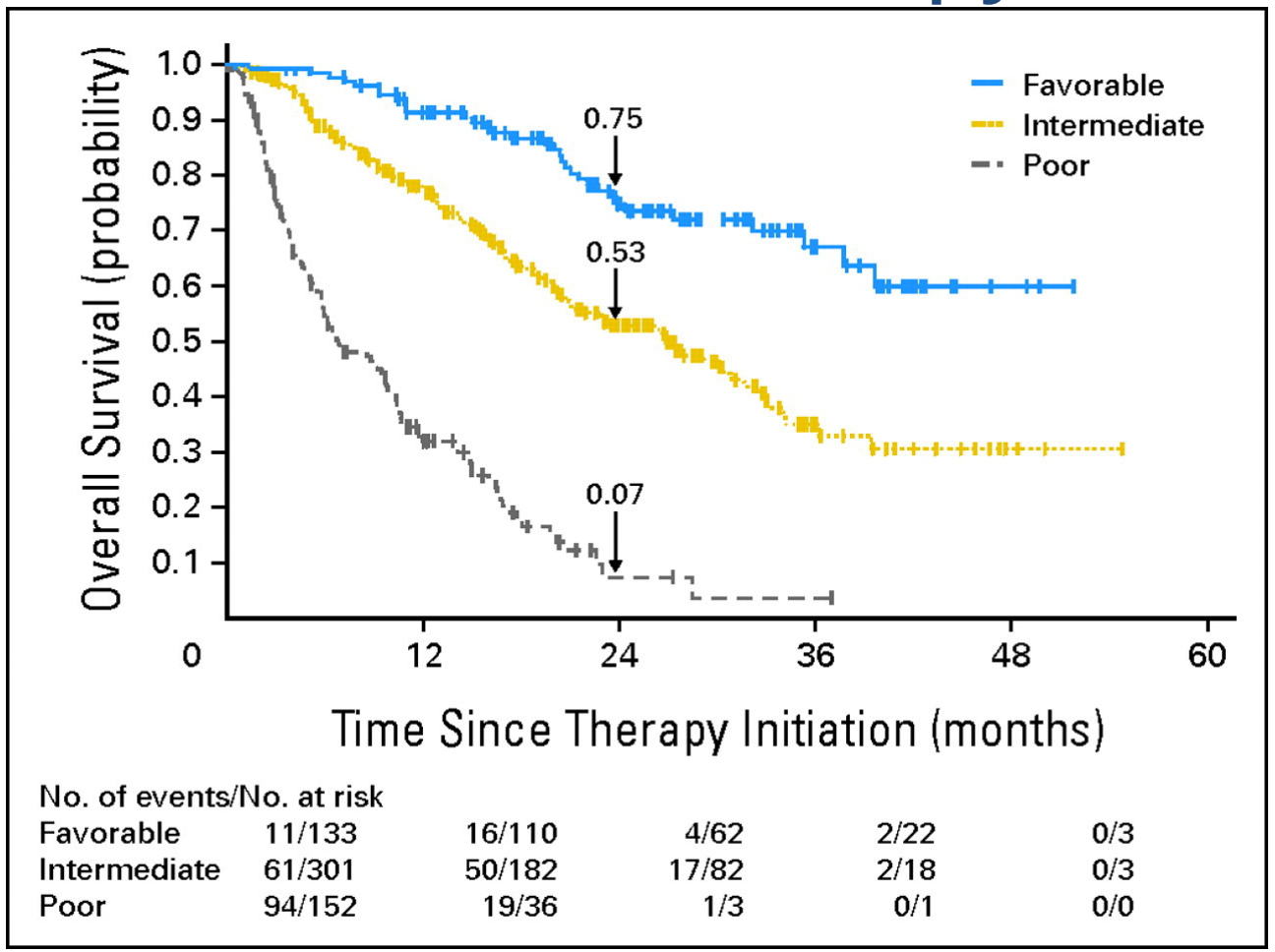
Legend:

KPS = Karnofsky Performance Score (e.g., are cancer symptoms affecting normal activities?)
LLN = Lower Limit of Normal
ULN = Upper Limit of Normal
IMDC = International Metastatic Renal Cell Carcinoma Database

IKCC International Kidney Cancer Coalition

10-FOR-I.O.* *immuno-oncology

IMDC (Heng) Prognostic Criteria for patients treated with 1st line anti-VEGF therapy before the era of immunotherapy



Heng. JCO. 2009

FAVORABLE RISK

70 yo woman with Clear Cell RCC

- Felt fine until she noticed blood in her urine.
- Tumor on the kidney was found and promptly removed surgically
- 1 year later: CT scan shows a single tumor deposit in the lung. This was removed via surgery
- 2 years later: Imaging shows slowly growing tumor deposits in three spots in the lung. We elected to observe due to very slow growth.

Now 73 yo woman with Clear Cell RCC

- After 3 years of very slow growth of tumors in the lung, a new abnormal lymph node appeared.
- We decided to start treatment. She had favorable risk

Current FDA approved first line options available in the US:

A. Pazopanib
B. Sunitinib
C. Axitinib + Pembrolizumab
D. Axitinib + Avelumab
E. Ipilimumab + Nivolumab
F. Bevacizumab + Interferon

