Advanced RCC: Are we Curing the Incurable?



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imdc

Disclosures

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Almost everyone gets a doublet first-line

Definite success with doublets.

No success with triplets yet.

We can’t predict who should get monotherapy

International mRCC Database Consortium

17,150 patients with treated metastatic RCC from 50+ international institutions

University of Calgary
Sunnybrook Health Sciences Centre
UHN Princess Margaret Cancer Centre
University of Alberta
Stanford Medicine
uOttawa
Western University · Canada
GONORTE Grupo Oncológico
Dana-Farber Cancer Institute
University of Michigan
Barbara Ann Karmanos Cancer Institute
Peter Mac — Peter MacCallum Cancer Centre Victoria Australia
BC Cancer Agency — Care + Research
CancerCare Manitoba
UC San Diego
Monash University
UZ Leuven
Dalhousie University — Inspiring Minds
Universität Greifswald — Wissen lockt. Seit 1456
London Health Sciences Centre — Caring for You. Innovating for the World.®
Beth Israel Deaconess Medical Center
Auckland District Health Board — Te Toka Tumai
Huntsman Cancer Institute — University of Utah
National Cancer Centre Singapore — SingHealth
Aarhus University Hospital
Hellenic Republic — National and Kapodistrian University of Athens
IAF — Instituto Alexander Fleming
Cleveland Clinic
Università di Pavia
McMaster University
NHS — Barts Health NHS Trust
ASAN Medical Center
Yonsei University Health System
onko zentrum zürich
UT Southwestern Medical Center
Médica Sur — Excelencia médica, calidez humana.
Netherlands Cancer Institute — Antoni van Leeuwenhoek
BWH — Brigham and Women's Hospital — A Teaching Affiliate of Harvard Medical School
Italy
公益財団法人がん研究会 — Japanese Foundation for Cancer Research
City of Hope
CKCis — Canadian Kidney Cancer Information System
KRAB — Kidney Cancer Australian Registry and Biobank
Hospital Universitario 12 de Octubre — SaludMadrid
St Claraspital — In besten Händen.
VHIO — Vall d'Hebron Institute of Oncology

www.IMDConline.com

International mRCC Database Consortium

WORKING TOGETHER AGAINST KIDNEY CANCER



IMDC Risk Calculator

Karnofsky Performance status
Is the Karnofsky Performance status < 80%? — No | Yes

Time from diagnosis to treatment
Has it been < 1 year from time of diagnosis to systemic therapy? — No | Yes

Hemoglobin < Lower limit of normal
Usually ~120 g/L (12.0 mg/dL) for females and ~135 g/L (13.5 mg/dL) for males* — No | Yes

Neutrophils > Upper limit of normal
Usually ~7-8 x 10^9/L or 7000-8000/mm^3* — No | Yes

Platelets > Upper limit of normal
Usually ~400-450 cells/µL* — No | Yes

Corrected Calcium > Upper limit of normal
Usually ~2.6 mmol/L or ~ 10.6 mg/dL* — No | Yes

First line | Second line | Third line | Fourth Line | First line non-clear-cell

Instructions

How to Use | IMDC Criteria | References

How to Use

- For use in patients with mRCC for prognostication and treatment selection.

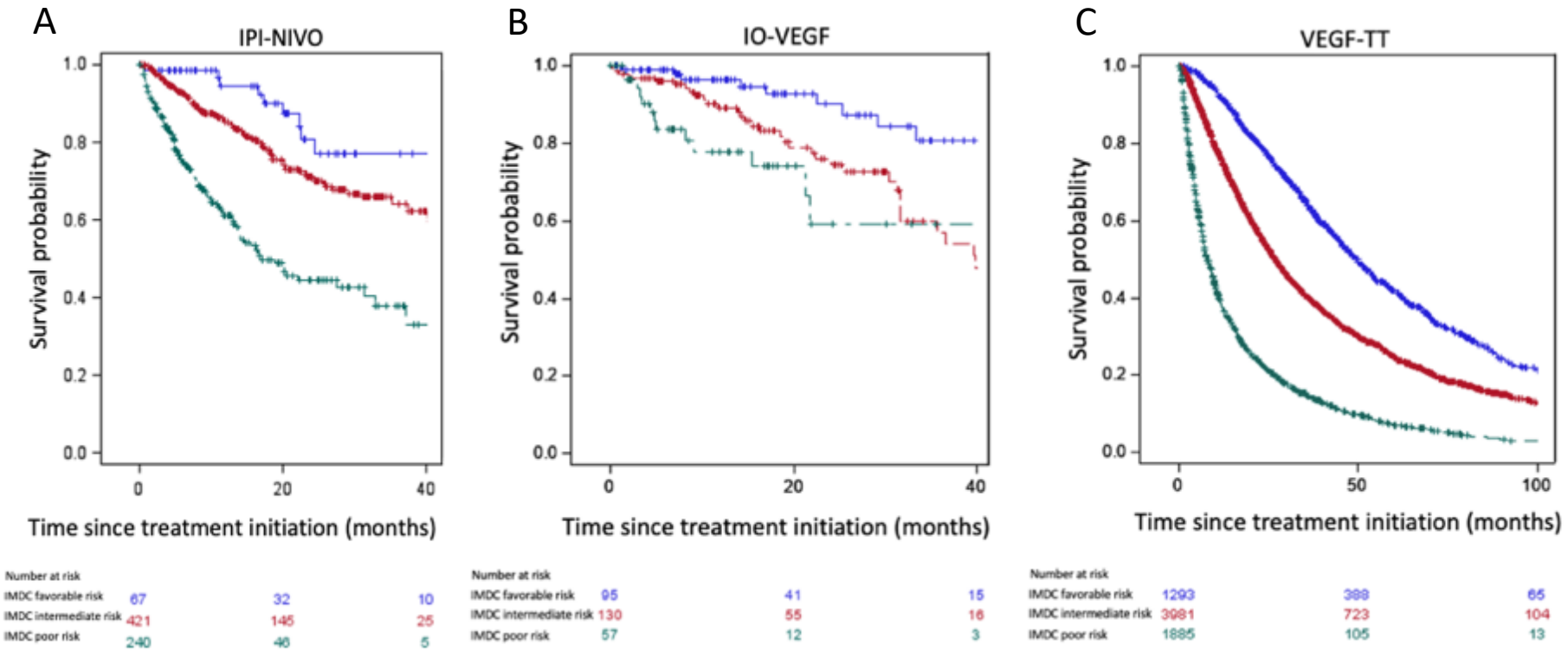
- Select Yes for each risk factor present, then select the setting of interest: first line, second line, third line, fourth line, or first line non-clear-cell. The risk group and corresponding estimated median survival in the TKI era will be displayed at the bottom of the calculator.

- Use baseline factors at the start date of the current line of systemic therapy, except for the "time from diagnosis to systemic therapy" criterion, which is always relative to first-line therapy.

- Always use albumin-corrected calcium concentration.

- These are population medians only and are not meant to guide or

IMDC OS Benchmarks Improved With IO Combinations





Overall survival by IMDC favorable (blue), intermediate (red), and poor (black) risk for (A) IPI-NIVO (log-rank $p < 0.0001$), (B) IO-VEGF (log-rank $p = 0.0003$), and (C) VEGF-TT (log-rank $p < 0.0001$). IPI-NIVO is not indicated in favorable risk and must be interpreted with caution.

