1:30-2:10
KIDNEY CANCER UPDATES

Mayer Fishman, MD PhD

Tampa General Hospital Cancer Institute: Genitourinary Oncology

University of South Florida Morsani College of Medicine

Riverview – Brandon Healthplex -- TGH

Tampa General Hospital Cancer Institute

Learning Objectives

- Recognize available therapies for the treatment of kidney cancer
- Discuss important factors needed to make personalized selections of treatments in different clinical contexts

1:30-2:10 KIDNEY CANCER UPDATES

Kinds of kidney cancer

Kinds of medications

A few biomarkers

Initial medical therapy of advanced disease

VEGF medications

PD-1 combinations

mTOR

HIF2

Checkpoint inhibition

Nephrectomy decisions

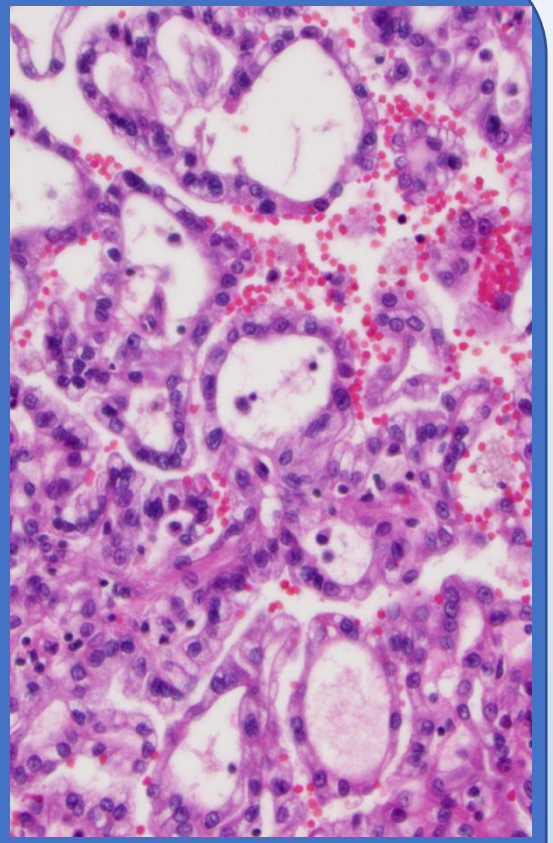
Adjuvant treatments

Challenges in clinical practice

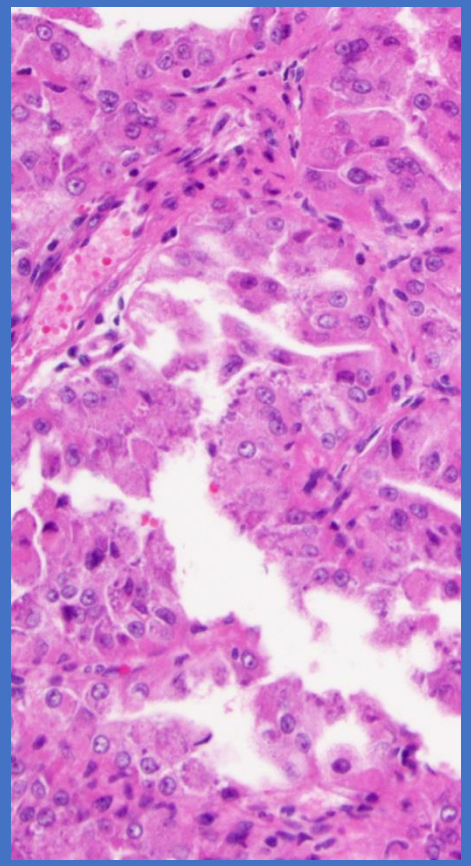
Summary and what's next?

Kinds of kidney cancer

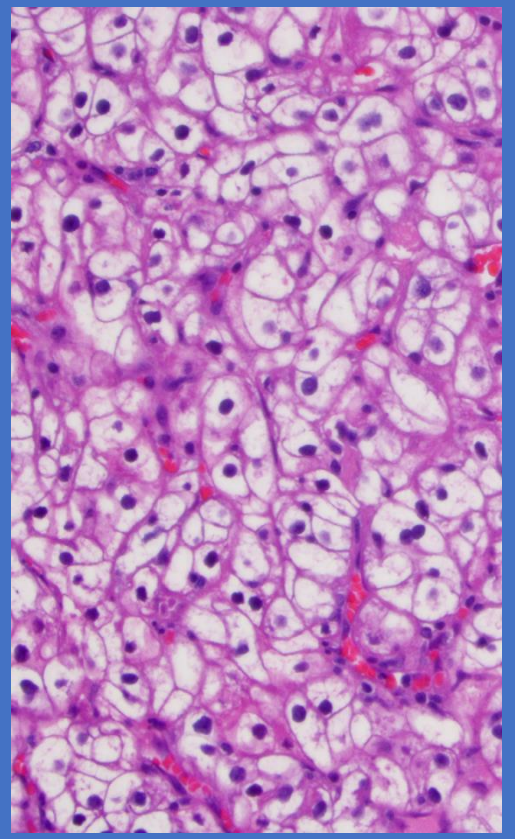
Different RCC subtypes



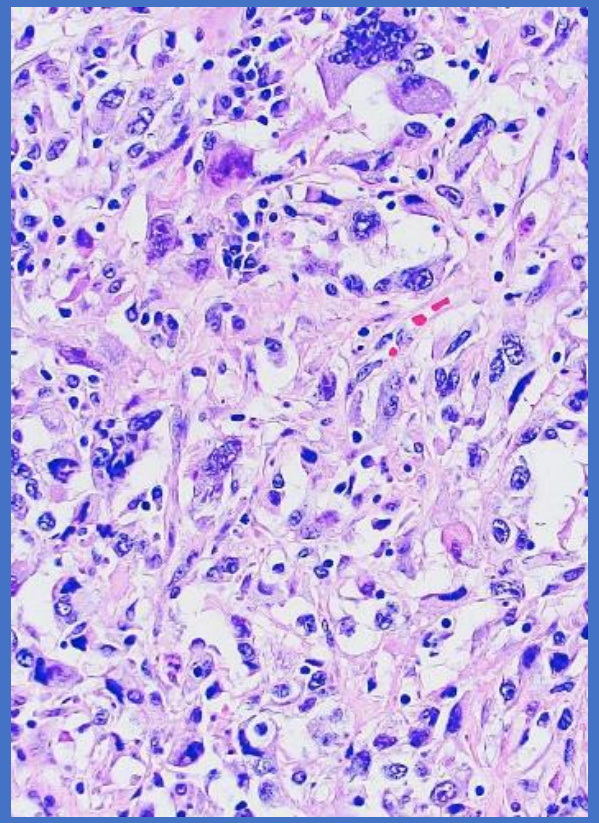
Papillary
type 1



Papillary
type 2



Clear cell,
Fuhrman grade 2



Areas of pleomorphic, atypical spindled cells arising from clear cell RCC. (grade 4)
[Daniel Anderson, M.D., M.B.A.]
https://www.pathologyoutlines.com/topic/kidneytumormalignantrccsarcoma.html

courtesy Jasreman Dhillon

Many other recognized subtypes:


European Association of Urology

The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours

Holger Moch[a,*], Antonio L. Cubilla[b], Peter A. Humphrey[c], Victor E. Reuter[d], Thomas M. Ulbright[e]

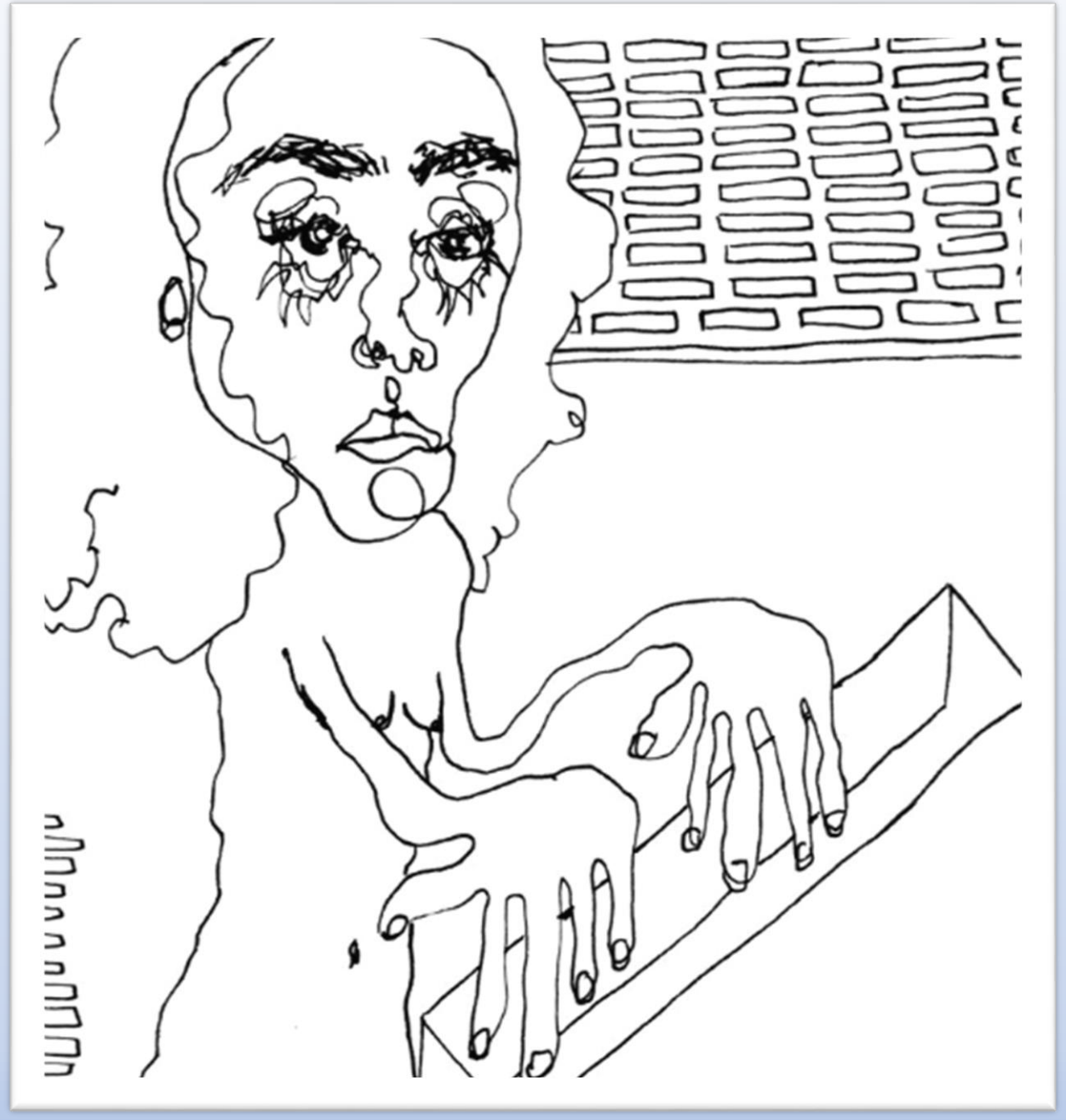
Clear cell type is about 75% of renal cancers