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F. Bevacizumab + Interferon

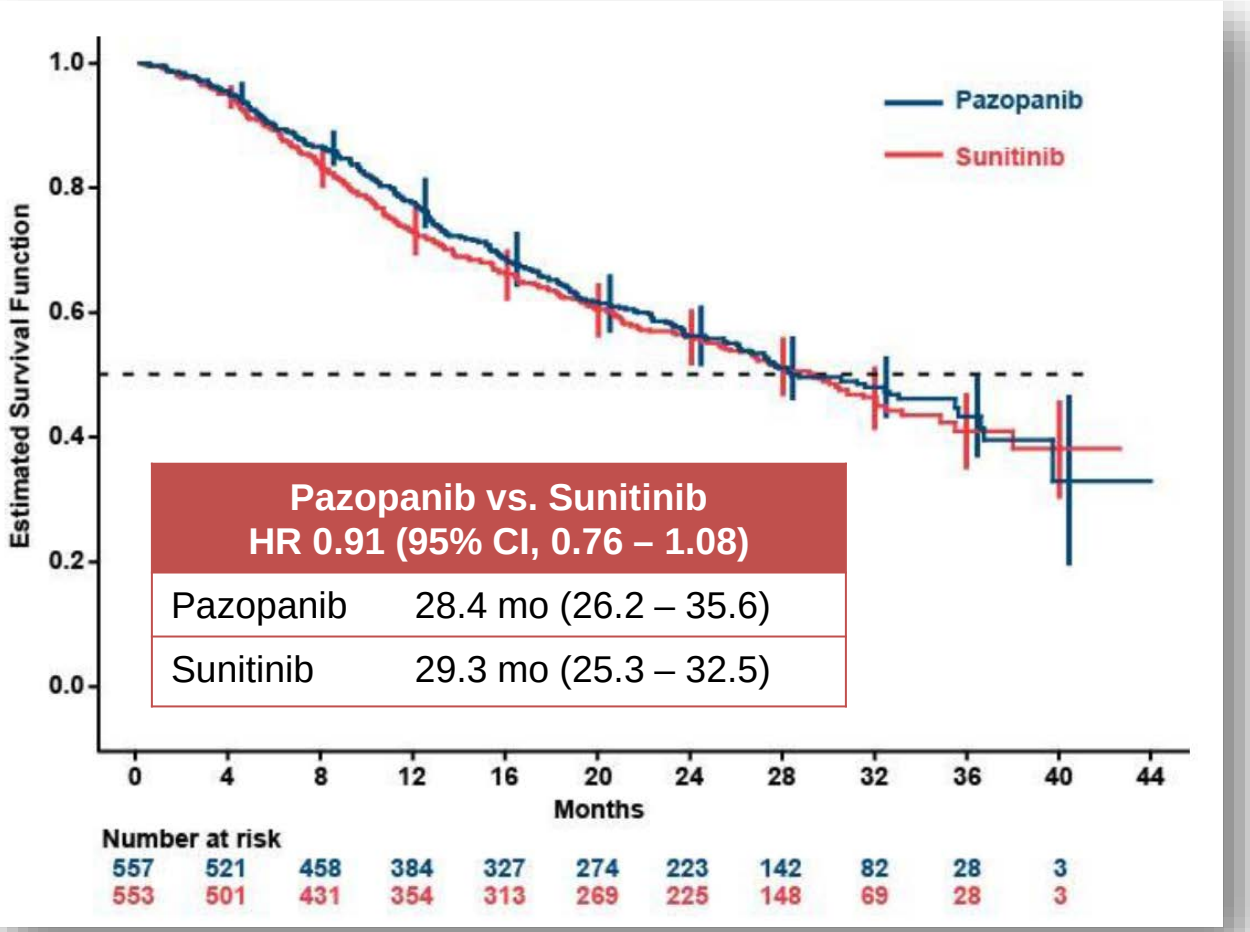
Started pazopanib at reduced dose (75% of max)

Our Current Approach in First Line mRCC

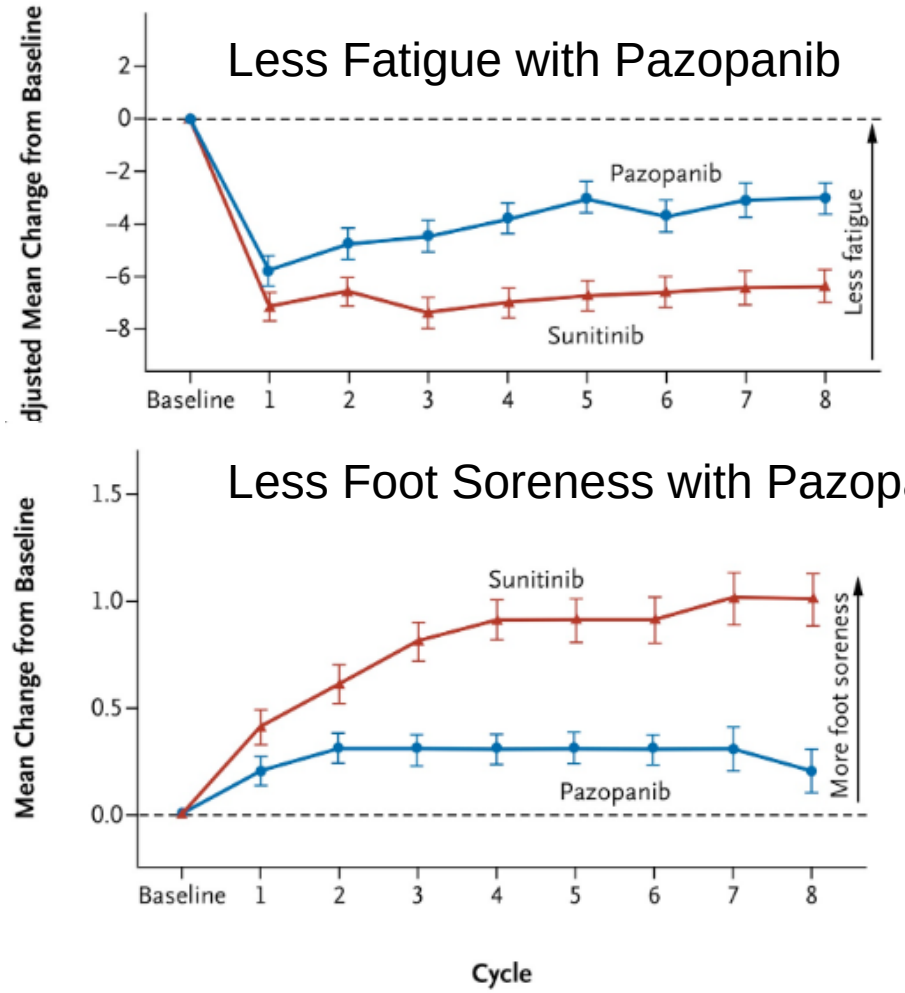
IMDC Risk	Preferred Regimens in First Line
Favorable	Pazopanib Axitinib + Pembrolizumab
Poor/Intermediate	Axitinib + Pembrolizumab Ipilimumab + nivolumab