Ernst Matthew et al Eur Urol 2023

Choices

Ipi/Nivo

Len/Pembro

Cabo/Nivo

Axi/Pembro

Choices

Ipi/Nivo	Len/Pembro	Cabo/Nivo	Axi/Pembro
VEGF Monotherapy	Active Surveillance	Metastatectomy or SBRT	Cytoreductive Nephrectomy

IMDC first-line comparisons: IPI NIVO vs IO VEGF in int/poor risk mRCC

D Maj et al GU ASCO 2025

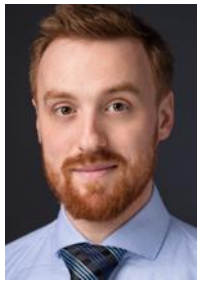


Table 1: Baseline Characteristics

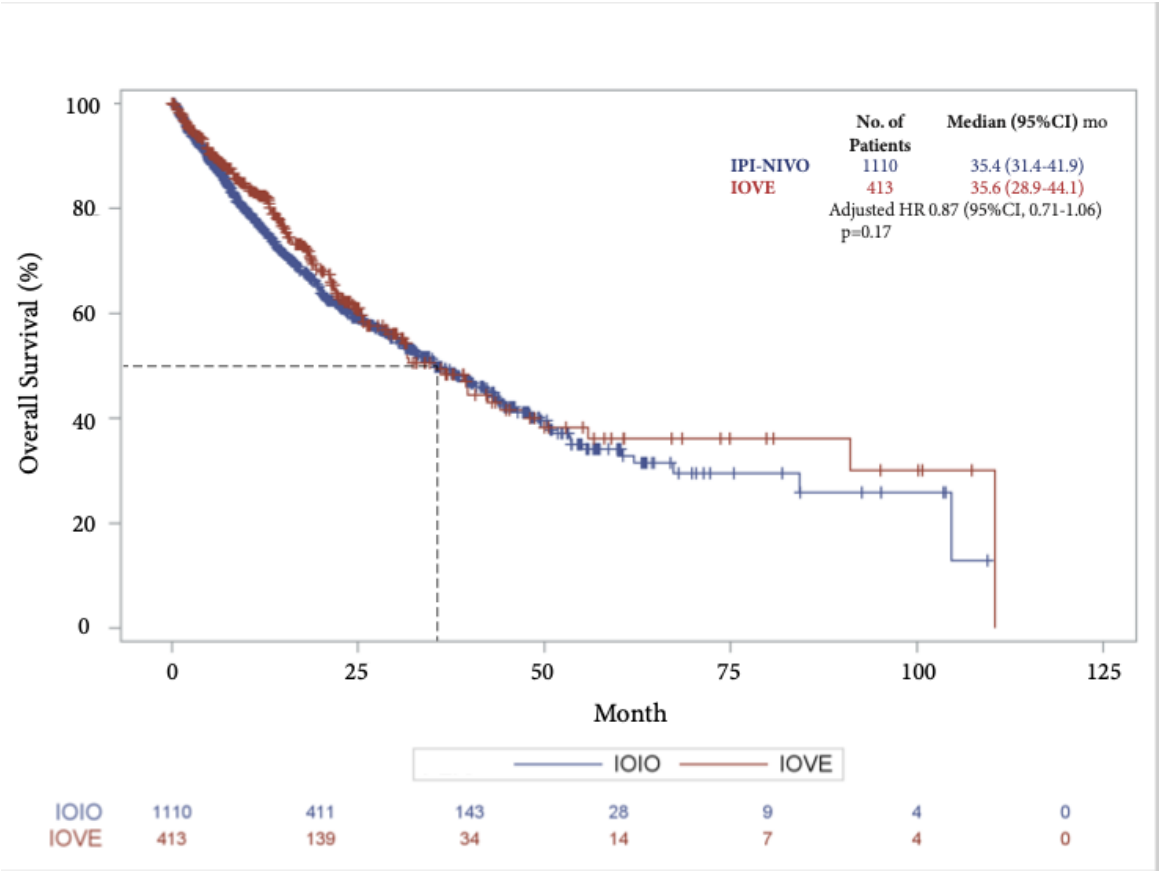
Characteristic, N(%)	IPI-NIVO N = 1110	IOVE N = 413	P-Value
Male	808 (73)	303 (73)	0.82
Age Over 65	287 (26)	132 (32.0)	0.02
IMDC Intermediate/Poor Risk	730/280 (66/34)	274/139 (66/33)	0.83
Pre-Existing Autoimmune Condition	16 (2.6)	12 (4.6)	0.13
Non-Clear Cell Histology	139 (16)	57 (16)	0.84
Sarcomatoid	147 (21)	50 (17)	0.14
Nephrectomy	613 (55)	239 (58)	0.37
Greater than 1 Site of Met	814 (81)	321 (82)	0.46
Brain Metastasis	90 (8.4)	23 (5.7)	0.08
Bone Metastasis	373 (34.3)	173 (43)	0.003
Liver Metastasis	218 (20)	65 (16)	0.06
Lung Metastasis	751 (69)	279 (68)	0.84

IMDC first-line comparisons: IPI NIVO vs IO VEGF in int/poor risk mRCC



Table 2: Objective Response Rate

	IPI-NIVO N = 1110	IOVE N = 413	P-Value
ORR	39.1%	48.0%	0.004
CR	6.4%	4.2%	
PR	32.2%	45.6%	
SD	31.6%	32.8%	
PD	29.9%	22.6%	



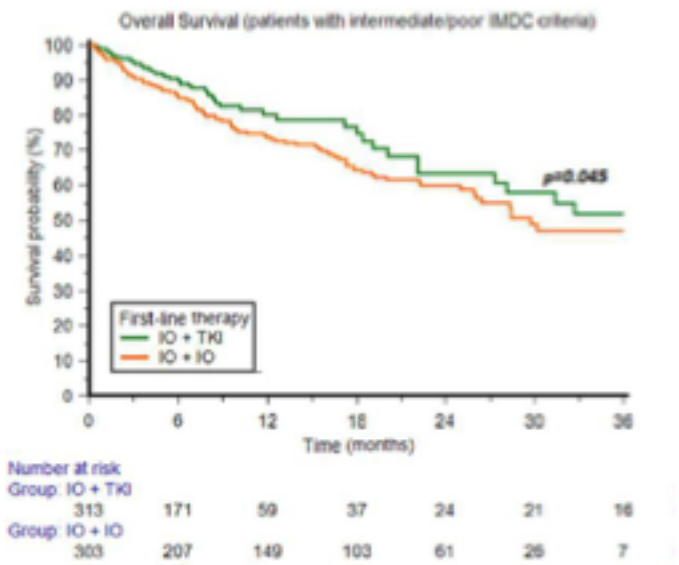
OS HR Adjusted for IMDC, brain, bone, liver mets:
HR 0.87 (95%CI 0.71-1.06, p=0.17)

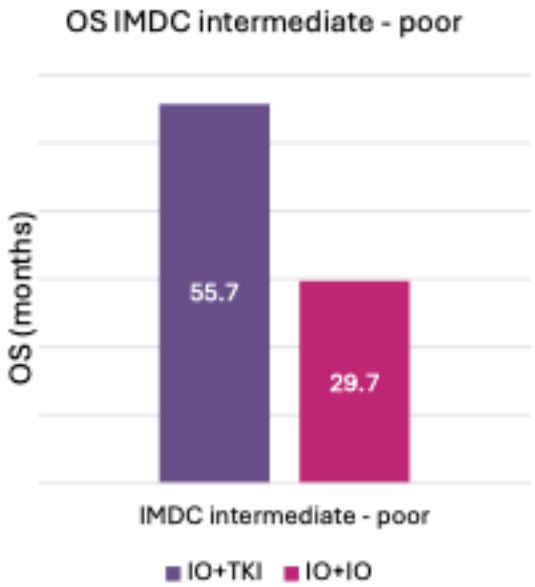
D Maj et al GU ASCO 2025

ARON-1: IO+TKI vs IO+IO subgroup analyses:
OS in intermediate + poor IMDC patients by treatment type

Intermediate – poor IMDC status OS: IO+TKI vs IO+IO

Intermediate – poor IMDC status IO+TKI vs IO+IO (p=0.045)	
IO+TKI	**55.7** (27.3 – 60.8)
IO+IO	29.7 (25.9 – 40.1)





N = 616

At the time of data cut off;
- nivolumab plus ipilimumab was ongoing in 158 of 313 pts and the median follow up time for this combination was 18.8 months (95% CI 15.5-88.8).
- TKI+IO was ongoing in 307 of the 416 pts with a median follow up time of 17.6 months (95% CI 16.9-64.3).