100% of the pivotal trials for RCC medications were 100% clear cell type

Fuhrman grade 1-2-3-4 helps define the histologic pattern

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1*
Papillary renal cell carcinoma	8260/3
Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3*
MiT family translocation renal cell carcinomas	8311/3*
Succinate dehydrogenase–deficient renal carcinoma	8311/3
Mucinous tubular and spindle cell carcinoma	8480/3*
Tubulocystic renal cell carcinoma	8316/3*
Acquired cystic disease–associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0

Kinds of medications



Types of medications:

Targets:

VEGF
VEGFR1
* VEGFR2
VEGFR3

PDGFR alpha
PDGFR beta

* C-MET
* AXL

FGFR1
* FGFR2
* FGFR3
FGFR4

HIF2 alpha

mTOR

VEGF chelation:
Bevacizumab

Small molecule inhibitors of TKs:
SUFFIX: "-inib":
Axitinib
Cabozantinib (+c-met, +axl)
Lenvatinib (+ fgfr)
Pazopanib
Sorafenib (- vegfr1)
Sunitinib
Tivozanib

HIF2 alpha inhibition
Belzutifan

mTOR inhibition
Everolimus
Temsirolimus

Immunotherapy
IL-2 receptor

PD-1
CTLA-4

Human antibodies
SUFFIX: -umab

Lymphocyte drugs:
-l- umab
or: -leuk-

Interleukin-2

Nivolumab (PD-1)
Pembrolizumab (PD-1)
Avelumab (PD-L1)

Ipilimumab (CTLA4)

Key up-front clear cell RCC treatment combinations
(with positive phase III studies vs monotherapy with sunitinib)

* Axitinib + pembrolizumab (OS and PFS)

* Lenvatinib + pembrolizumab (OS and PFS)

* Cabozantinib + nivolumab (OS and PFS)

* Ipilimumab + nivolumab (OS and PFS, but only intermediate/high risk category)

Lenvatinib and everolimus. (Better than sunitinib; not better than lenvatinib + pembrolizumab)

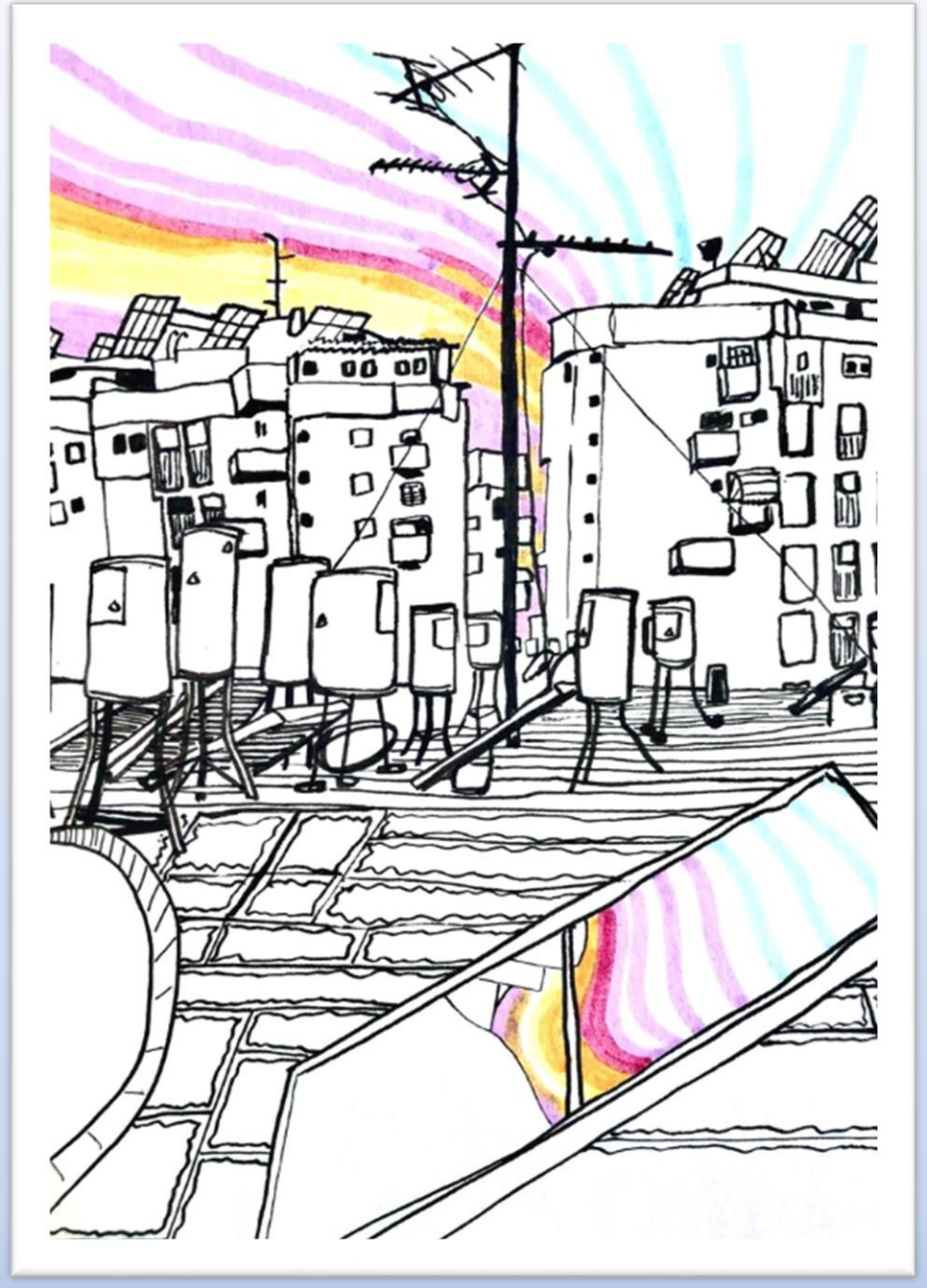
Other phase III trials:

Axitinib + avelumab (PFS only)

Atezolizumab (PD-L1) + bevacizumab (VEGF)

* Key contemporary options—
More on these later

A few biomarkers



RCC biomarkers

PD-L1:
Adverse marker for VEGF response (!)

Not much higher overall response rate with PD-1 axis medications.

Not used to select for PD-1 therapy

Correlation of PD-L1 Tumor Expression and Treatment Outcomes in Patients with Renal Cell Carcinoma Receiving Sunitinib or Pazopanib: Results from COMPARZ, a Randomized Controlled Trial

Clin Cancer Res; 21(5); 1071–7. 2014 .

Toni K. Choueiri[1], David J. Figueroa[2], André P. Fay[1], Sabina Signoretti[1], Yuan Liu[2], Robert Gagnon[2], Keith Deen[2], Christopher Carpenter[2], Peter Benson[3], Thai H. Ho[4], Lini Pandite[5], Paul de Souza[6], Thomas Powles[7], and Robert J. Motzer[8]

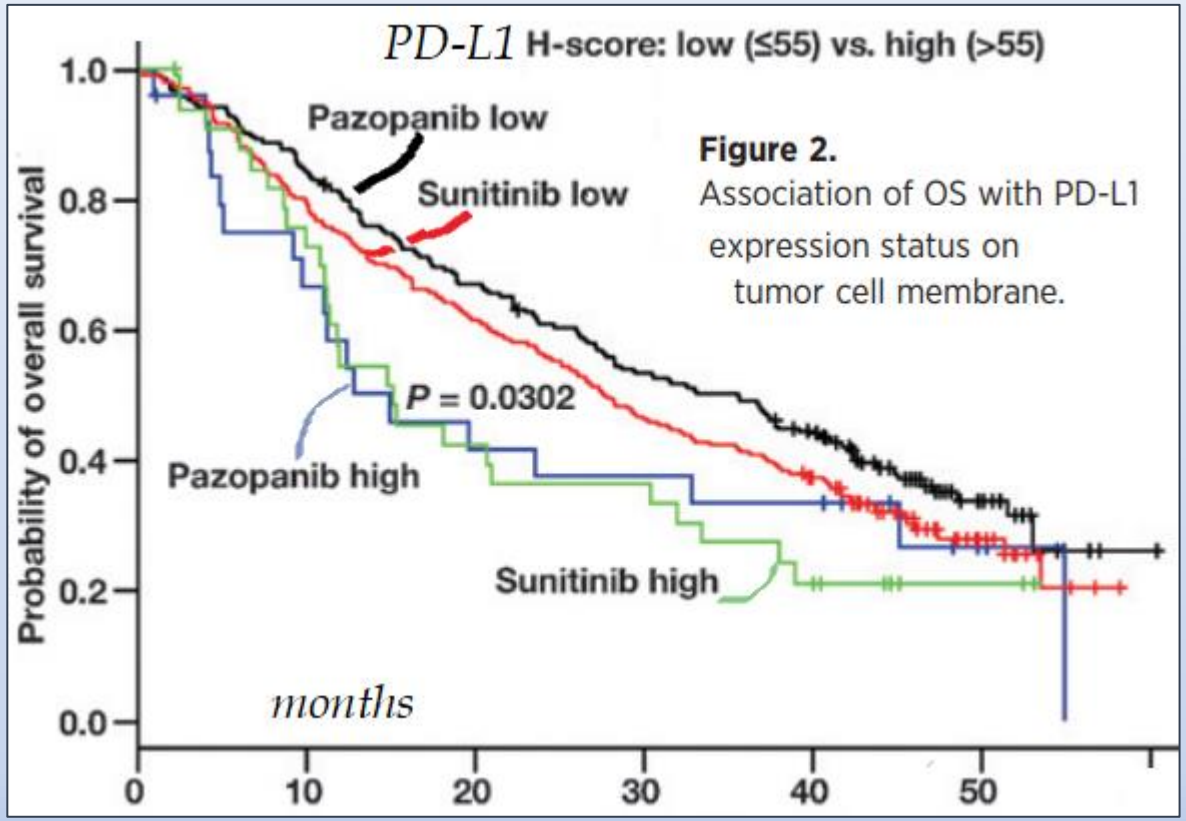


Figure 2.
Association of OS with PD-L1 expression status on tumor cell membrane.

RCC biomarkers

PD-L1:
Adverse marker for VEGF response (!)

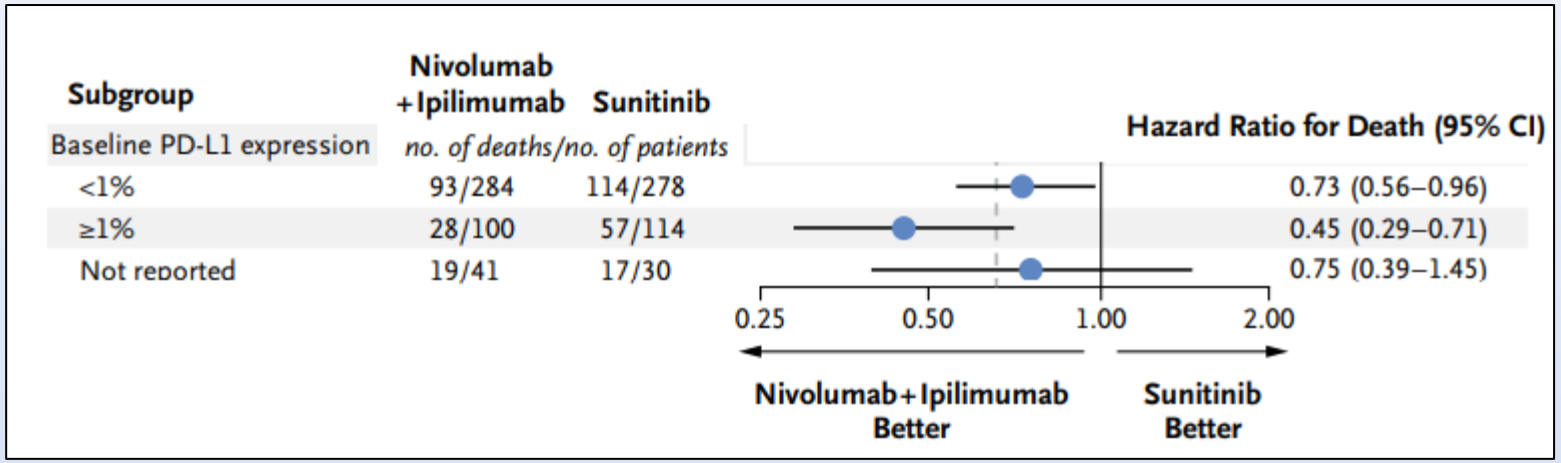
Not much higher overall response rate with PD-1 axis medications.