Sunitinib and Pazopanib are equally effective
Pazopanib has fewer side effects

Overall Survival



Pazopanib vs. Sunitinib HR 0.91 (95% CI, 0.76 – 1.08)	
Pazopanib	28.4 mo (26.2 – 35.6)
Sunitinib	29.3 mo (25.3 – 32.5)



Motzer et al. NEJM 2013

For favorable risk, response rate and PFS are better with sunitinib vs ipi + nivo

	N = 249[a]	
Outcome	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) ***P* < 0.0001**	

Escudier et al. ESMO 2017 (NEJM 2018)

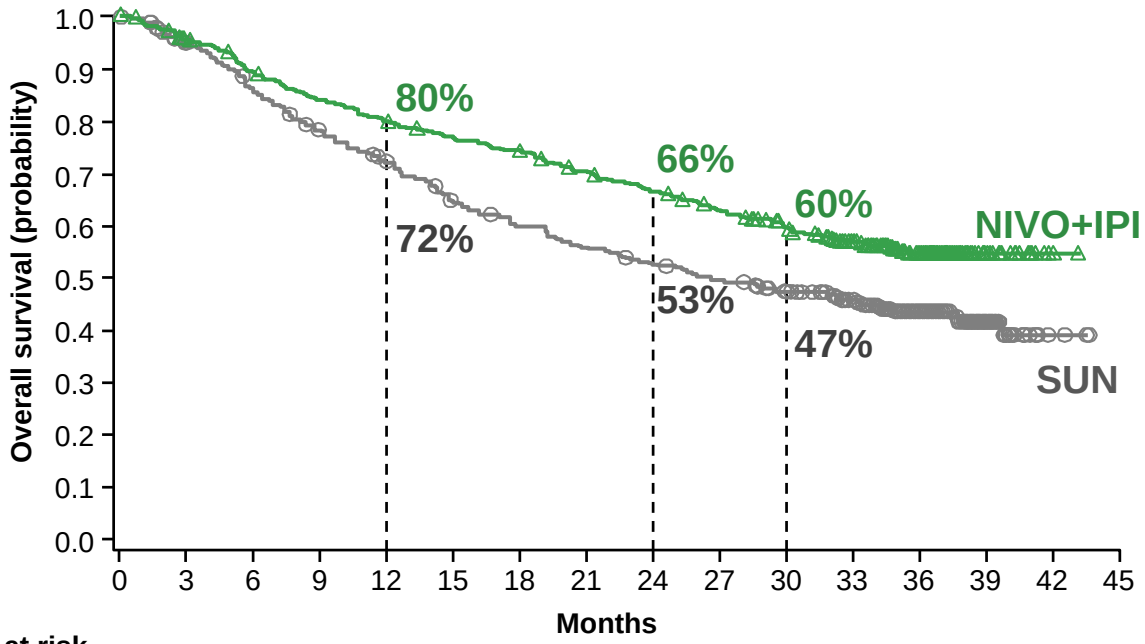
Ipi + Nivo vs Sunitinib: OS by IMDC Risk
(minimum follow up 30 months)

Intermediate/poor risk

Median OS, months (95% CI)

NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)
P < 0.0001



No. at risk

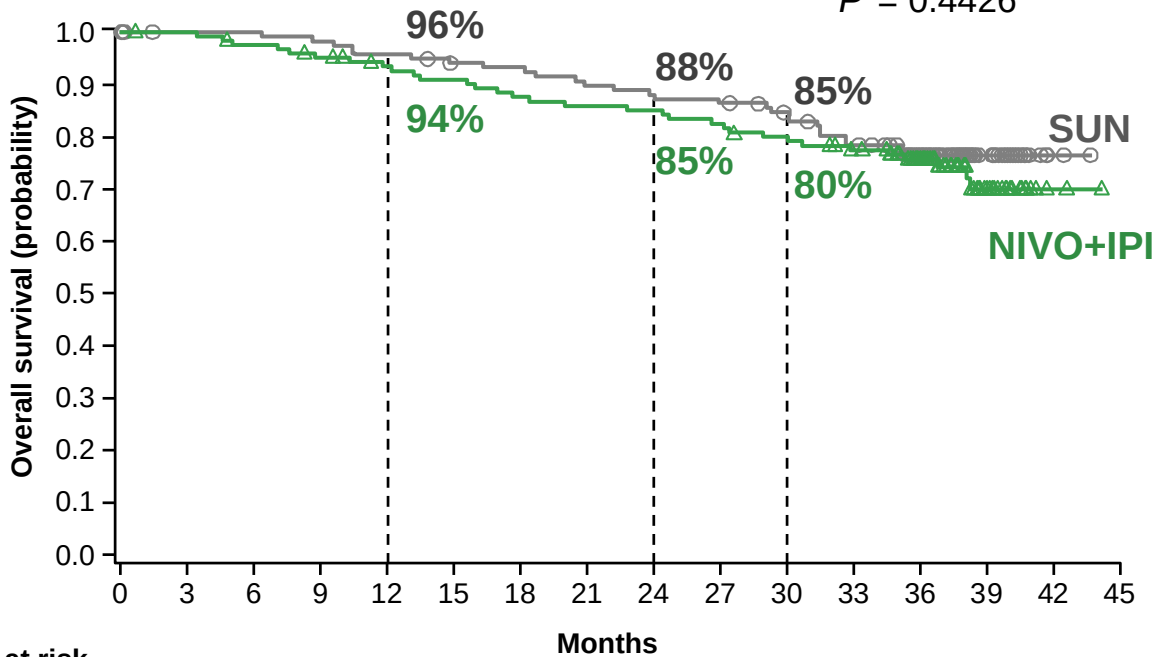
NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

Median OS, months (95% CI)

NIVO+IPI	NR (NE)
SUN	NR (NE)

HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426



No. at risk

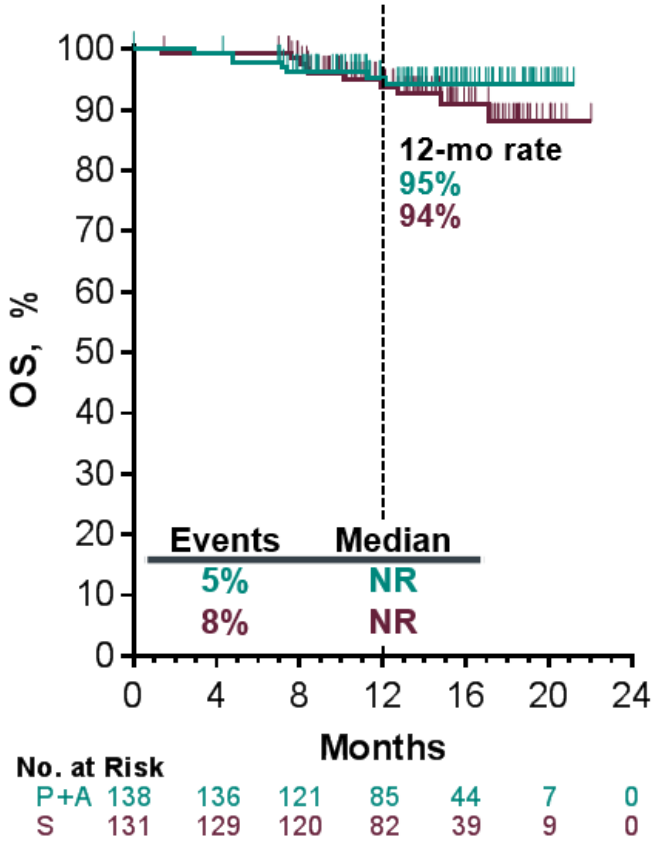
NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Tannir et al. GU ASCO. 2019

KN426: Axitinib + Pembrolizumab for Favorable Risk

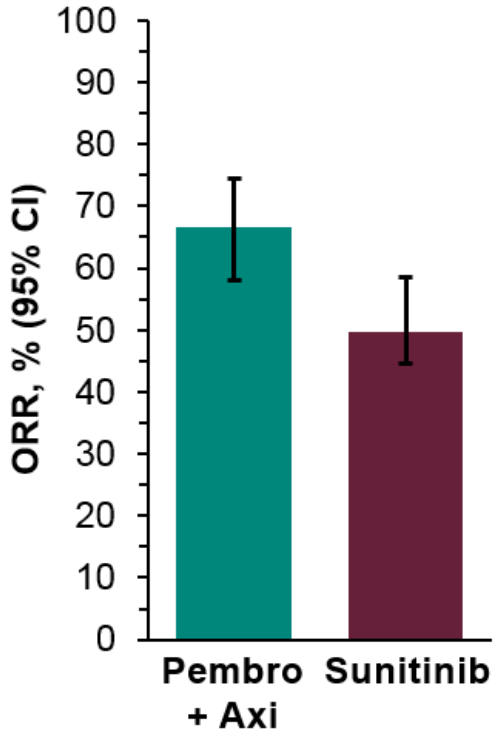
Overall Survival

HR 0.64 (95% CI 0.24–1.68)