CABOZANTINIB +NIVOLUMAB

Sartoni 2023: Targeted Oncology (18:559-570)

Choosing Therapy Based on Prognosis & Beyond

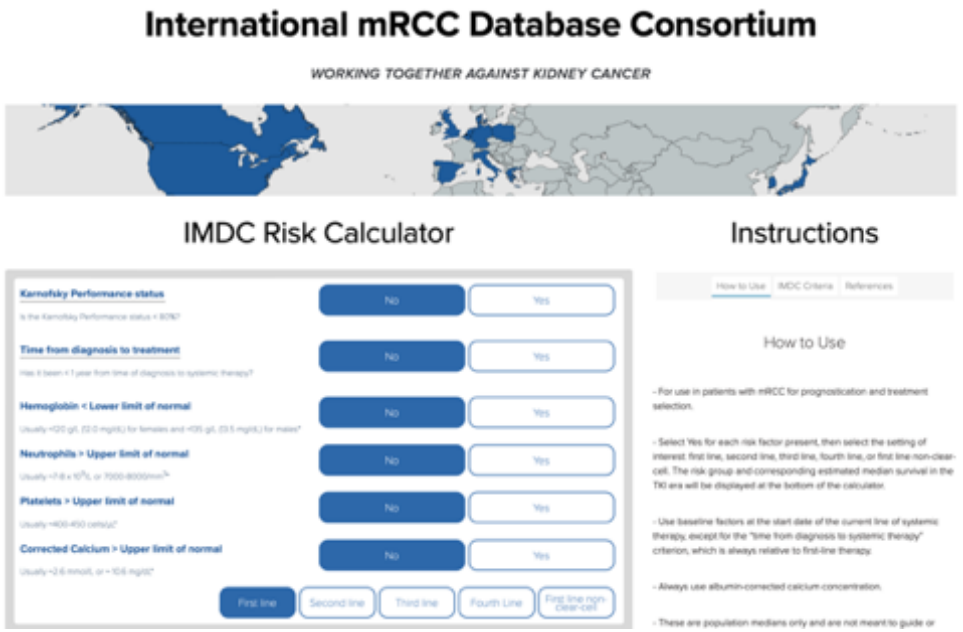
Favourable | **Intermediate** | **Poor**

Asymptomatic

Oligometastases

Healthy

Non-Sarcomatoid



Symptomatic

High burden mets

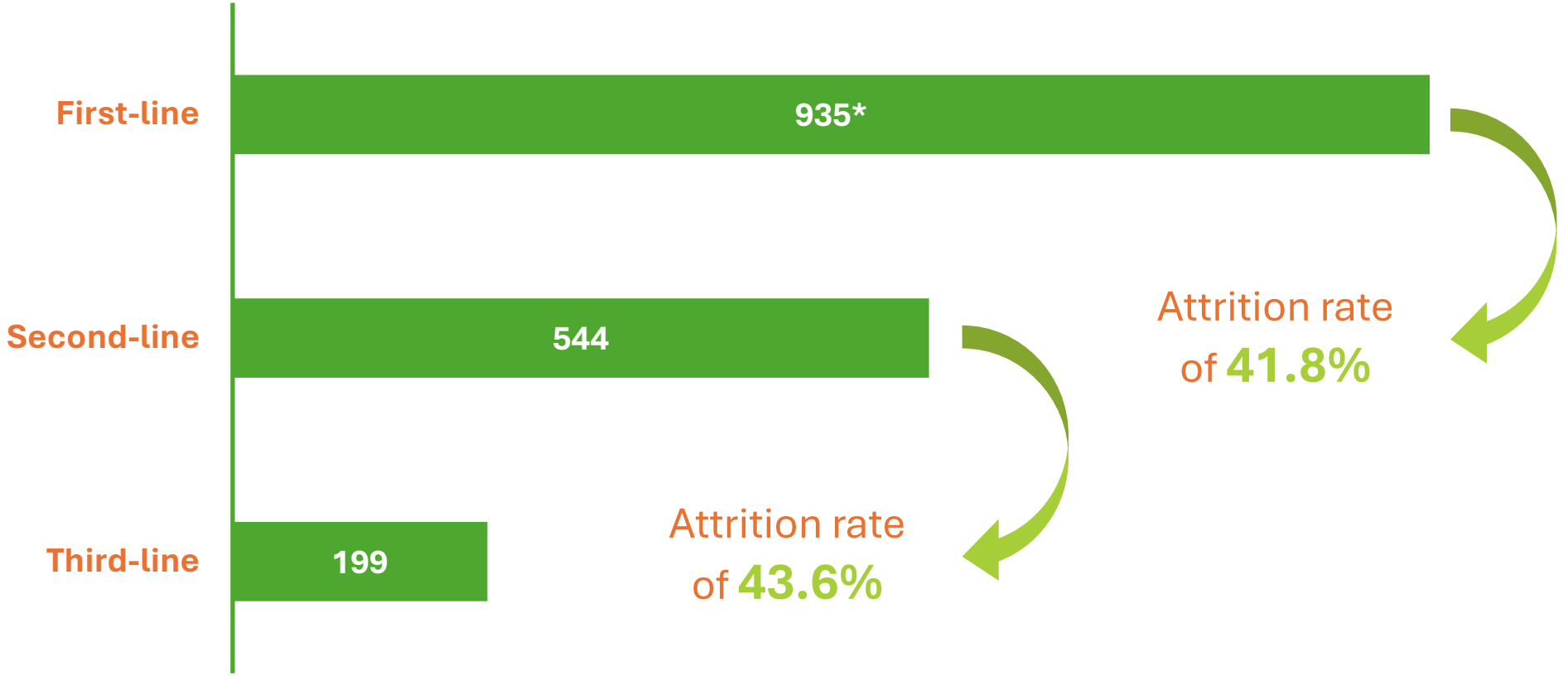
Comorbidities

Sarcomatoid

mRCC Patients Attrition Receiving Systemic Treatment

Number of patients receiving first-, second-, and third-line therapy for mRCC

IMDC analysis of treatment patterns in 1411 mRCC patients



*Patients eligible for second-line treatment.
IMDC, International mRCC Database Consortium; mRCC, metastatic renal cell carcinoma.
Lemelin A et al. *Clin Genitourin Cancer* 2026;24(1):102484.