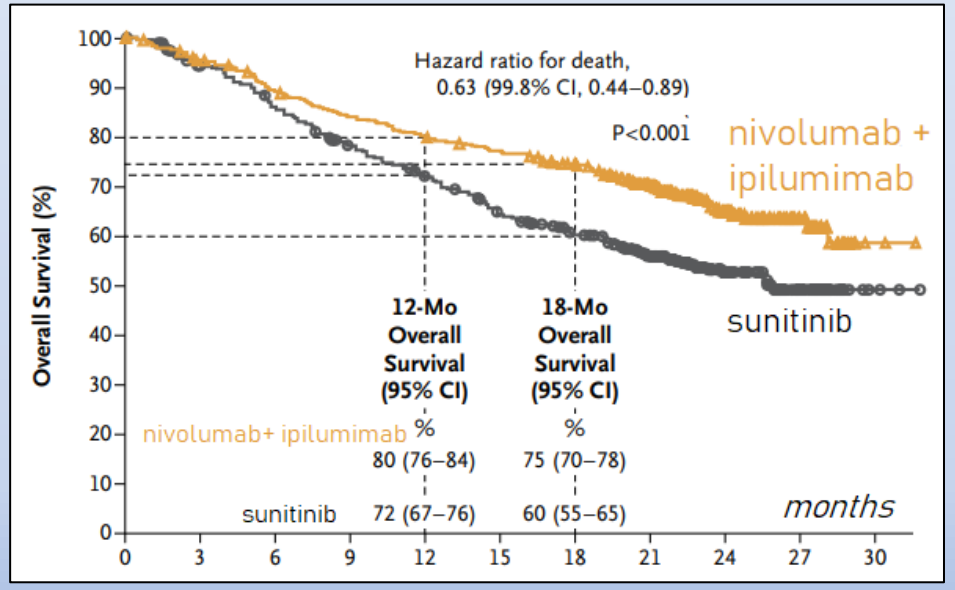
Not used to select for PD-1 therapy

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

N Engl J Med 2018;378:1277-90.

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*





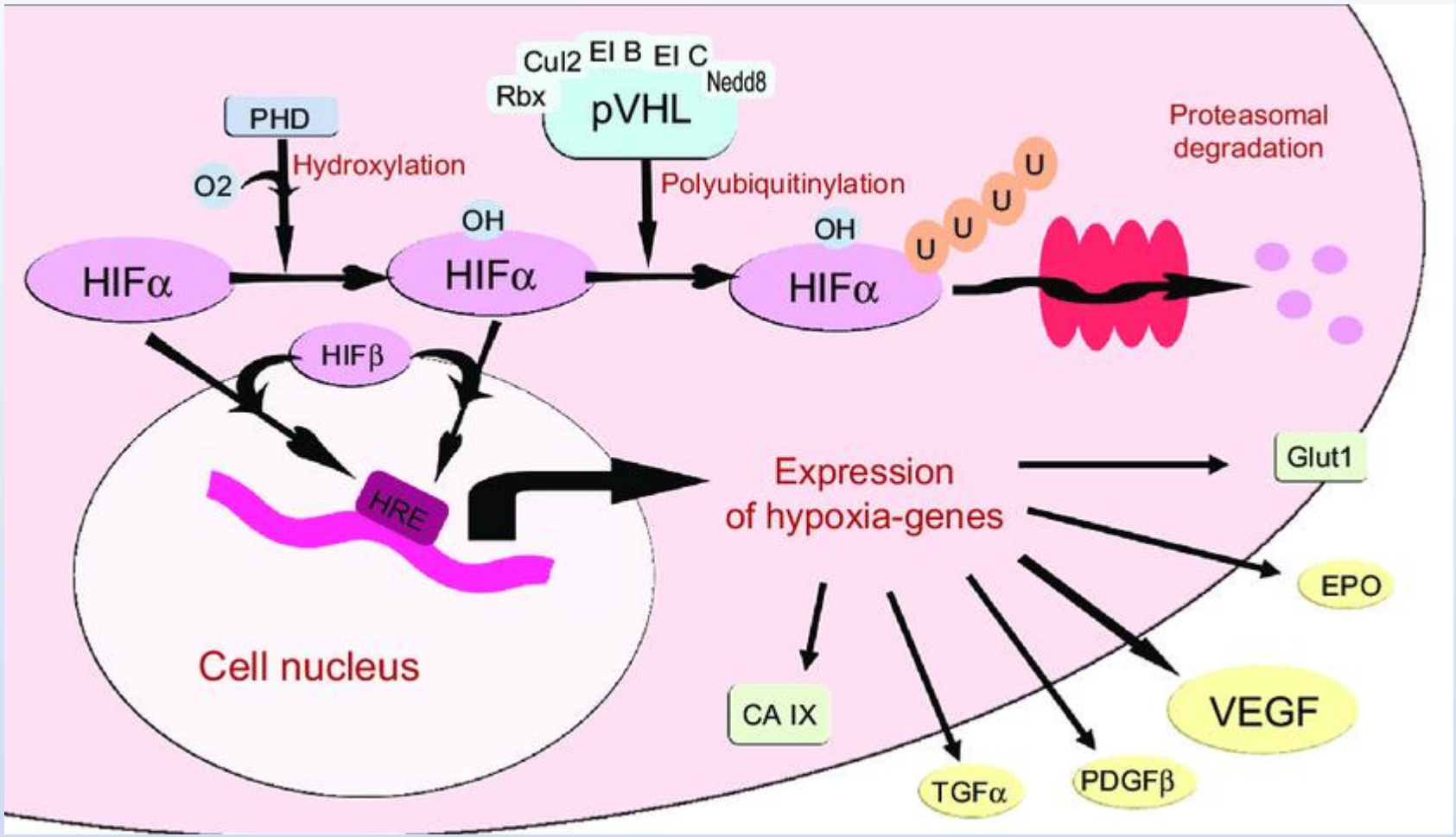
RCC biomarkers

Von Hippel-Lindau protein: pVHL

Always present as defect in *clear cell* RCC

Typically, one mutation and one deletion

Familial VHL syndrome: Inborn first knock-out mutation.



Edeline, Julien & Vauléon, Dr & Rioux-Leclercq, Pr & Perrin, Dr & Vigneau, Pr & Bensalah, Karim & Laguerre, Dr & Edeline,. (2012). Safety and Efficacy of Sorafenib in Renal Cell Carcinoma. Cancer Growth and Metastasis. 5. 35. 10.4137/CGM.S7526.

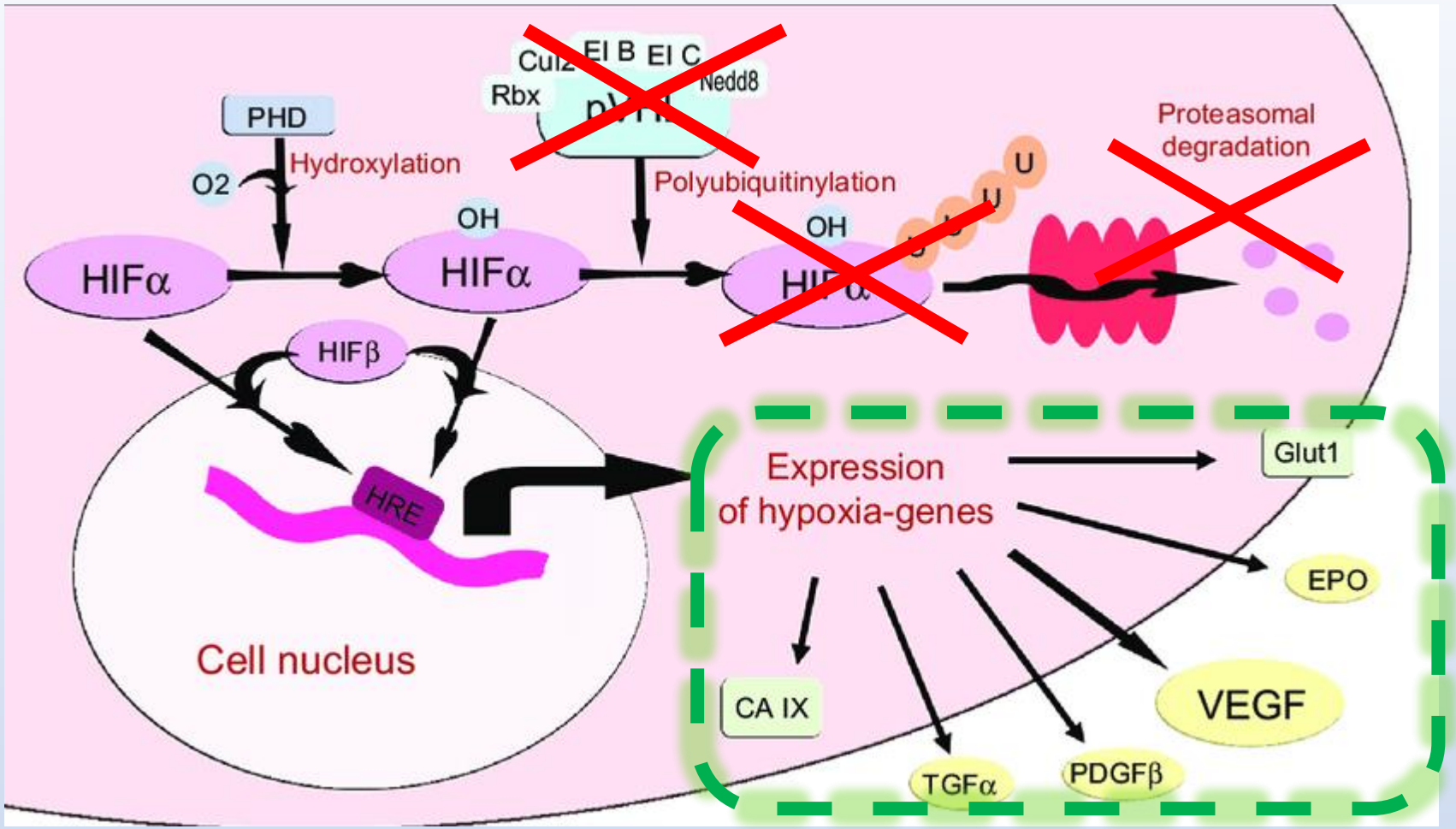
RCC biomarkers

Blocked pVHL

No degradation of HIF2alpha

More expression of
- VEGF
- TGF-alpha
- PDGF-beta
- Erythropoetin
- GLUT-1

(glucose transporter-1)



Edeline, Julien & Vauléon, Dr & Rioux-Leclercq, Pr & Perrin, Dr & Vigneau, Pr & Bensalah, Karim & Laguerre, Dr & Edeline,. (2012). Safety and Efficacy of Sorafenib in Renal Cell Carcinoma. Cancer Growth and Metastasis. 5. 35. 10.4137/CGM.S7526.