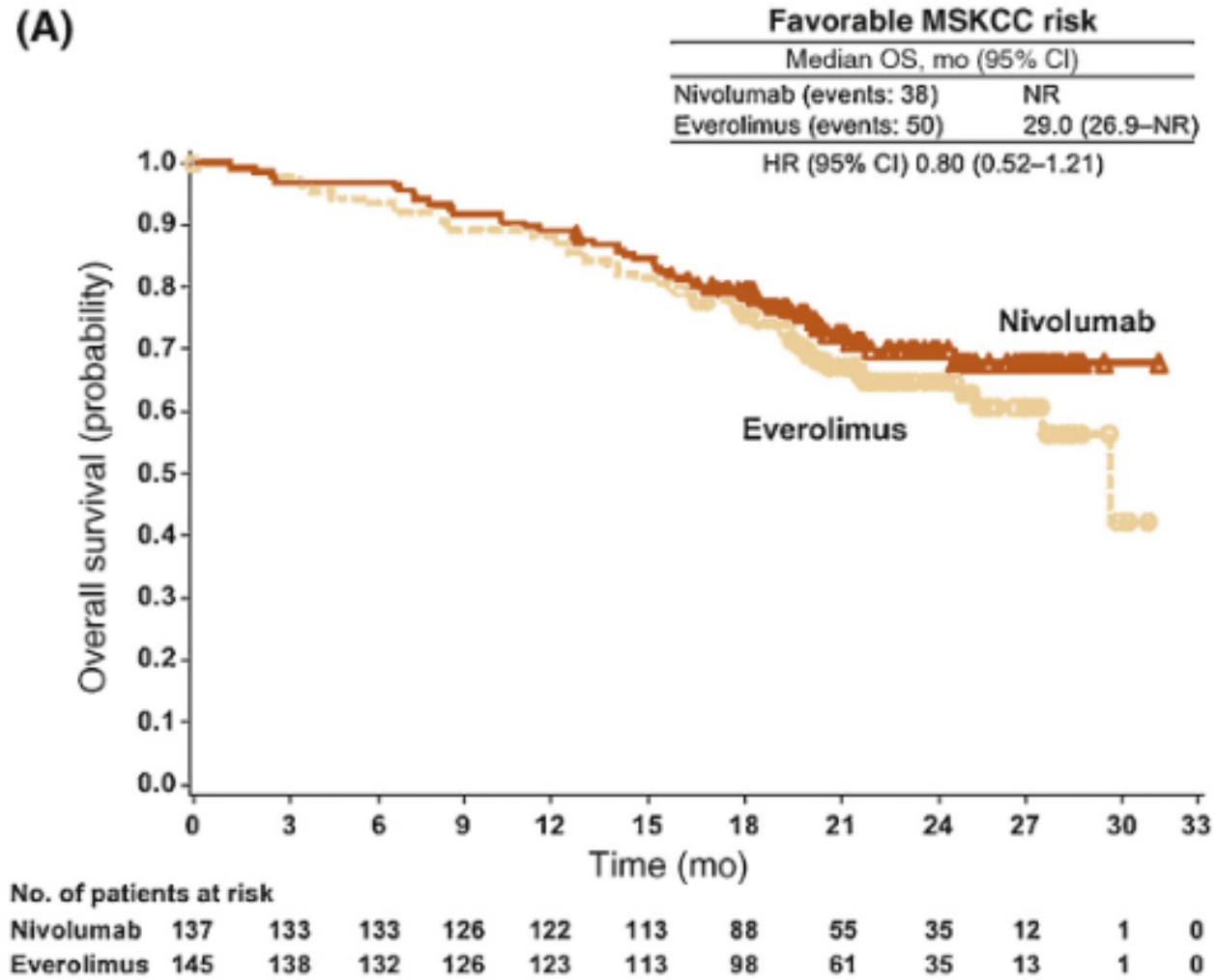
Response Rate

66.7% vs 49.6%



Rini et al. ASCO. 2019

But would sequential pazopanib → nivolumab be just as good? Here are results for nivolumab vs everolimus in favorable risk after first line VEGF



Escudier et al. EU 2017

Now 73.5 yo woman with Clear Cell RCC

- Started pazopanib 600 mg daily
- Dose reduced to 400 mg daily after 4 weeks due to multiple intolerable side effects (PPE, HTN, elevated LFTs)
  - Sore feet
  - High blood pressure
  - The beginnings of liver damage (abnormal liver blood tests)

How to manage side effects of pill-based “VEGF inhibitor” treatment

- When considering the long written list of potential side effects, note that nobody gets all of them!
- However, we cant predict which ones a given patient will experience.
- After you start treatment, keep a diary of how you feel including daily blood pressure
- If early side effects are severe or bothersome, call your doctor: Communication is key
- Be sure to see your doctor at 3-4 weeks to detect emerging side effects early

How to manage side effects of pill-based “VEGF inhibitor” treatment

- When side effects start to emerge, your doctor may hold your pills for a few days and restart at reduced dose
  - Do not give up on the treatment altogether just because you have side effects at the highest dose
  - Do not continue until the side effects become so bad you can’t stand it.
- For patients on a combination of immunotherapy and VEGF inhibitor pills, it might be hard to tell which one is the problem. In this case it is best to stop both drugs and:
  - If the problem resolves, attribute to the pill (short half life)
  - If the problem persists, attribute to immunotherapy (effects are lasting and require steroids to reverse

Now 73.5 yo woman with Clear Cell RCC

- CT scan showed shrinkage of her tumor deposits, but sje continued to have side effects at the lowest dose.
- We discontinued pazopanib
- Next line options:

A. **Axitinib**
B. Axitinib + Pembrolizumab
C. Nivolumab
D. Ipilimumab + Nivolumab
E. Cabozantinib
F. Lenvatinib + Everolimus

Axitinib at reduced dose 3 mg BID

Our Current Approach For Subsequent Therapy

Single Agent	Combination
Cabozantinib Nivolumab Axitinib Pazopanib	Ipilimumab + nivolumab Axitinib + Pembrolizumab Lenvatinib + Everolimus

Principles of next line treatment selection

- If cancer is well controlled for over 1 year on pill-based (VEGF) treatment alone, consider sequential similar agent such as Cabozantinib or Axitinib
- If the response to VEGF treatment was brief, consider adding immunotherapy Axitinib + Pembrolizumab [extrapolating from 1st line evidence]
- If there was no response to first line VEGF, drop VEGF and switch to immunotherapy: Ipilimumab + Nivolumab or Nivolumab
- In third line and beyond, consider options above, or alternatively Lenvatinib + Everolimus. Everolimus is an mTOR inhibitor pill.

Now 80 yo woman with Clear Cell RCC

- Started **axitinib** at 3 mg bid
- After one year, dose was further reduced to 2 mg bid due to cumulative low grade side effects (epistaxis, diarrhea, fatigue)
- Continues on 2 mg bid with stable asymptomatic disease now 6 years later

10 years of disease control with

observation, metastasectomy, and VEGF TKIs in sequence for favorable risk metastatic ccRCC

INTERMEDIATE/POOR RISK

40 yo man with Clear Cell RCC

- Nephrectomy
  - Recurrent to lungs 9 months later
  - Low hemoglobin
  - Normal ANC
  - Normal platelets
  - Normal Calcium
  - Karnofsky PS = 80%
- Started on phase Ib study of axitinib + nivolumab