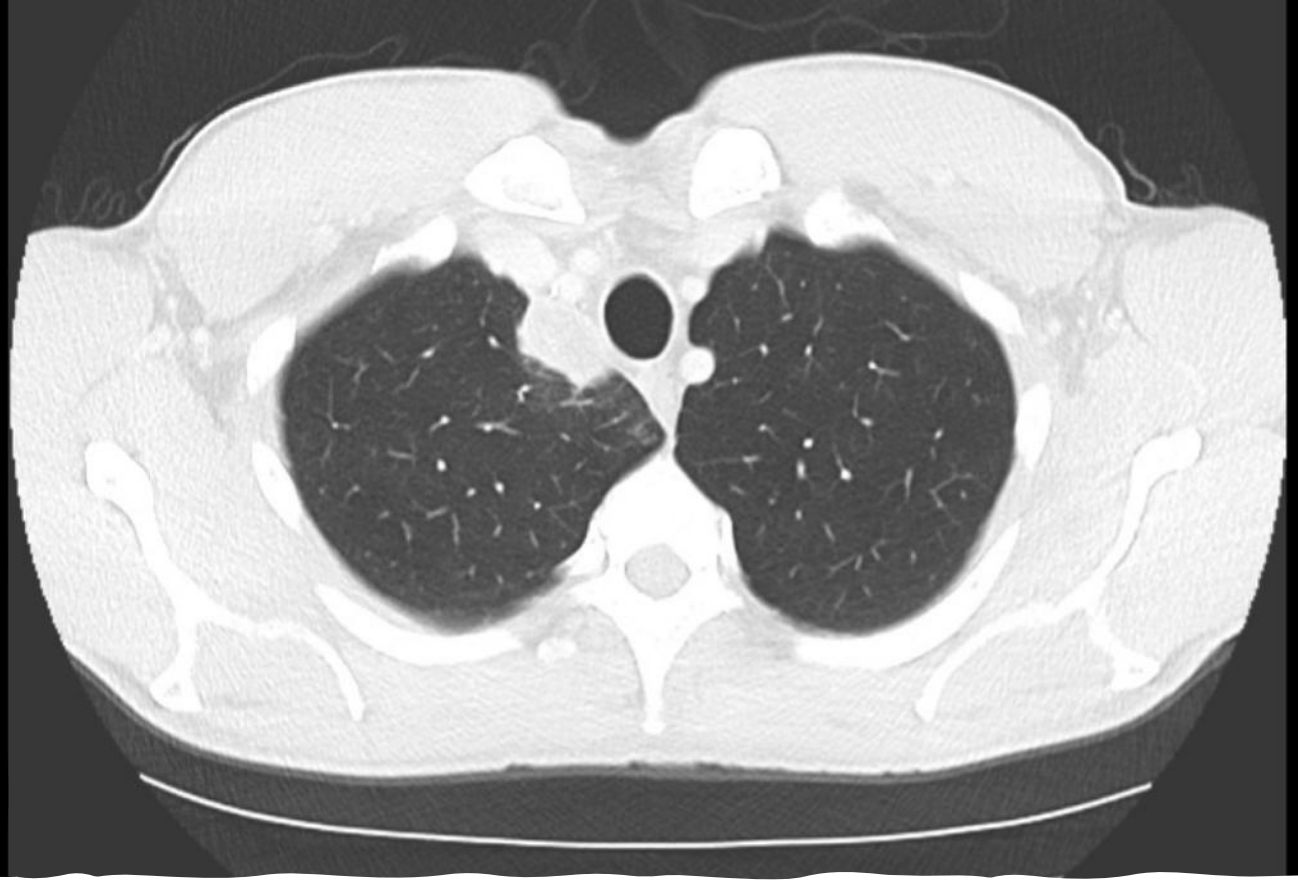
Case 1

Metastatic Renal Cell Carcinoma

Case Presentation

- 45 y.o. male with IMDC poor risk stage IV metastatic renal cell carcinoma with sarcomatoid features to the lung
- Flank pain, Hematuria, Night sweats, weight loss, looks sick
- Kidney biopsy: ccRCC with sarcomatoid features
- Huge kidney mass and multiple lung metastases up to 3 cm, left renal vein tumor thrombus and intra-abdominal LN. CT Head normal.
- Hb 86, Plt 532, Ca 2.38N, Neut 7.3, KPS 70, DxTx < 1 year
- NIVO/IPI initiated November 4, 2023, tolerated well

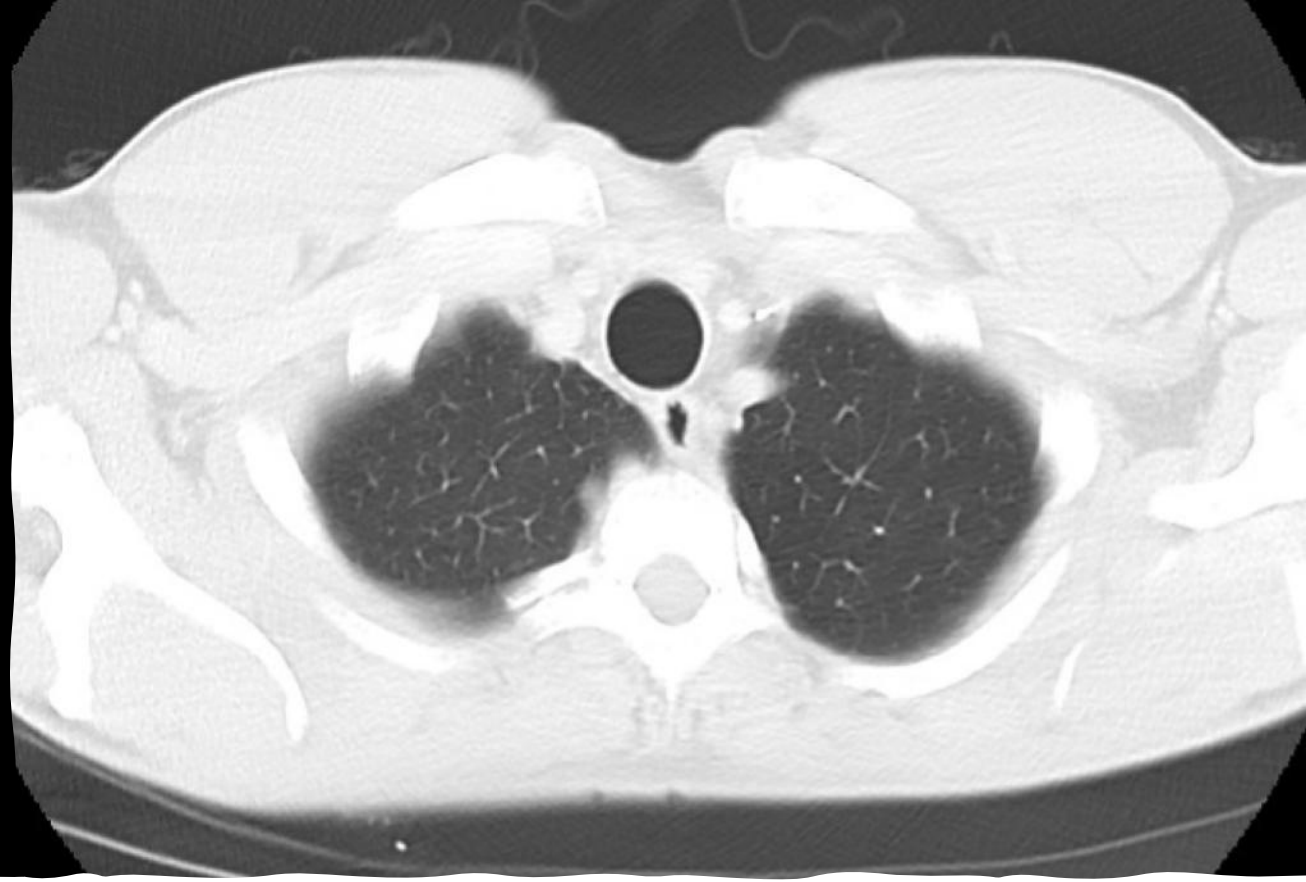




Nov 2023

- Large kidney mass, lung nodules, retroperitoneal lymph nodes and renal vein thrombus