RCC biomarkers

The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma

CJ Ricketts et al. Cell Reports 23, 313–326, April 3, 2018

Adverse:

clear cell

P53

BAP-1

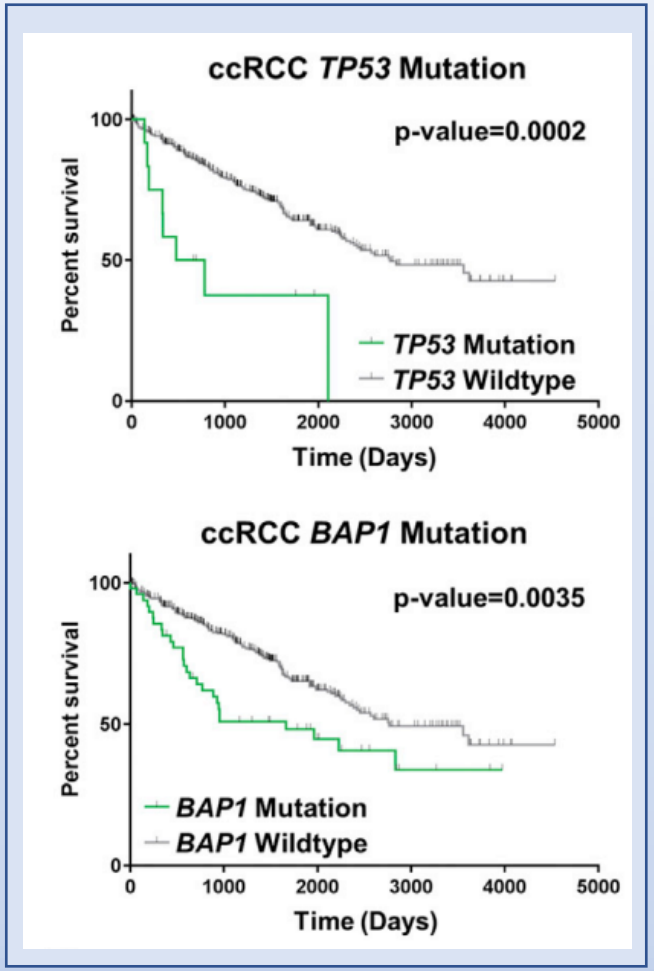
papillary

P53

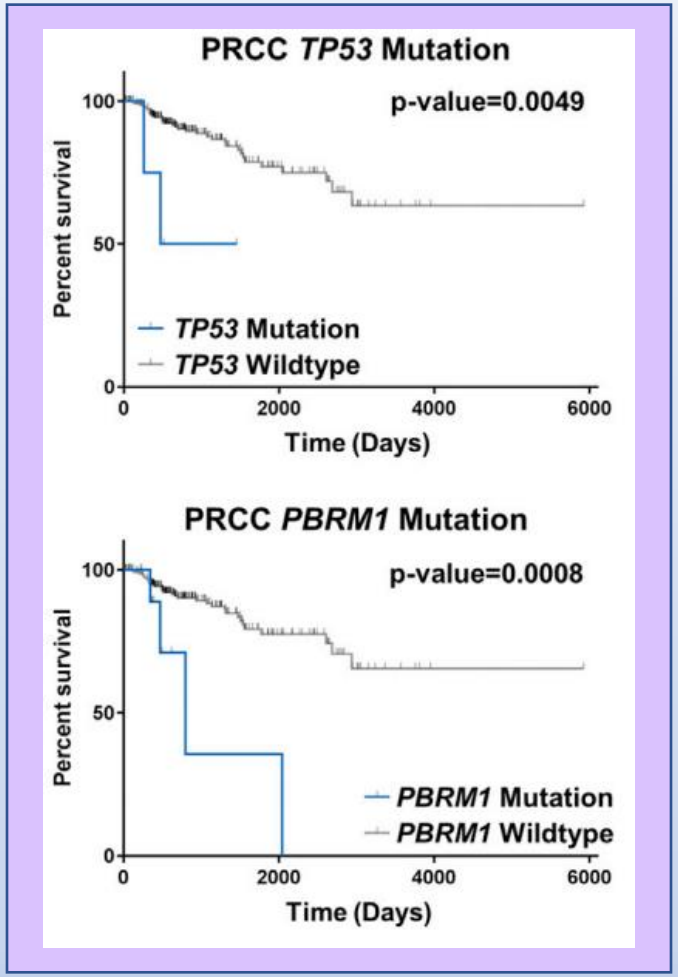
PBRM-1

chromophobe

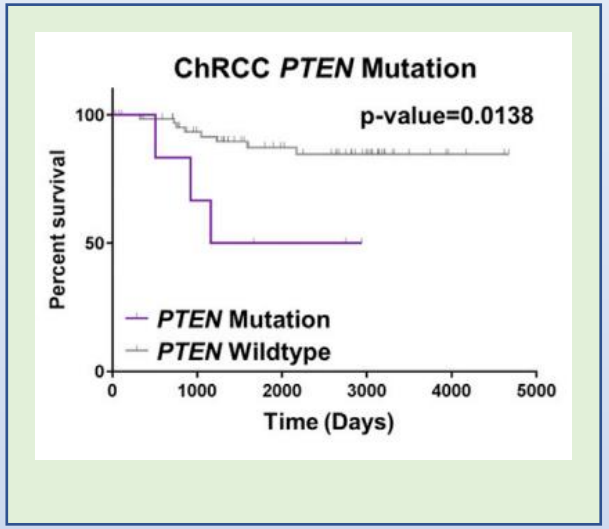
PTEN



clear cell



papillary



chromophobe

RCC biomarkers

Patients with ClearCode34-Identified Molecular Subtypes of Clear Cell Renal Cell Carcinoma Represent Unique Populations with Distinct Comorbidities

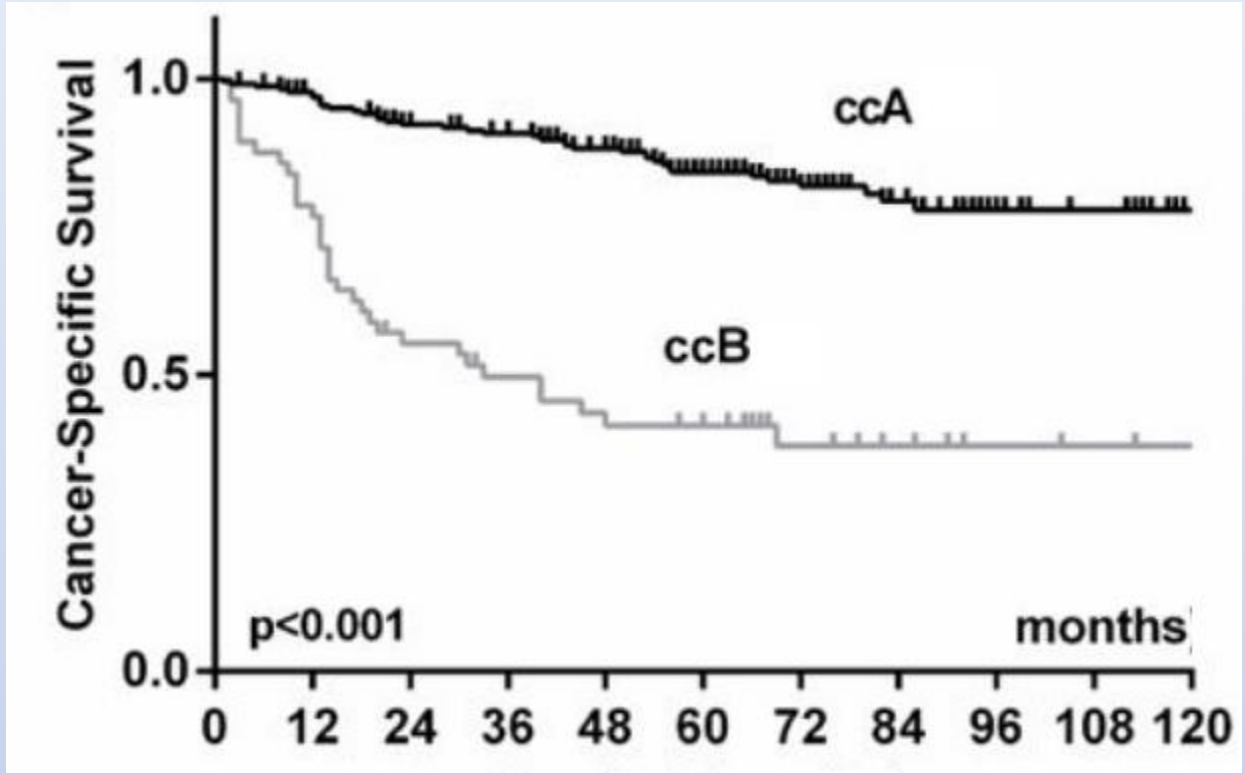
Urol Oncol. 2016 March ; 34(3): 122.e1–122.e7.

Scott M. Haake[a], Samira A. Brooks[b], Eric Welsh[c], William Fulp[d], Dung-Tsa Chen[c], Jasreman Dhillon[e], Eric Haura[f], Wade Sexton[g], Philippe E. Spiess[f], Julio Pow-Sang[g], W. Kimryn Rathmell[a], and Mayer Fishman[g]

Clear-code34
ccA vs ccB type signature

ClearCode34 Gene Expression Profile

ccA		ccB
ARNT	NRP1	CCNO
BNIP3L	PDGFD	FLJ23867
C11orf1	PHYH	FOXM1
CDH5	PRKAA2	GALNT10
EHBP1	RGS5	GALNT4
EPAS1	SLC4A4	KCNN4
ESD	SPRYD7	MOXD1
FZD1	ST13	ROR2
GIPC2	STK32B	SERPINA3
LEPROTL1	TCEA3	SLC4A3
MAOB	TLR3	
MAPT	VCAM1	