Our Current Approach in First Line mRCC

IMDC Risk	Preferred Regimens in First Line
Favorable	Axitinib + Pembrolizumab Pazopanib
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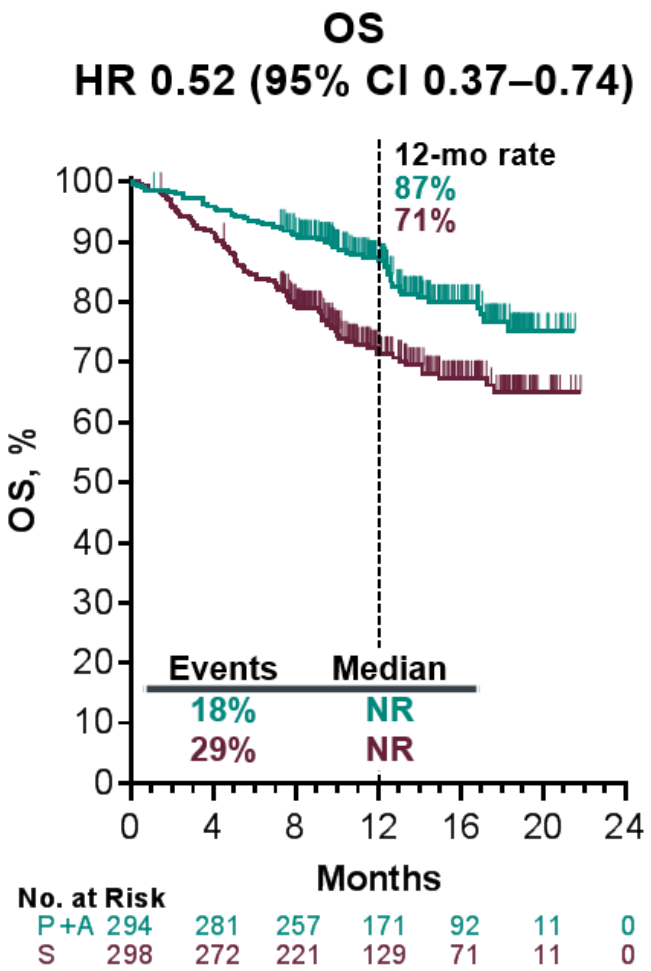
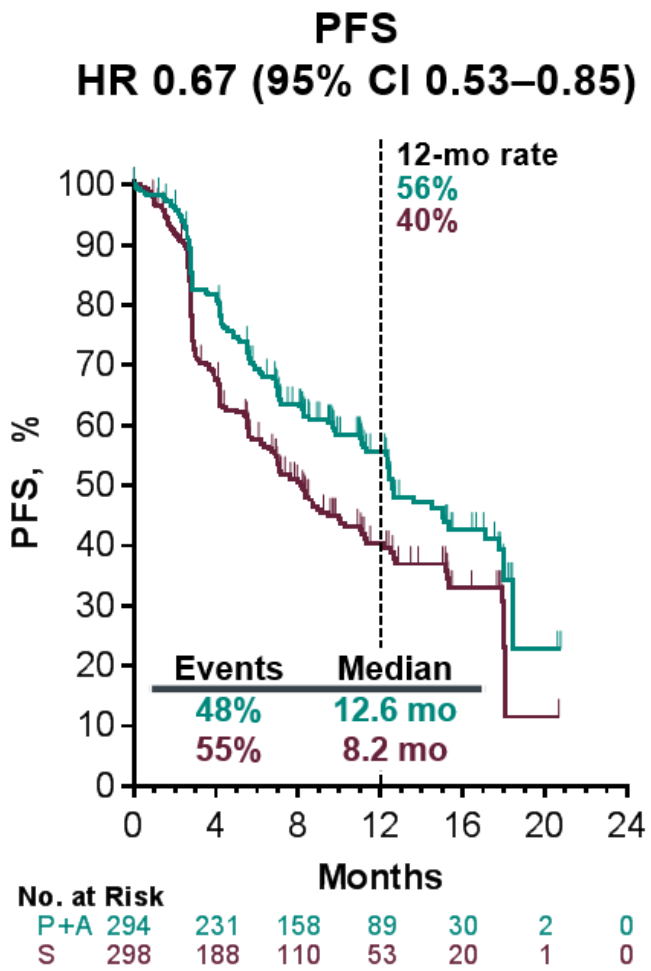
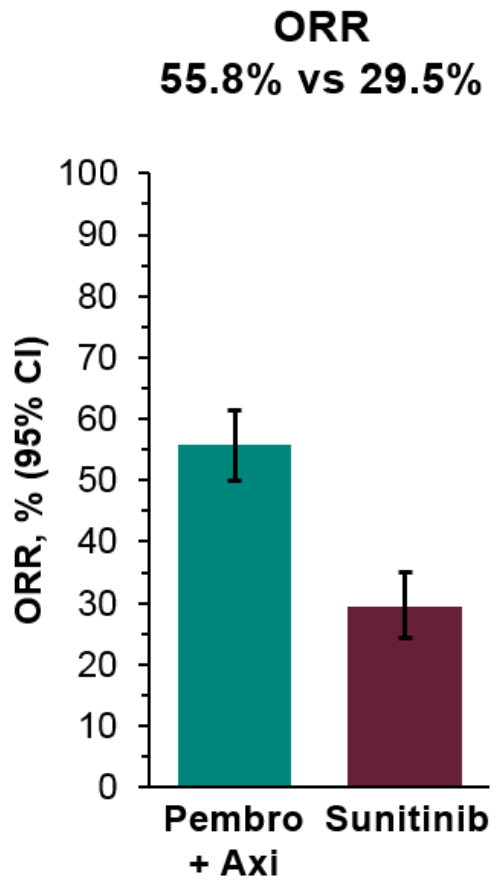
KN426: Axitinib + Pembrolizumab for Intermediate/Poor Risk







Rini et al. ASCO. 2019

Ipi + Nivo: Updated OSby IMDC Risk (minimum follow up 30 months)

Intermediate/poor risk

Median OS, months (95% CI)

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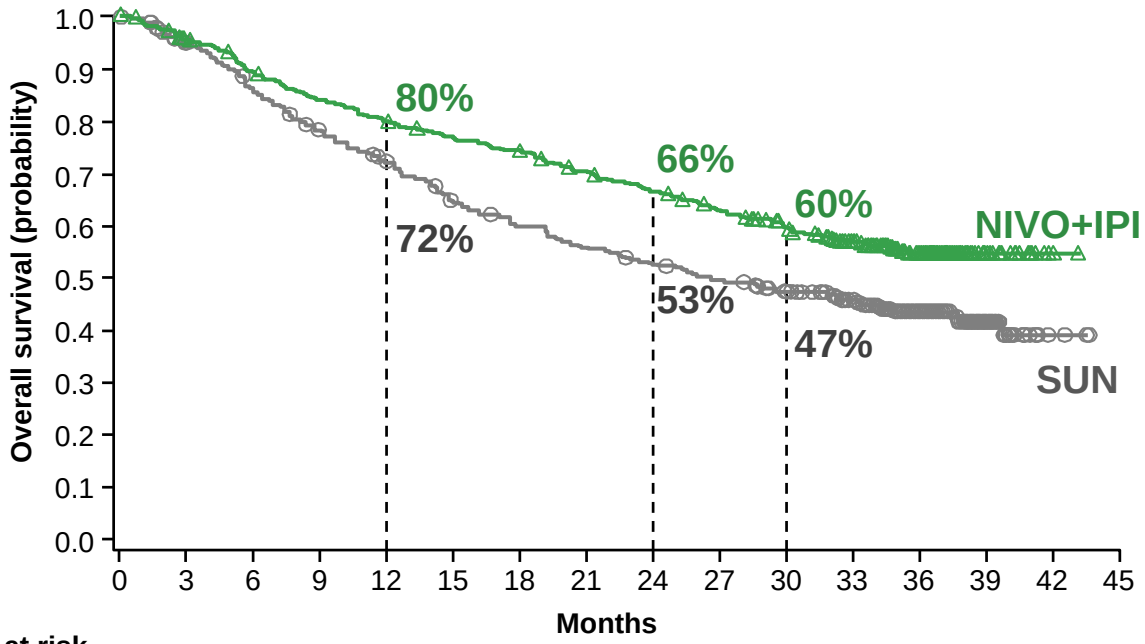