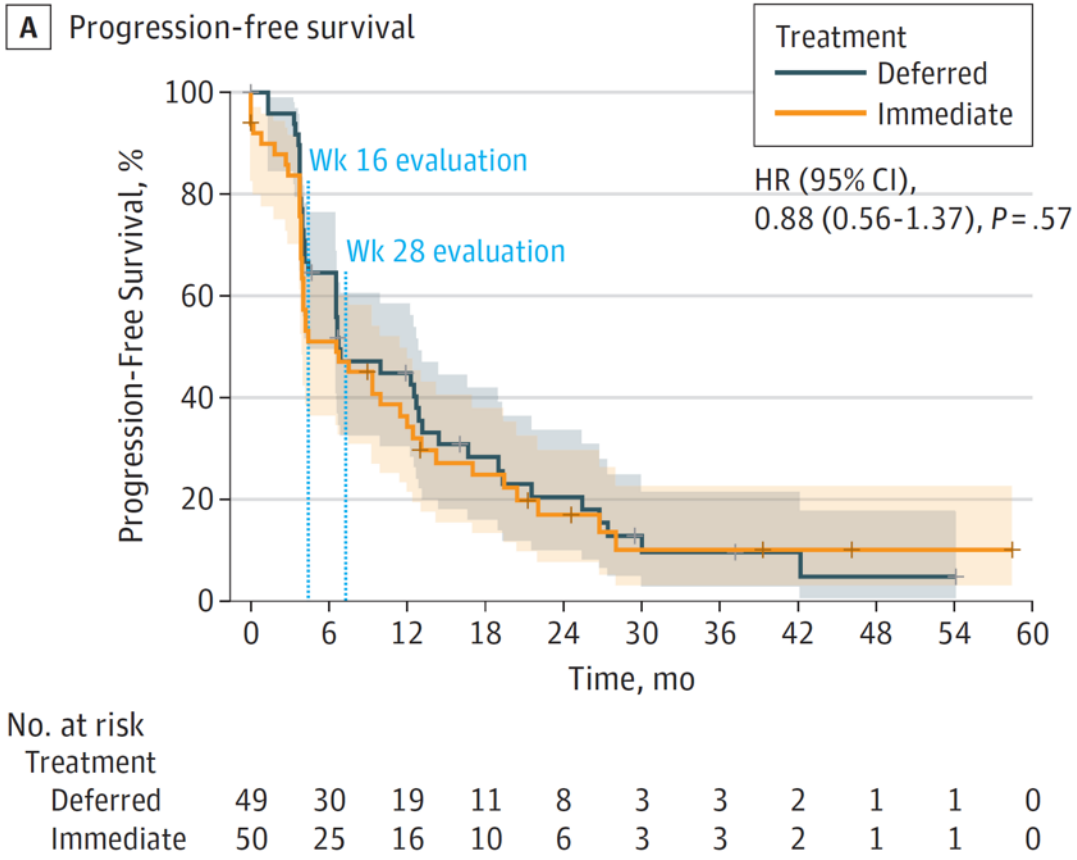


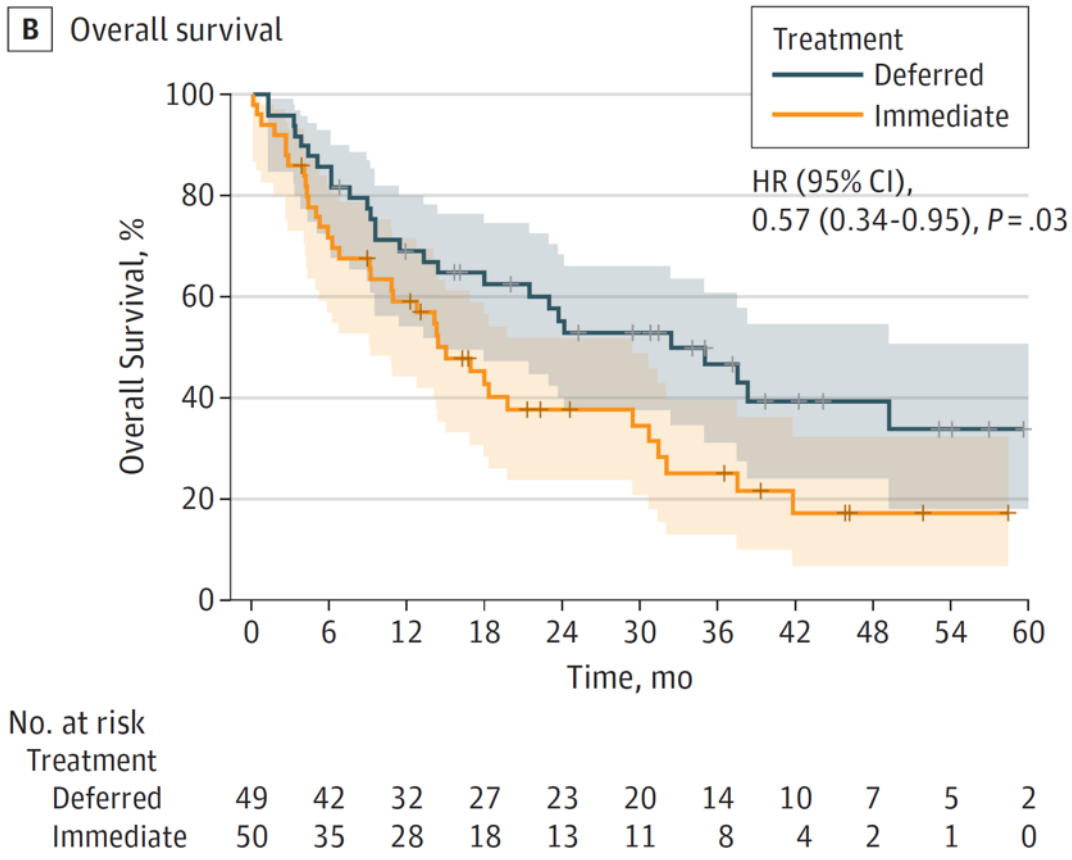


Jan 2024

- Kidney became more necrotic and lung nodules shrank and eventually disappeared

SURTIME: Delayed Cytoreductive Nephrectomy





Patients with Deferred Nephrectomy are well-selected, so have better outcomes

Bex et al JAMA Oncol 2018

Delayed Cytoreductive Nephrectomy to CR

Waited a couple CT scans to ensure durable excellent response while on single agent maintenance nivolumab

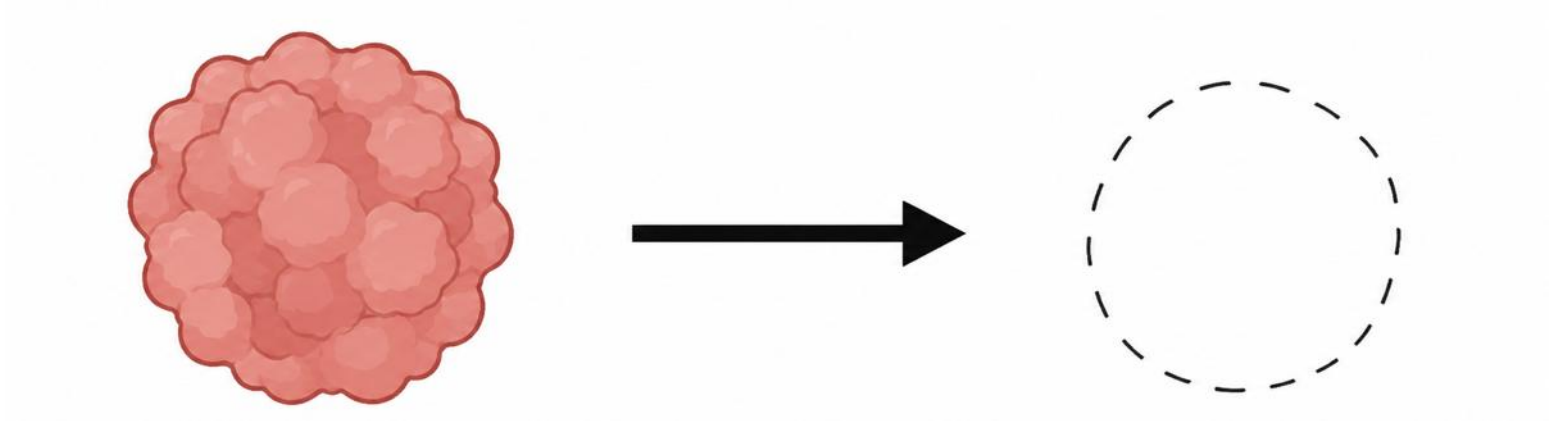
Cytoreductive nephrectomy October 21, 2024. Pathology showed an ccRCC with sarcomatoid features, WHO grade 4/4, 8.9 cm in size with extensive necrosis; ypT3aNx

Continued on maintenance nivolumab, CT continues to be in complete response

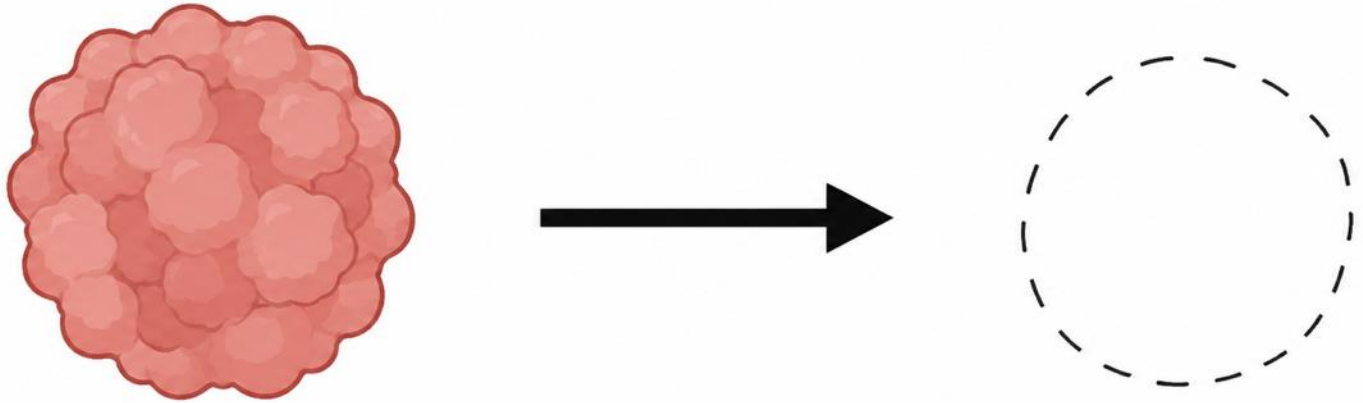
We have discussed nivolumab discontinuation but he is fearful of recurrence.