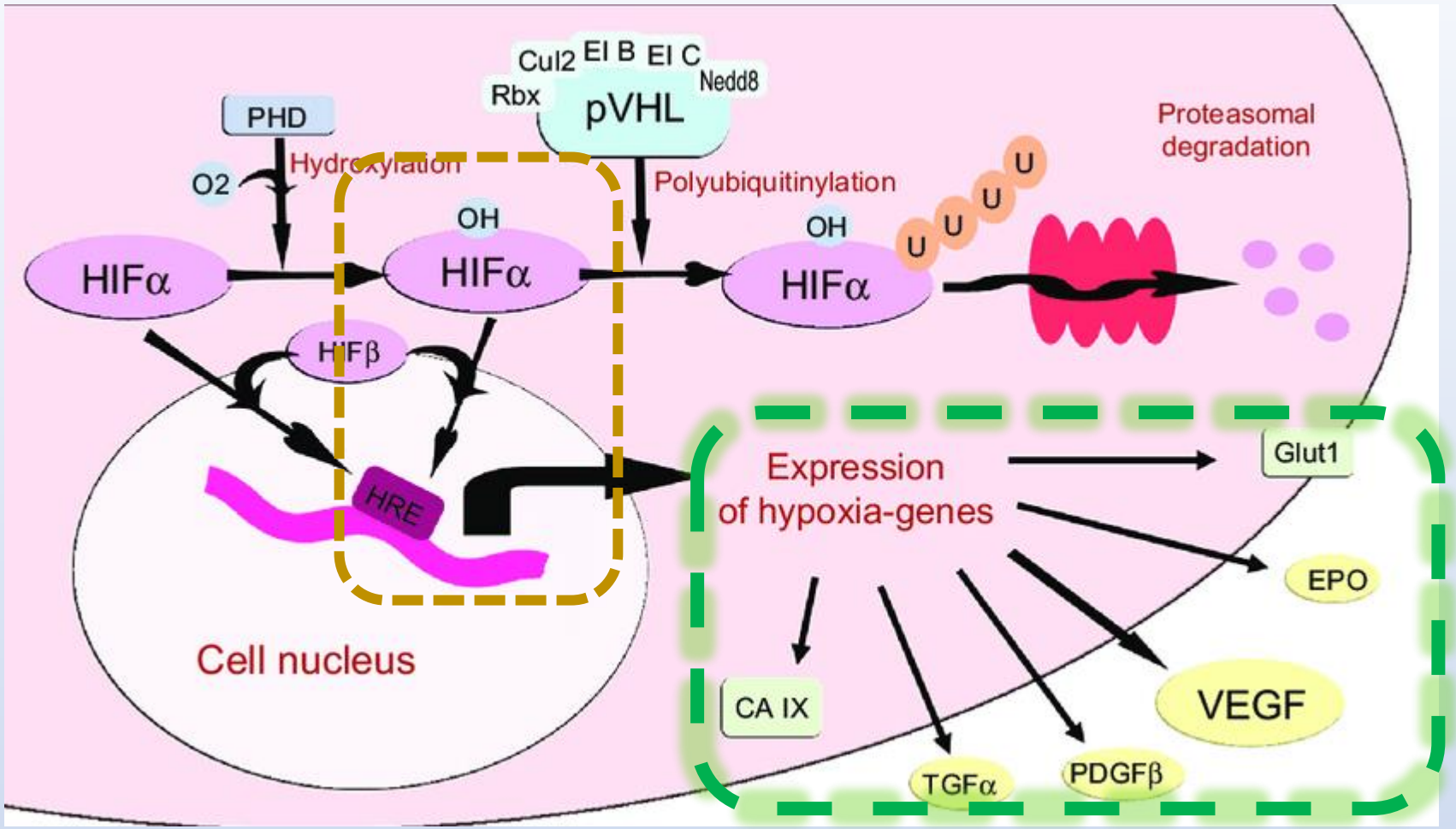
Molecular targets of clear cell RCC

Blocked pVHL

No degradation of HIF2alpha

TKI drugs:

- VEGF-R (r1-r2-r3)
- PDGF-R (-α and -β)
- C-MET
- AXL
- FGFR (-1-2-3-4)



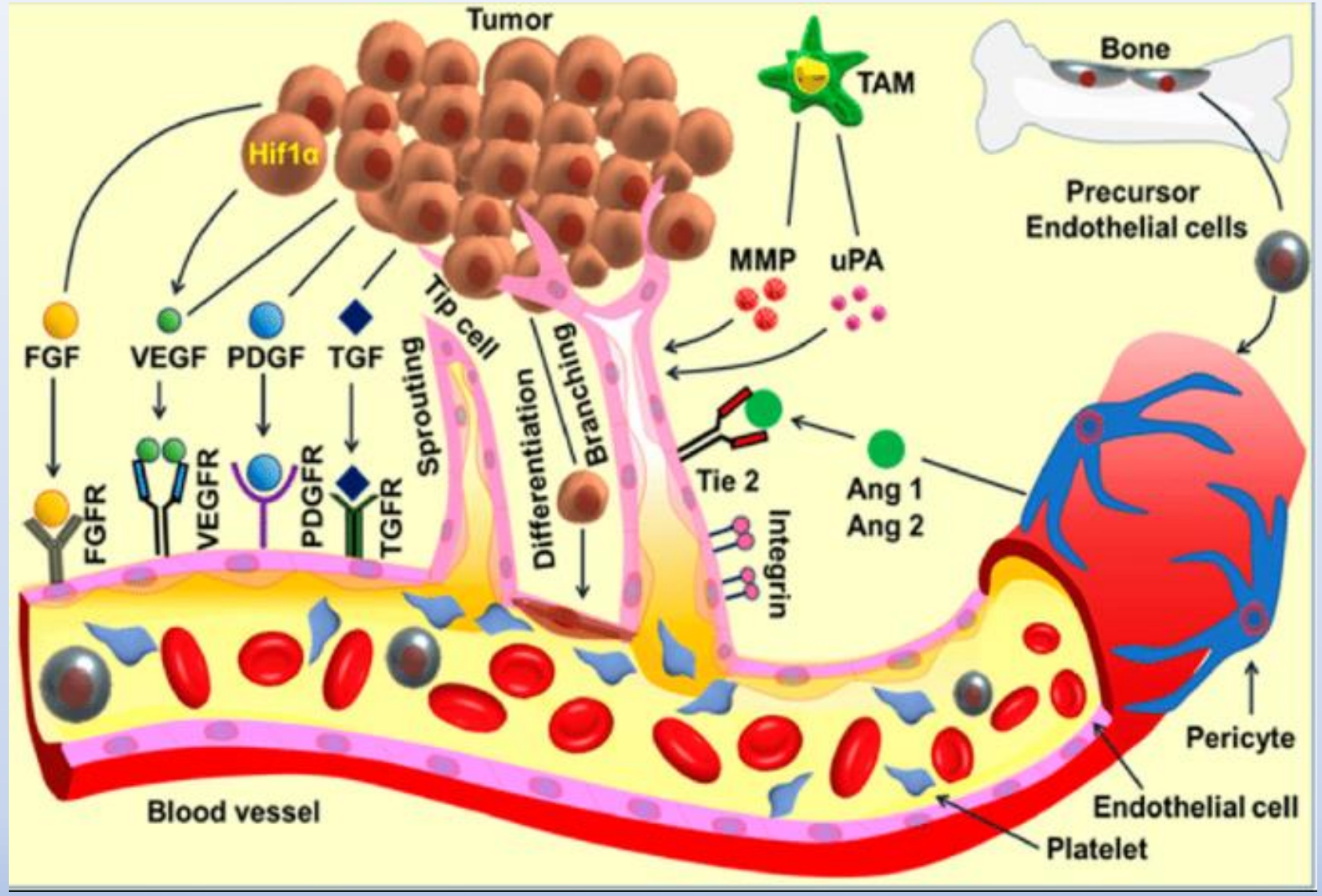
Edeline, Julien & Vauléon, Dr & Rioux-Leclercq, Pr & Perrin, Dr & Vigneau, Pr & Bensalah, Karim & Laguerre, Dr & Edeline,. (2012). Safety and Efficacy of Sorafenib in Renal Cell Carcinoma. Cancer Growth and Metastasis. 5. 35. 10.4137/CGM.S7526.

Angiogenic TKI targets – as the tumor grows, the blood supply is stimulated and integrated.

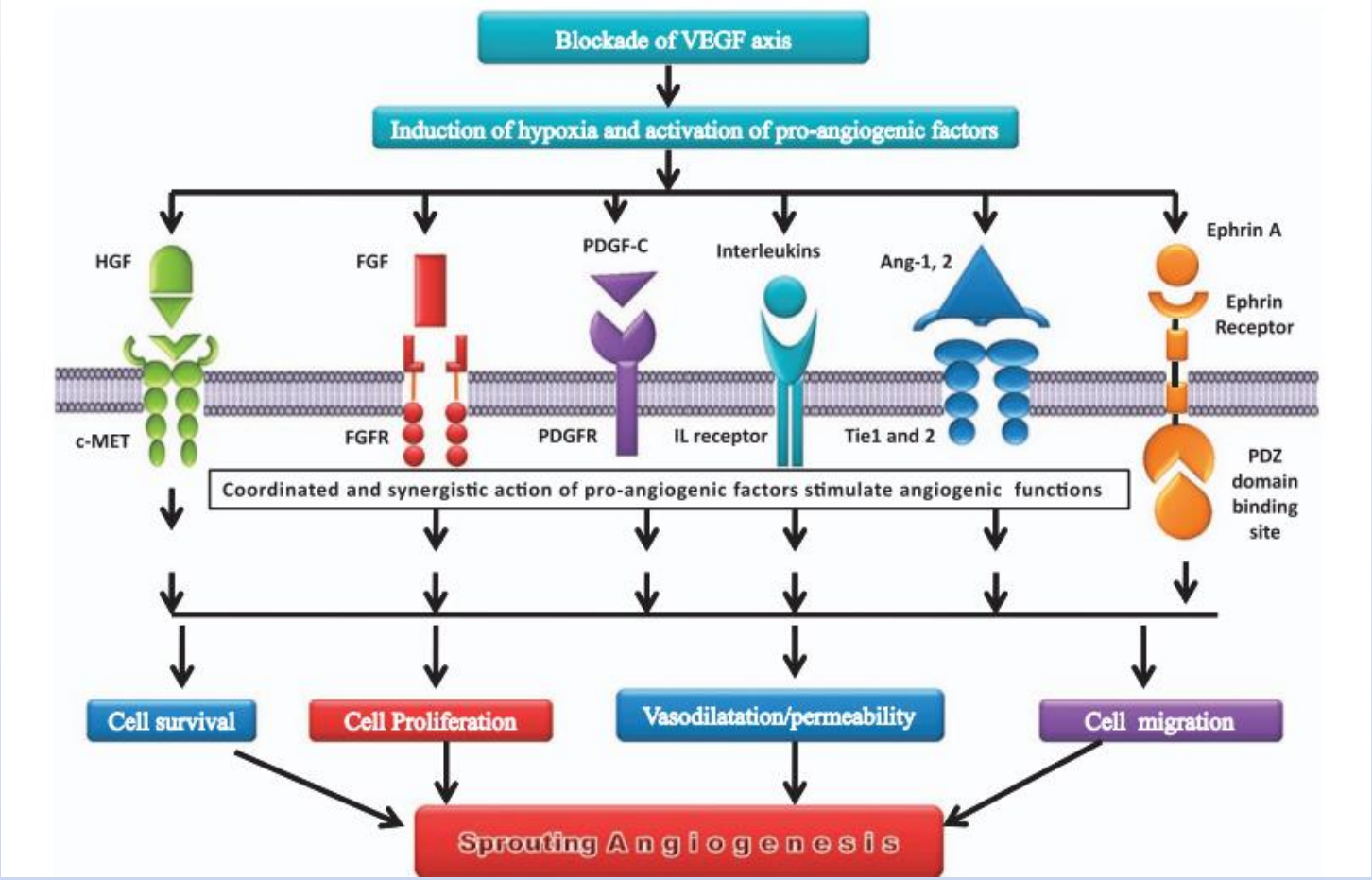
Int. J. Mol. Sci. **2020**, *21*, 455; doi:10.3390/ijms21020455