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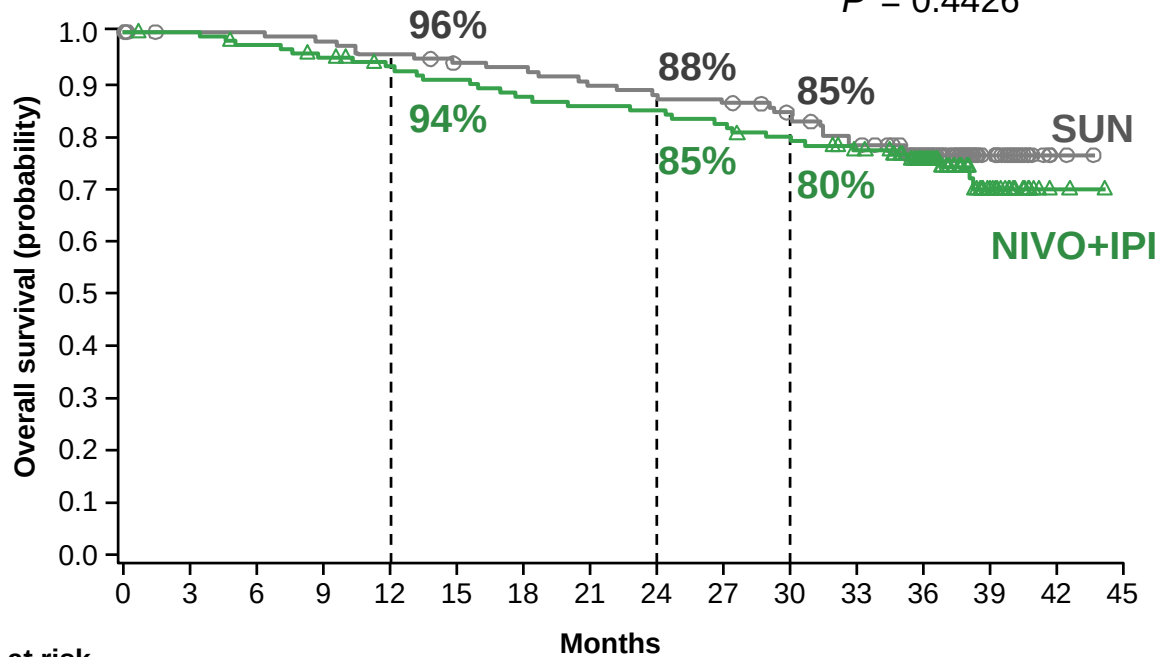

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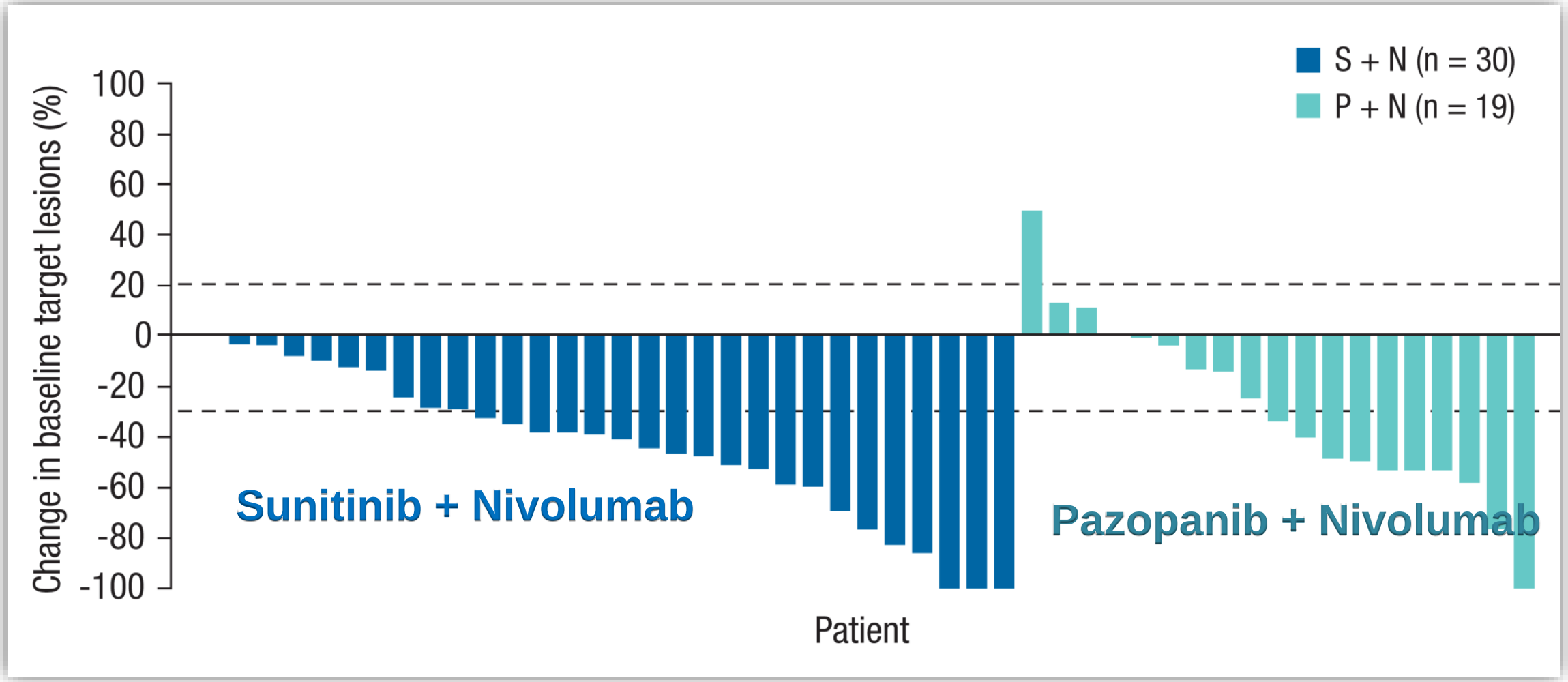
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Tannir et al. GU ASCO. 2019