Eventually stopped nivolumab after 3 normal CT scans and remains disease-free

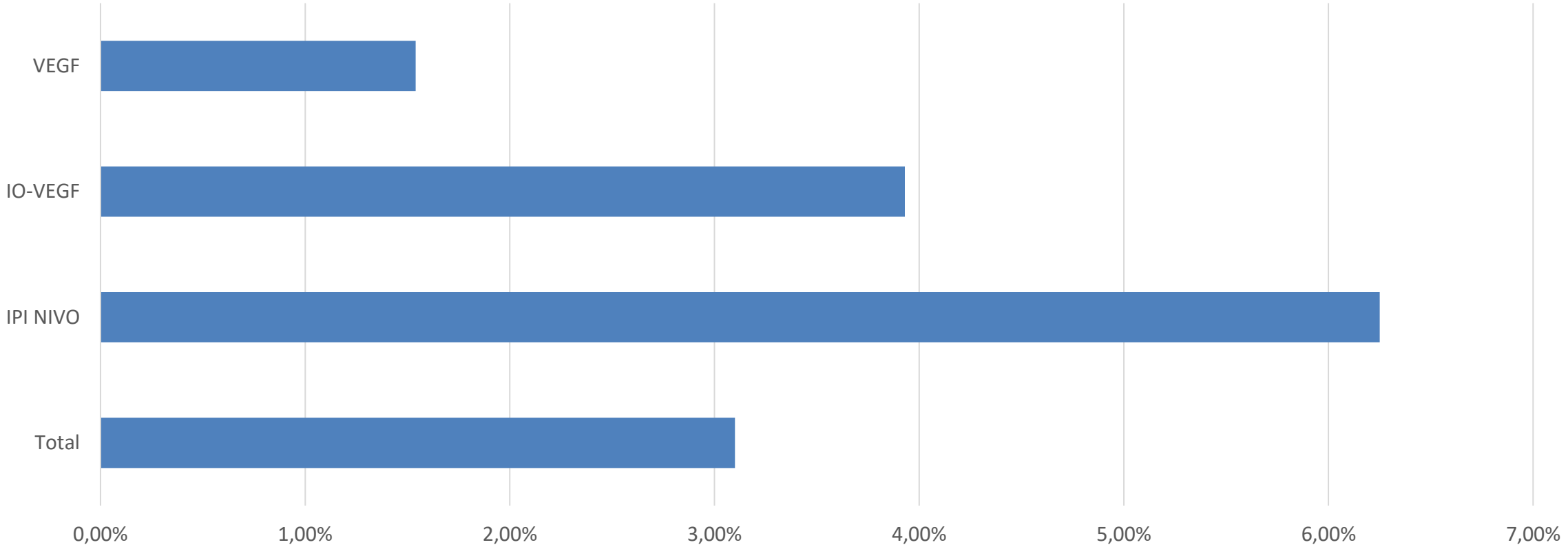
Complete Responders







Complete Responders



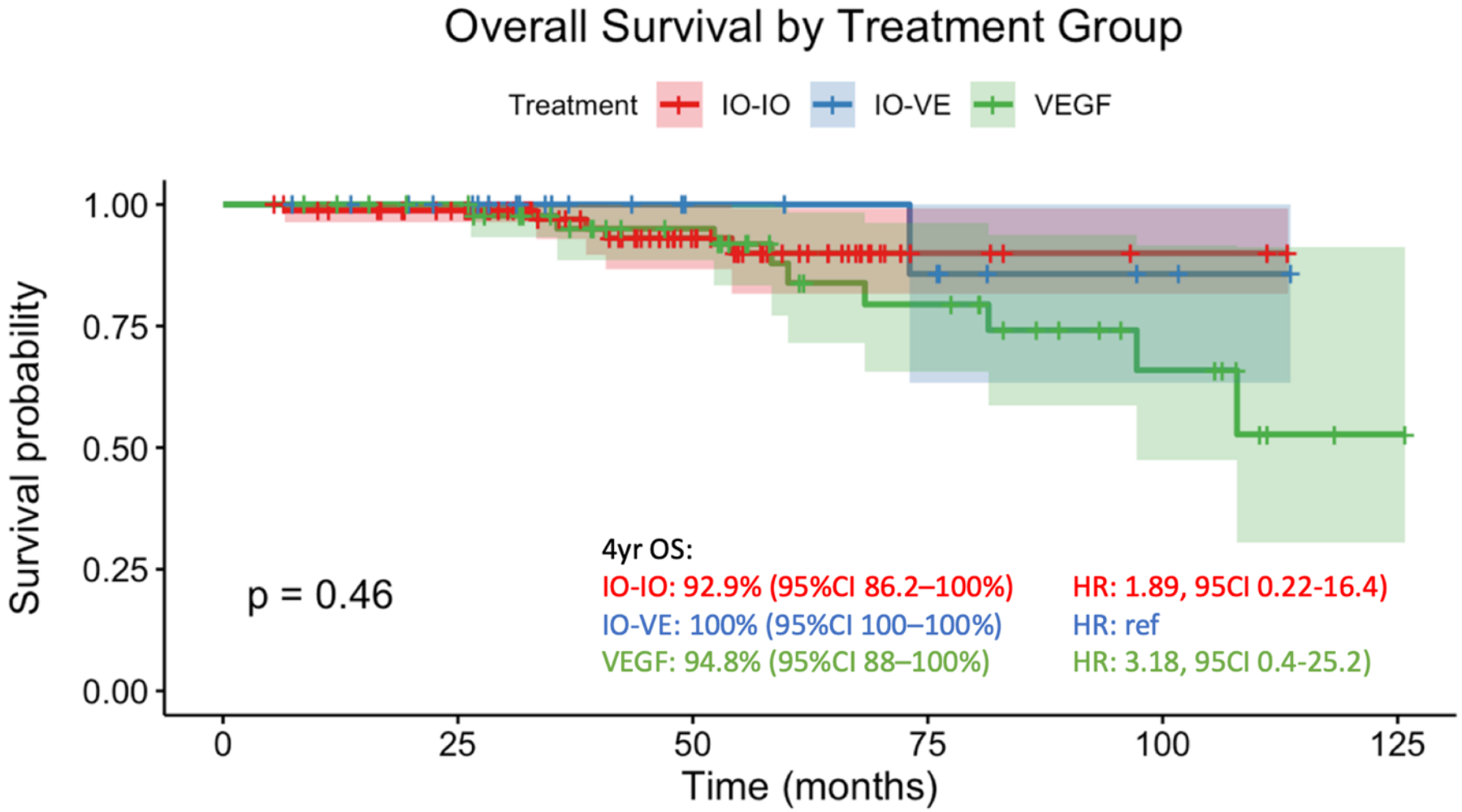
Zarba et al Clin GU Cancer 2026

Complete Responders to IO Combos

	IO-IO 82	IO-VE 24	VEGF 48	P value
Mean age (SD)	60.6 (10.5)	57.1 (11.1)	59.8 (10.0)	0.353
Male (%)	65 (79.3)	15 (62.5)	34 (70.8)	0.214
Nephrectomy (%)	74 (90.2)	21 (87.5)	45 (93.8)	0.654
Non-Clear cell (%)	12 (14.6)	0 (0)	3 (6.5)	0.018
More than 1 site of metastasis (%)	52 (63.4)	16 (66.7)	29 (60.4)	0.606
Liver metastasis (%)	10 (12.2)	3 (12.5)	4 (8.3)	0.776
Bone metastasis (%)	8 (9.8)	3 (12.5)	6 (12.5)	0.304
Brain metastasis (%)	6 (7.3)	1 (4.2)	1 (2.1)	0.565
IMDC Risk Fav/Int/Poor (%)	5 (7.7) / 41 (63.1) / 19 (29.2)	4 (16.6)/ 13 (54.2)/ 3 (12.5)	6 (12.5)/ 18 (37.5) / 6 (12.5)	0.120