Recent Advancements of Nanomedicine towards Antiangiogenic Therapy in Cancer

Anubhab Mukherjee , Vijay Sagar Madamsetty, Manash K. Paul and Sudip Mukherjee



Angiogenic TKI targets – after VEGF is blocked:



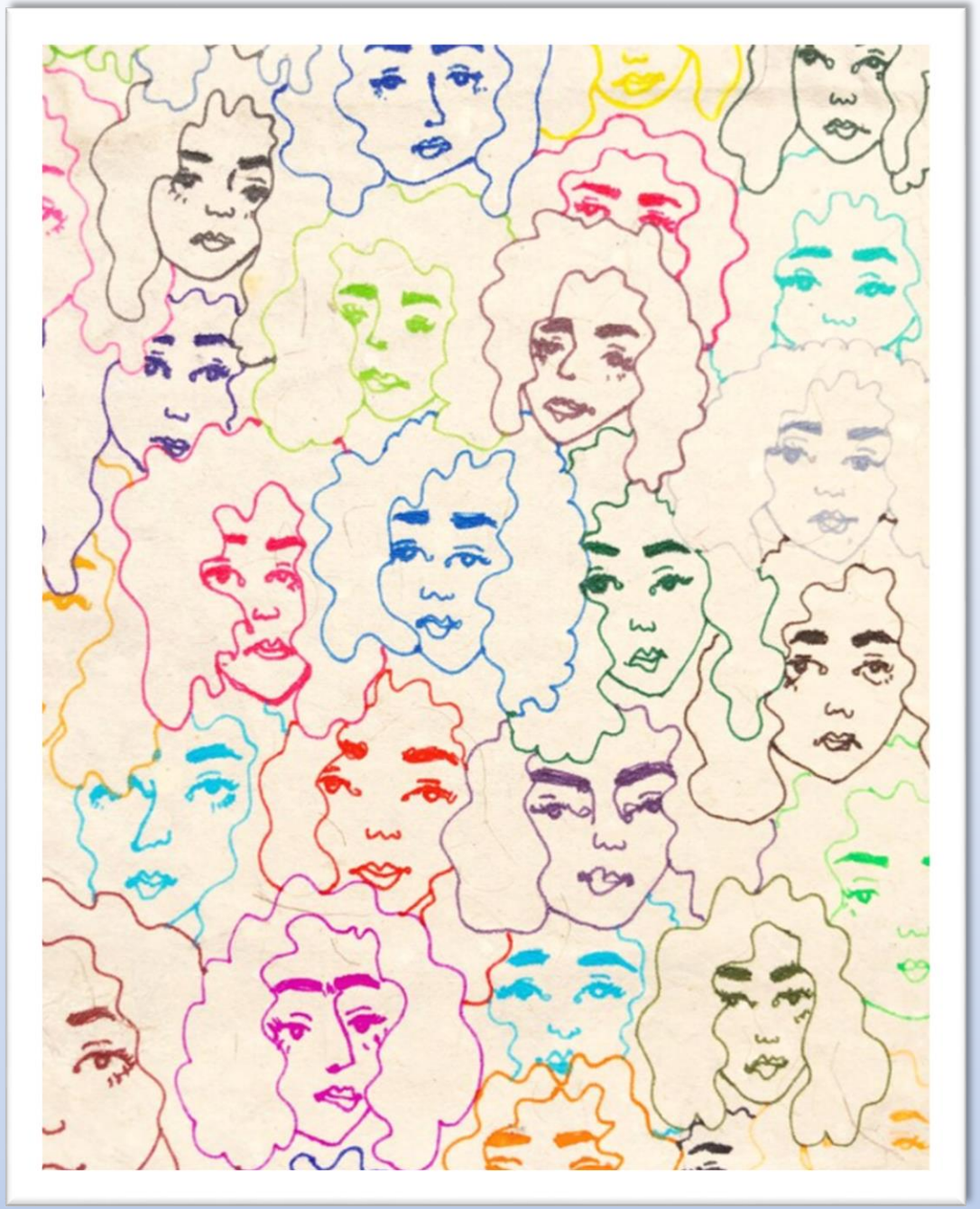
Compensatory angiogenesis and tumor refractoriness

RN Gacche

Citation: Oncogenesis (2015) **4**, e153; doi:10.1038/oncsis.2015.14

www.nature.com/oncsis

Initial medical therapy
of advanced disease



VEGF medicines

Antiangiogenesis drugs: >>8<< on-label, for RCC

Antibodies binding VEGF-A

bevacizumab

Block VEGFR1/2/3 and other targets

cabozantinib (& C-MET, AXL)

lenvatinib (& FGFR [more])

pazopanib (& FGFR)

Block VEGFR1/2/3

axitinib

sorafenib

sunitinib

tivozanib

And HIF-2 alpha:

belzutifan

Antiangiogenesis drugs: Dose comparisons

Antibodies binding VEGF-A

- bevacizumab 10 mg/kg/dose, q 2 weeks

Block VEGFR1/2/3

- axitinib 5 mg po BID
- sorafenib 200 mg x2 = 400 mg po BID
- sunitinib 50 mg po, x 28 d/14 off; or 14/7
  (also available in 12.5, 25, 37.5)
- tivozanib 1.34 mg po x 21 d/ 7 off
  (also available 0.89)

Block VEGFR1/2/3 and others

- cabozantinib
  60 mg/d (monotherapy)
  40 mg/d (combination)
  20 mg also available.
- lenvatinib
  20 mg (or 18, or 14) po qD
  (comes in 10 & 4 mg sizes)
- pazopanib
  200 mg x4 = 800 mg po qD

Antiangiogenesis drugs: Typical side effects

- Diarrhea
- Hypertension
- Hypothyroidism
- Appetite less
- Fatigue
- Nausea
- Stomatitis

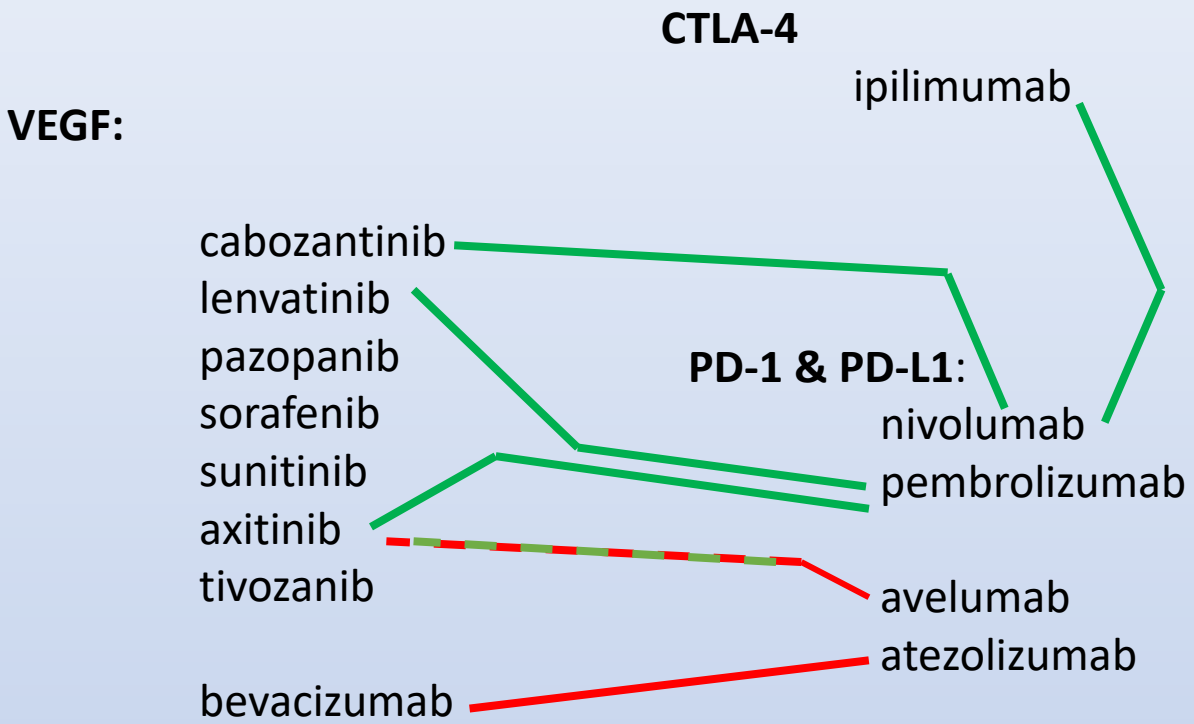
- Dysphonia/ hoarseness
- Weight loss
- Hand/foot syndrome
- Joint pain
- Rash
- Dysgeusia

Management

- Interrupt
- Wait for resolution
  - Axitinib half life: 2-6 h
  - Lenvatinb 28h
  - Pazopanib 30h
  - Sorafenib 25-40 h
  - Sunitinib 40-60h & N-desethyl sunitinib: 80-100.
  - Cabozantinib 120h
  - Tivozanib 4.5-5.1 days
  - Bevacizumab ~ 20 days
- Re-challenge:
  - Lower doses (on label)
  - Planned breaks (e.g. weekends)

PD-1 combinations

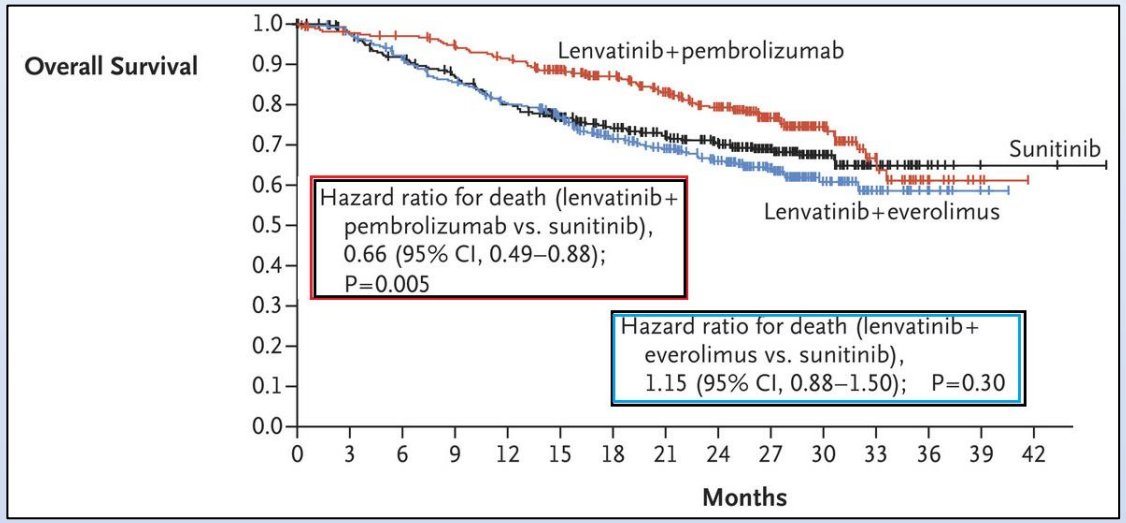
4 trials with combination superior to sunitinib.