Now 44 yo man with Clear Cell RCC

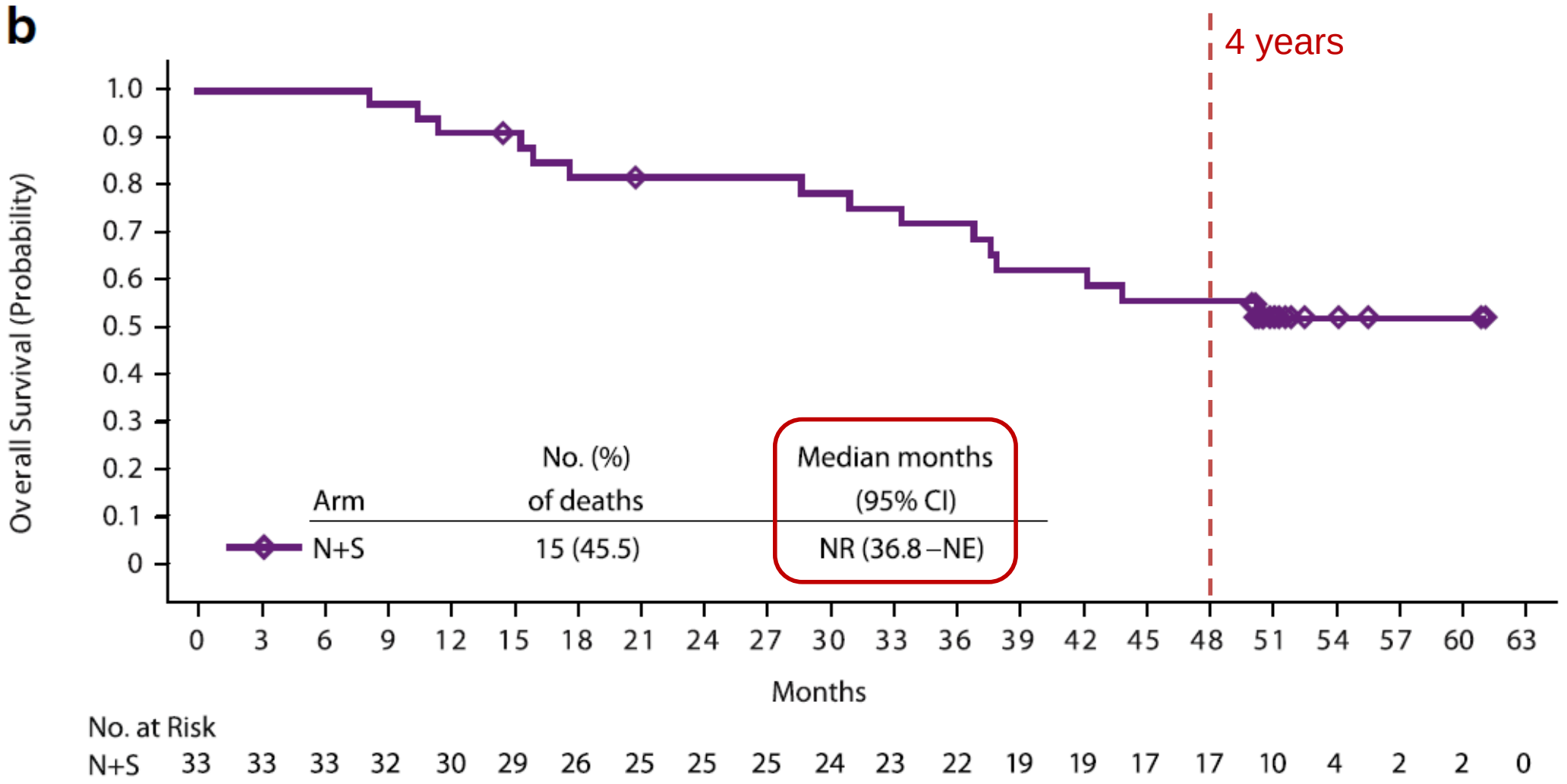
- Started on phase Ib study of axitinib + nivolumab
  - Near resolution of lung metastases at first scan
  - Pembrolizumab discontinued at 2 years
  - Axitinib discontinued at 3.5 years
- Response maintained to date at 4 years
- The patient asks – how long will my cancer stay controlled?

Learning for previous studies with combination Nivolumab + Sunitinib or Pazopanib



Amin A, et al. ASCO 2014, ESMO 2014, KCA 2014

Long term follow up: nivolumab + sunitinib



Amin et al. Journal for ImmunoTherapy of Cancer (2018)

Conclusions

- Until we can cure kidney cancer, our goal remains to keep our patients alive and feeling well for as long as possible.
- With many choices in advanced kidney cancer, careful consideration of multiple factors is required at each decision-point
  - What is the rate of growth of the cancer – can this be observed?
  - The IMDC Risk category can help guide selection of single vs. combination
  - Other health conditions are important to consider: vascular or autoimmune disease can increase risk of side effects for certain treatments
  - What do you, the patient, prefer? What are your values?
- Following patients on treatment for many years, or patients who stop treatment, will give us information on what treatments are best and how long we need to use them for.

THANK YOU