Zarba et al Clin GU Cancer 2026

Complete responders



Zarba et al Clin GU Cancer 2026

Very Favorable Risk mRCC



imdc

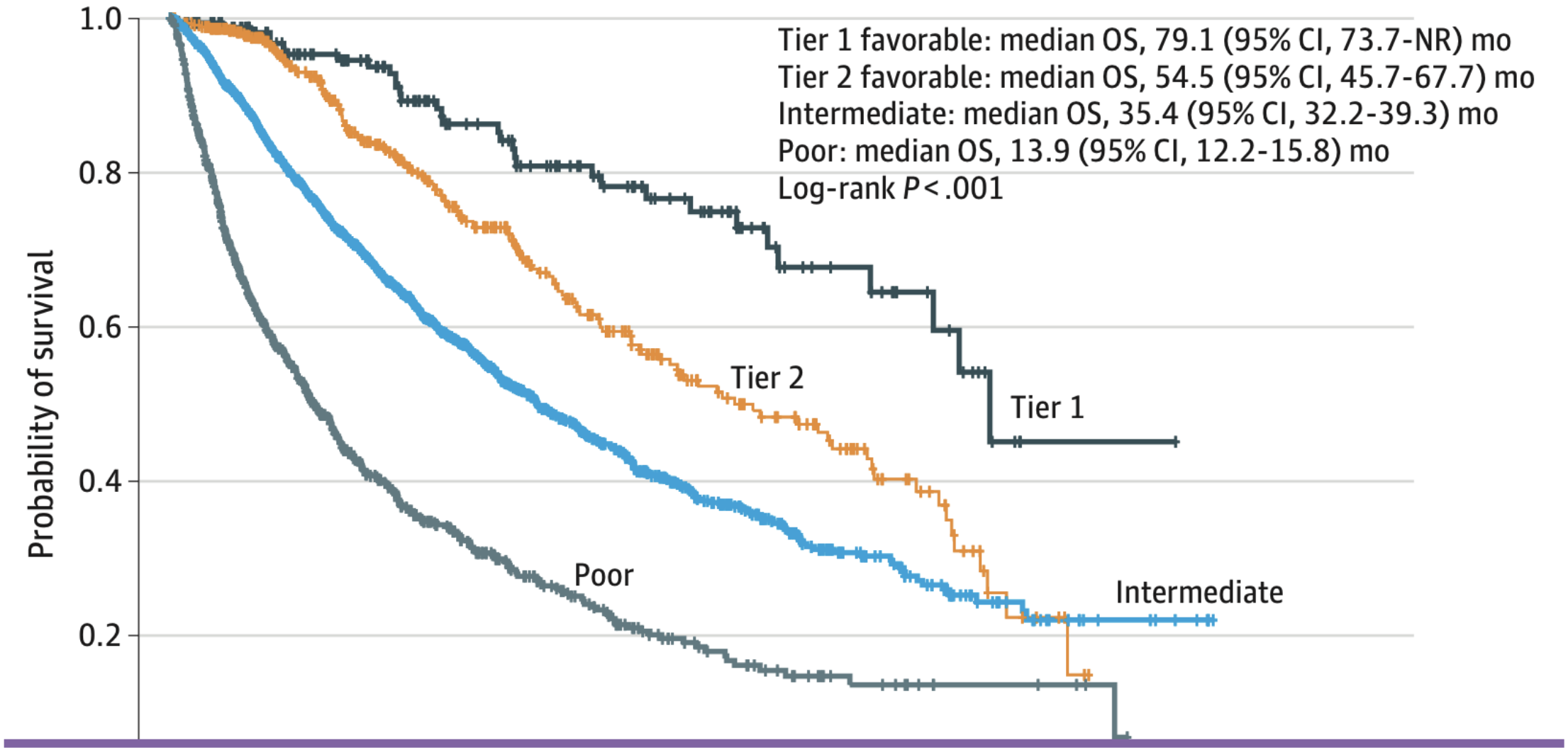
JAMA Network | Open™

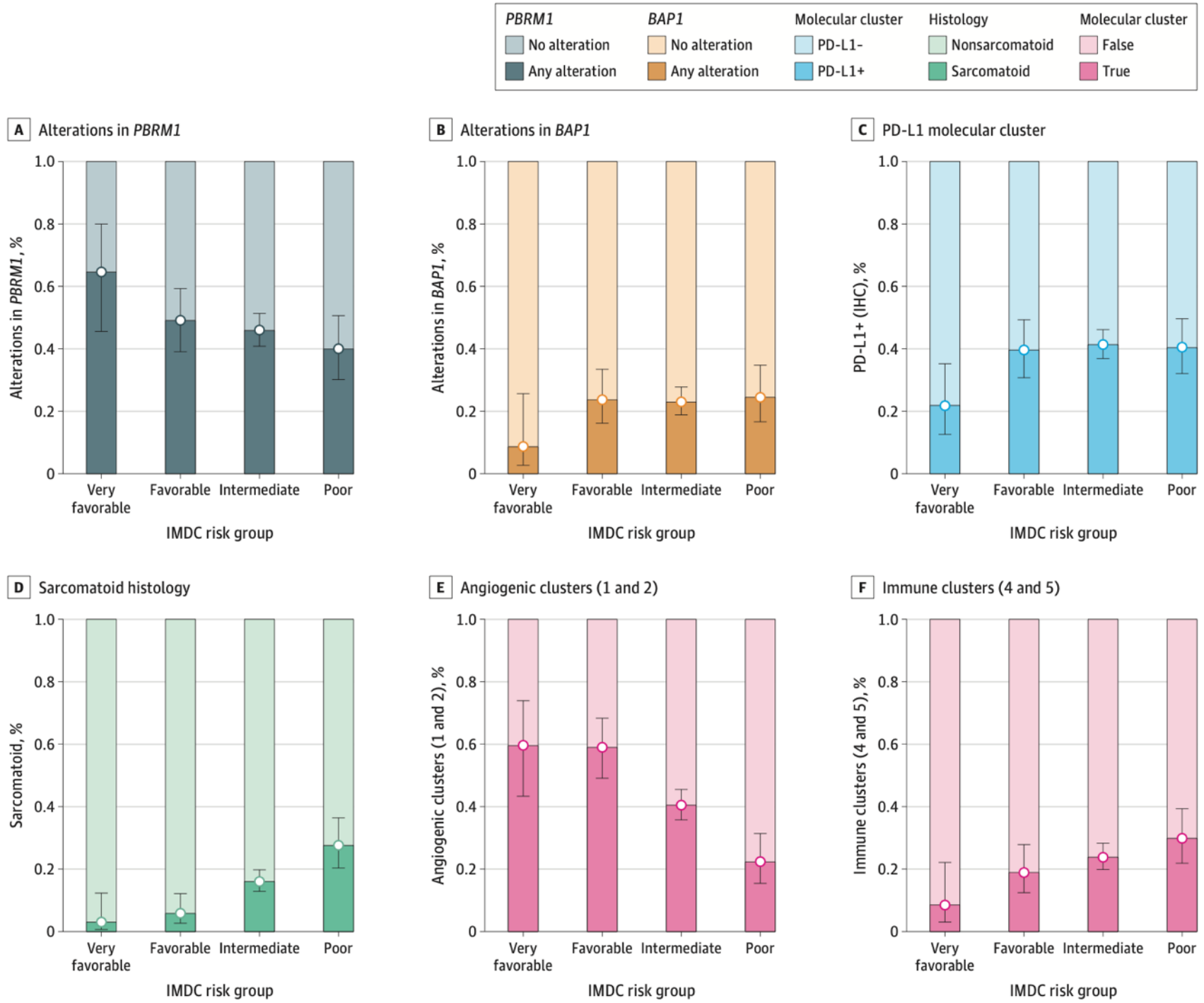
VERY FAVORABLE RISK = FAVORABLE RISK + No Brain Bone Liver mets KPS 90 / 100 Dx – Tx > 3 years