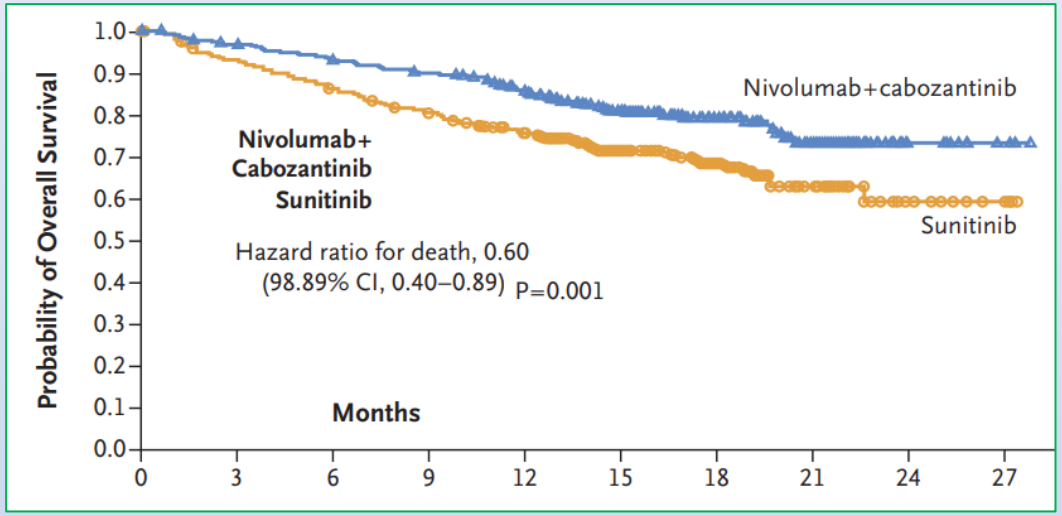
Two trials with combination that didn't meet OS improvement.

4 trials with combination superior to sunitinib.

CLEAR trial. Lenvatinib plus pembrolizumab or everolimus [vs sunitinib]
Motzer et al. NEJM 2021 384:1289-1300

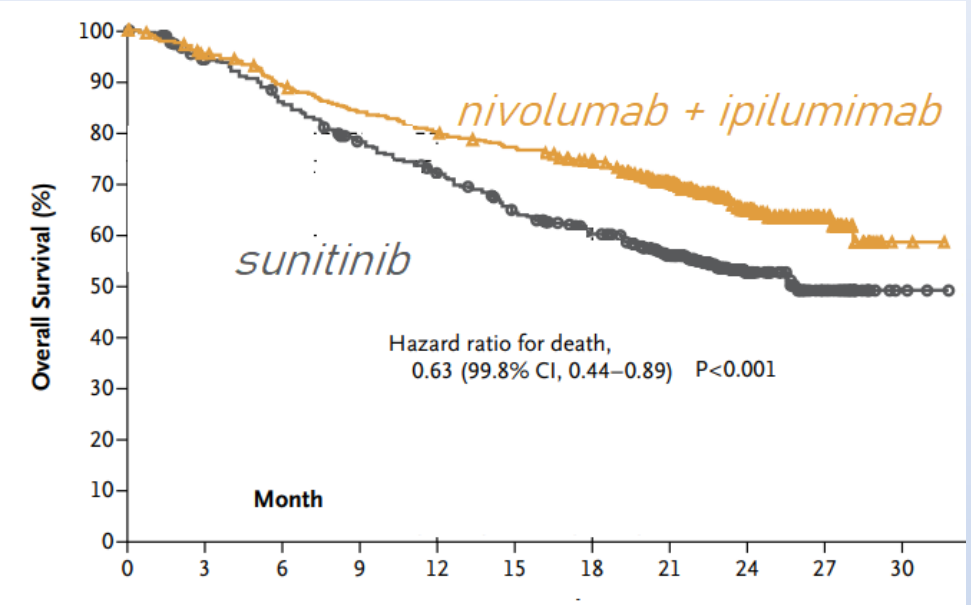


Checkmate 9ER. **Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma**
Choueiri et al. NEJM 2021 Mar 4;384(9):829-841



4 trials with combination superior to sunitinib.

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma [only intermediate and high risk] Motzer et al. NEJM 2018; 378:1277-1290



Favorable risk: none

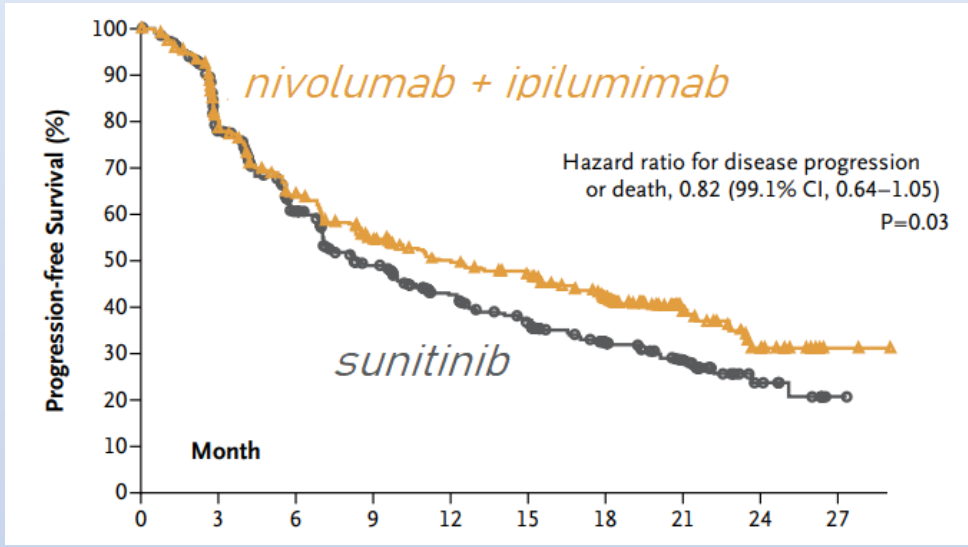
Intermediate: 1 – 2

High (poor): 3 -5:

Karnofsky PS below 80
< 12 months since diagnosis
Hgb under LLN
LDH > 1.5 ULN
Corrected calcium > 10 mg/dL

ULN == upper limit of normal

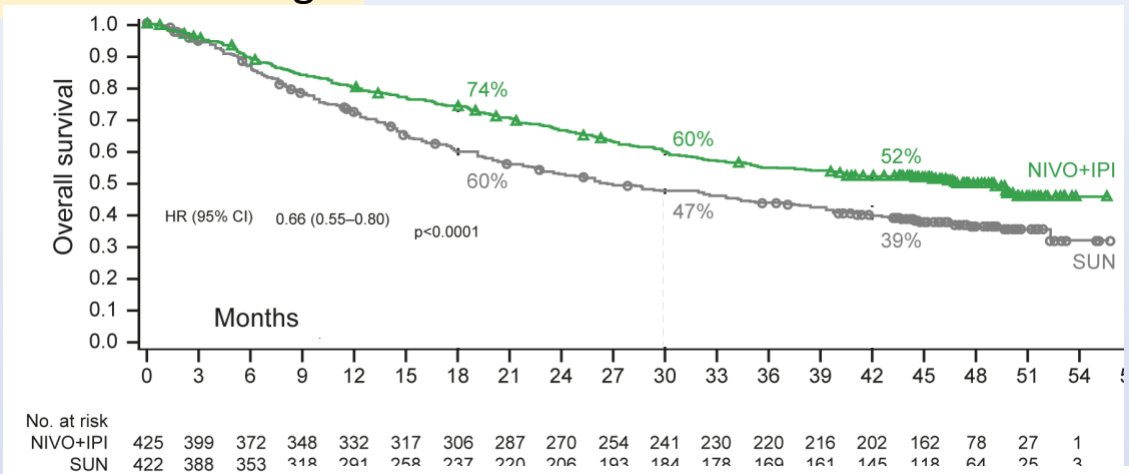
PFS: difference *less* than OS. First 6 months: no difference



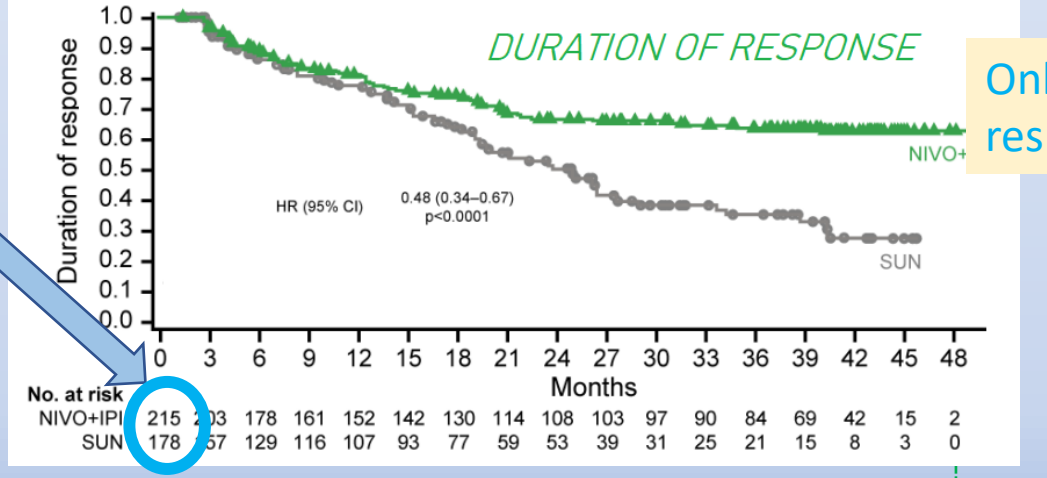
4 trials with combination superior to sunitinib.

Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. Motzer et al. J Immunother Cancer 2021