Original Investigation | Oncology

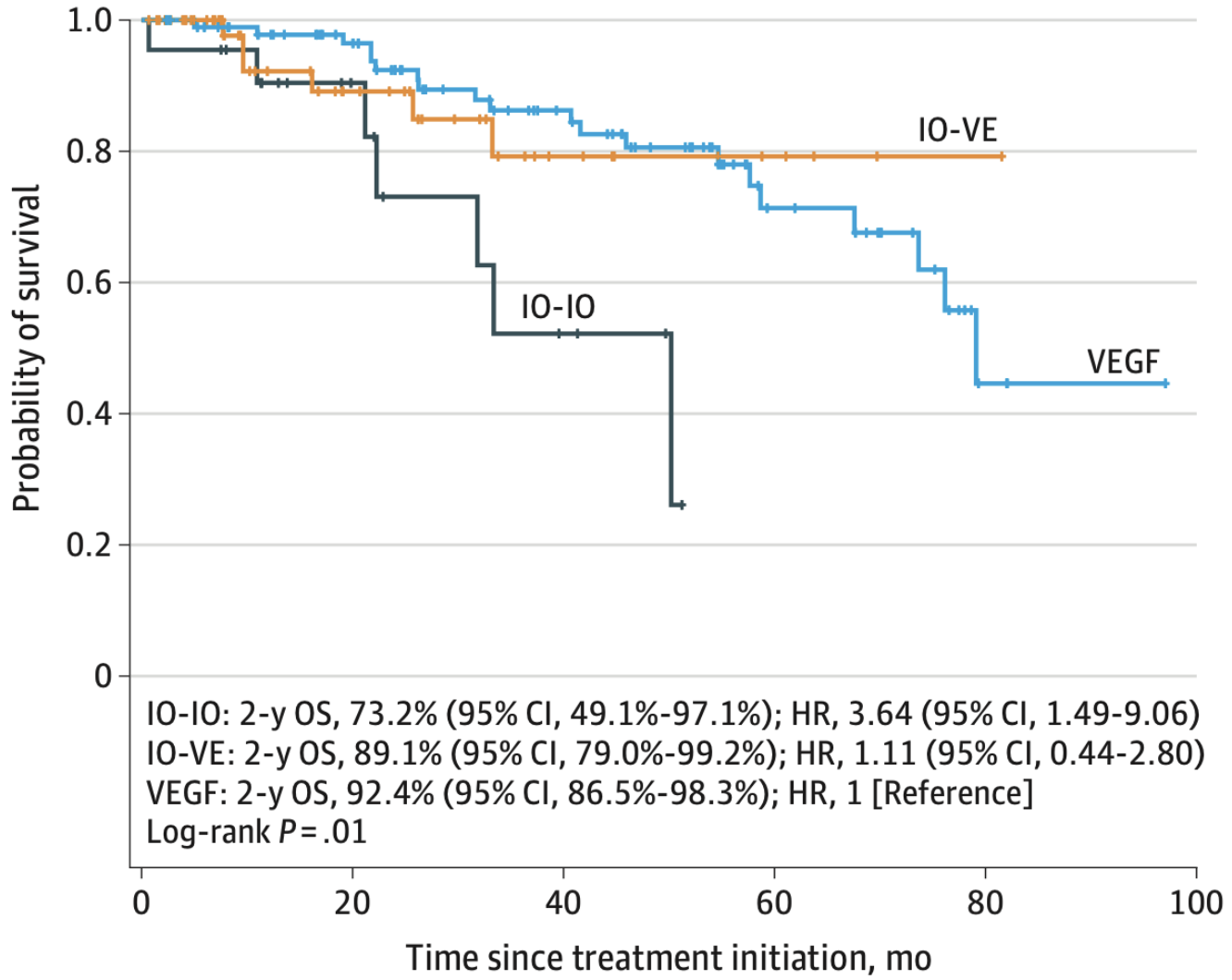
Clinical and Molecular Validation of the Very Favorable IMDC I in Metastatic Renal Cell Carcinoma

Martin Zarba, MD; Eddy Saad, MD; Karl Semaan, MD; Talal El Zarif, MD; Evan Ferrier; Connor Wells, MD; Razane El Hajj Chehad Hedyeh Ebrahimi, MD; Mahrukh Huseni, MBA; Romain Banchereau, PhD; Rana R. McKay, MD; Lori Wood, MD; Benoit Beuselir Kosuke Takemura, MD; Aly-Khan A. Lalani, MD; Haoran Li, MD; Lavinia Anne Spain, MD; Arnoud J. Templeton, MD; Thomas B. Guillermo de Velasco, MD; Toni K. Choueiri, MD; Daniel Y. C. Heng, MD


1.0
0.8
0.6
0.4
0.2
Probability of survival
Tier 1 favorable: median OS, 79.1 (95% CI, 73.7-NR) mo
Tier 2 favorable: median OS, 54.5 (95% CI, 45.7-67.7) mo
Intermediate: median OS, 35.4 (95% CI, 32.2-39.3) mo
Poor: median OS, 13.9 (95% CI, 12.2-15.8) mo
Log-rank P < .001
Tier 2
Tier 1
Poor
Intermediate


PBRM1
No alteration
Any alteration
BAP1
No alteration
Any alteration
Molecular cluster
PD-L1-
PD-L1+
Histology
Nonsarcomatoid
Sarcomatoid
Molecular cluster
False
True
A Alterations in PBRM1
Alterations in PBRM1, %
B Alterations in BAP1
Alterations in BAP1, %
C PD-L1 molecular cluster
PD-L1+ (IHC), %
D Sarcomatoid histology
Sarcomatoid, %
E Angiogenic clusters (1 and 2)
Angiogenic clusters (1 and 2), %
F Immune clusters (4 and 5)
Immune clusters (4 and 5), %
0
0.2
0.4
0.6
0.8
1.0
Very favorable
Favorable
Intermediate
Poor
IMDC risk group

C Tier 1 very favorable risk subgroup



No. at risk

IO-IO	22	11	4	0	[0/NA]	[0/NA]
IO-VE	59	25	10	4	1	0
VEGF	95	74	48	20	3	0

IMDC Spectrum of Disease

Favourable | Intermediate | Poor

More favorable features

VEGF axis important

Better prognosis

IO-VEGF to get better ORR/CR

More poor features

IO more important

Worse prognosis

IO-IO or IO-VEGF if need a response

Case 2

Metastatic Renal Cell Carcinoma

Case Presentation

43 M very healthy

Radical nephrectomy on December 2011 for a pT2 8.5 cm, grade 2/4, clear cell RCC.

In 2025 left chest wall pain for the last 10 months and has been feeling a lump in the area for the last couple of months.

7 cm soft tissue mass in the chest wall, eroding the 10th left rib.

Biopsy confirmed recurrence of ccRCC.

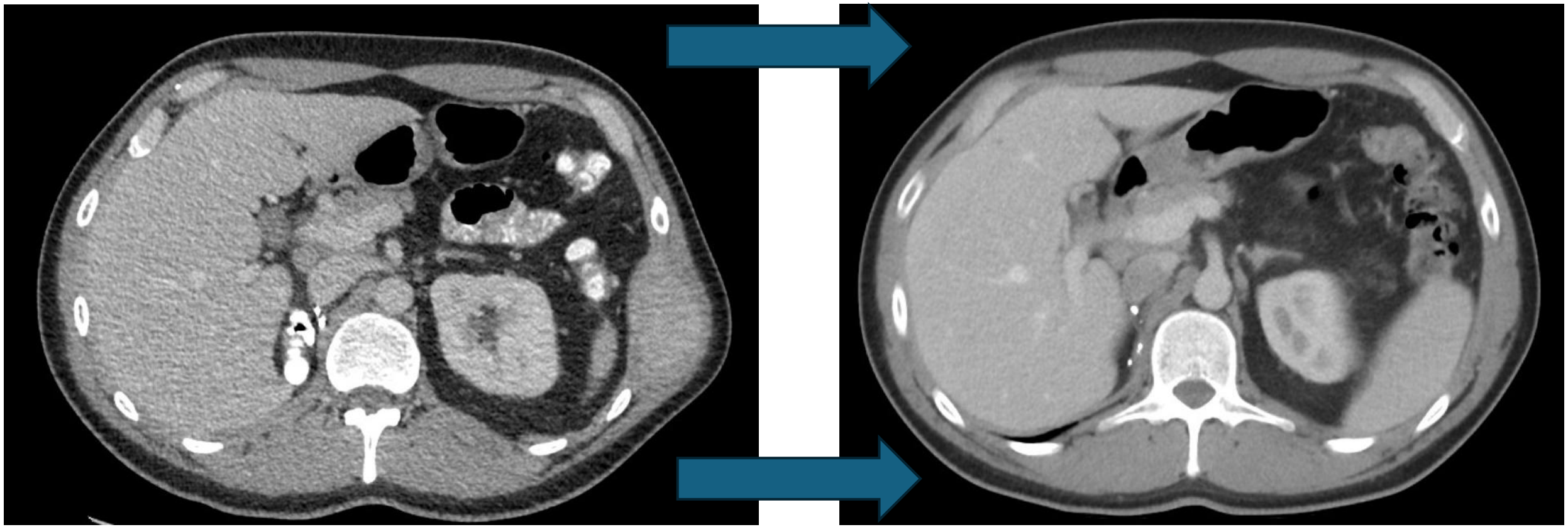
Another metastasis in the sacrum and iliac crest.

IMDC favorable risk

Case Presentation

- Started Lenvatinib 20 mg and Pembrolizumab
- Added zolendronic acid

From March 2025 (7cm) to June 2025 (2cm)
Effect of Lenvatinib / Pembrolizumab



Case Presentation

- Eventually the soft tissue completely disappeared around the rib
- SBRT to the sacrum and iliac bone to consolidate treatment
- Continues on Lenvatinib and pembrolizumab
  - Mild neutropenia and LFT abnormalities so eventually dose reduced to 14 mg daily.

- Do we stop the Lenvatinib? Do we stop the pembrolizumab?
- SBRT provides excellent local tumor control

IMDC Fellows are Awesome



Conclusions

- IOIO and IOVE combinations can have good long-term responses
- Complete responses are rare
- We have quadrupled overall survival in metastatic disease

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