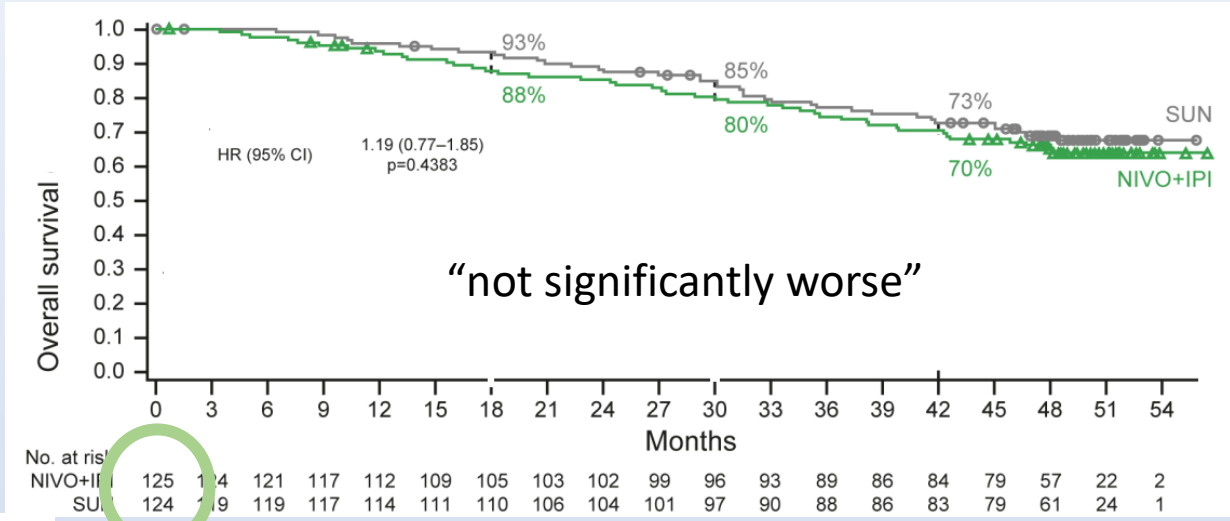
Intermediate-high



Only counting responders

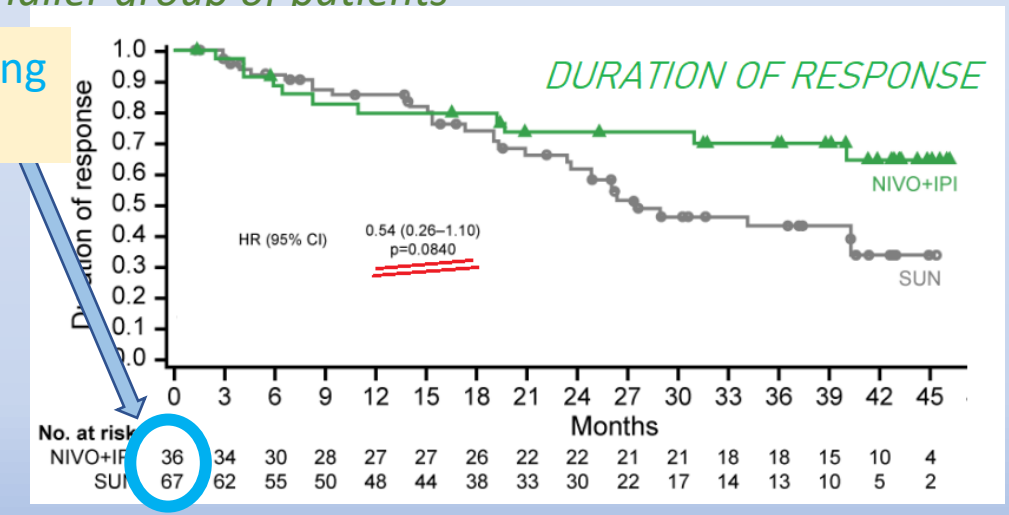


Favorable risk:



Smaller group of patients

Only counting responders



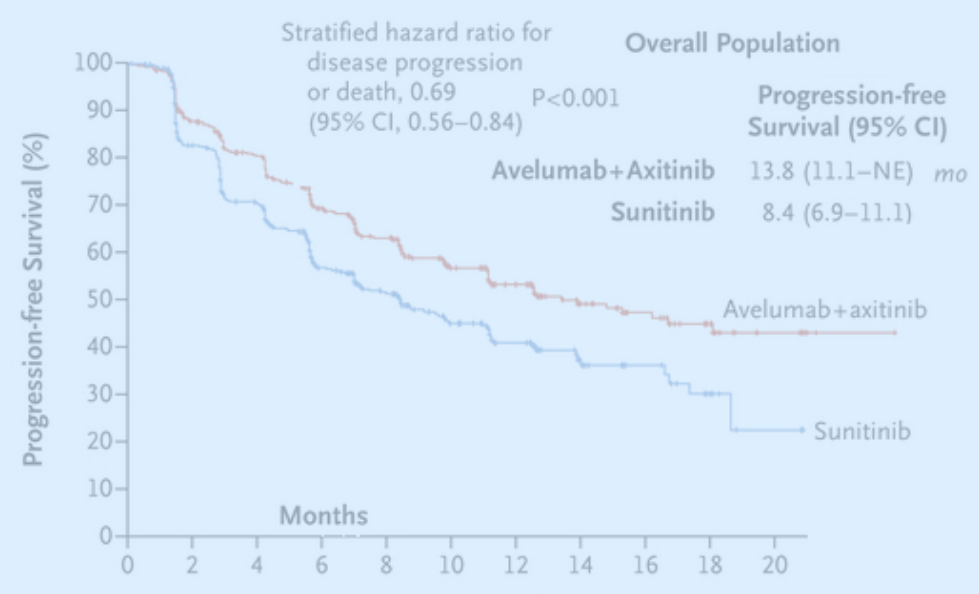
4 trials with combination superior to sunitinib.

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Motzer et al. NEJM 2019 Mar 21;380(12):1103-111

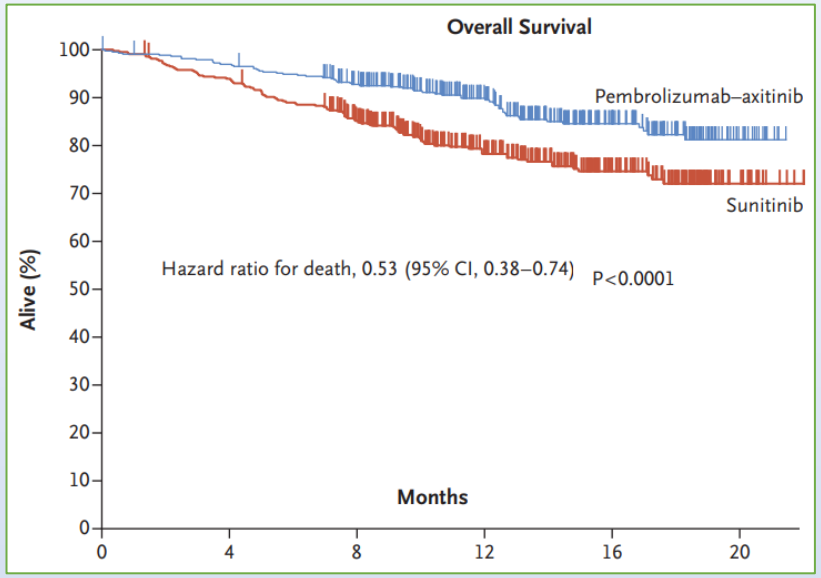
OS : not positive yet.

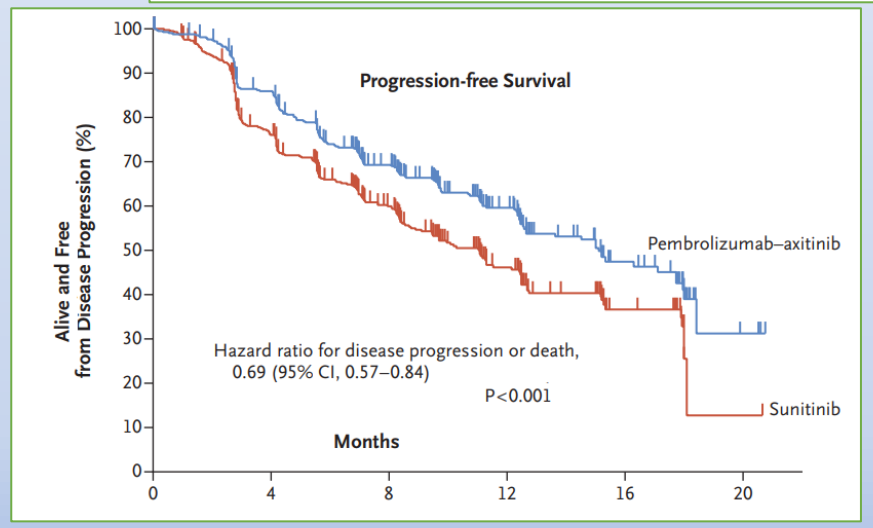
PFS results positive:



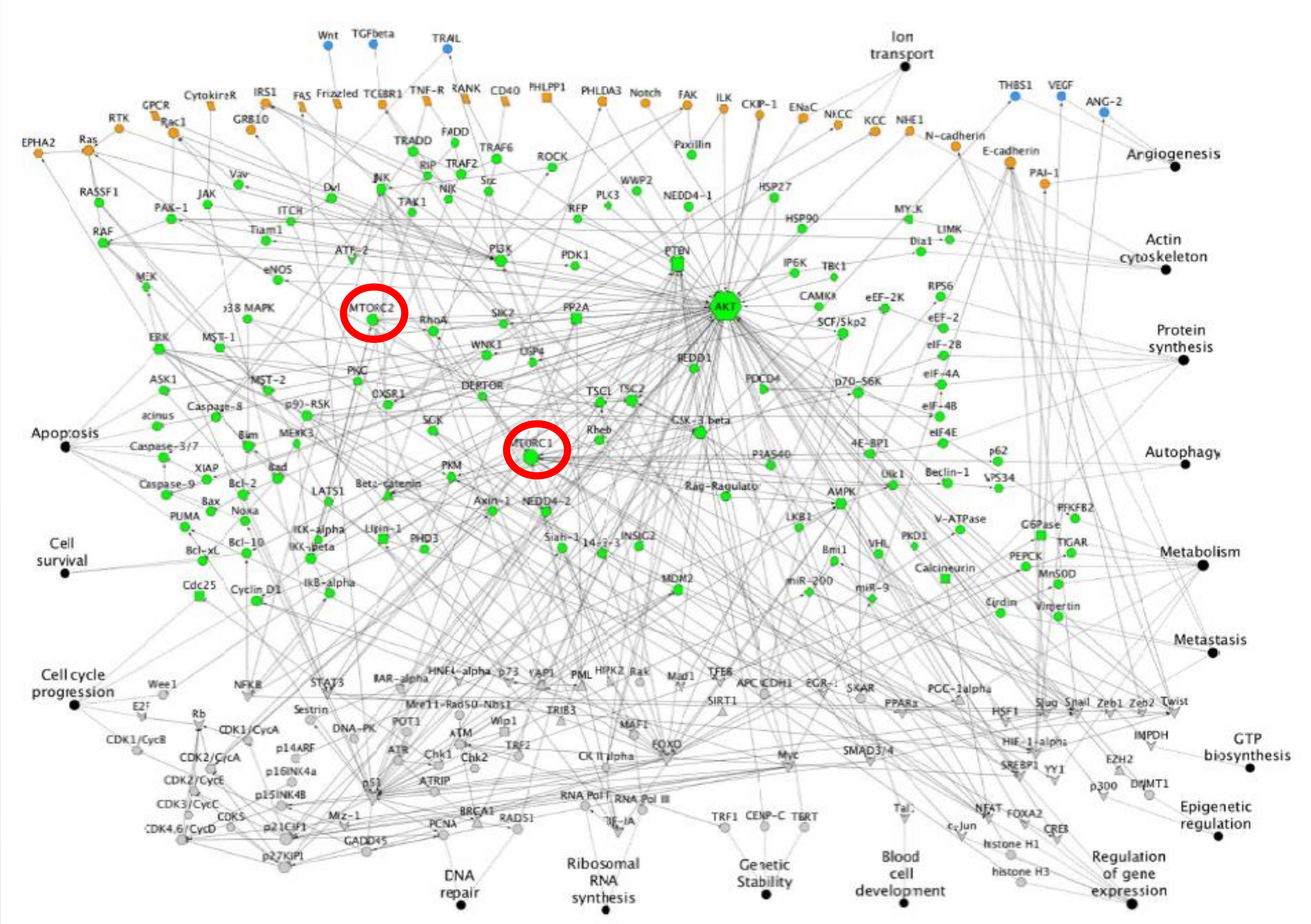
Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Rini et al. NEJM 2019 Mar 21;380(12):1116-1127





mTOR



Ion transport
Angiogenesis
Actin cytoskeleton
Protein synthesis
Autophagy
Metabolism
Metastasis
GTP biosynthesis
Epigenetic regulation
Regulation of gene expression
Blood cell development
Genetic Stability
Ribosomal RNA synthesis
DNA repair
Cell cycle progression
Cell survival
Apoptosis
AKT
MTORC1
MTORC2

What about mTOR?

Eukaryotic life on this planet depends on mTOR: Don't inhibit it too much

TOR: Yeast TOR target of rapamycin

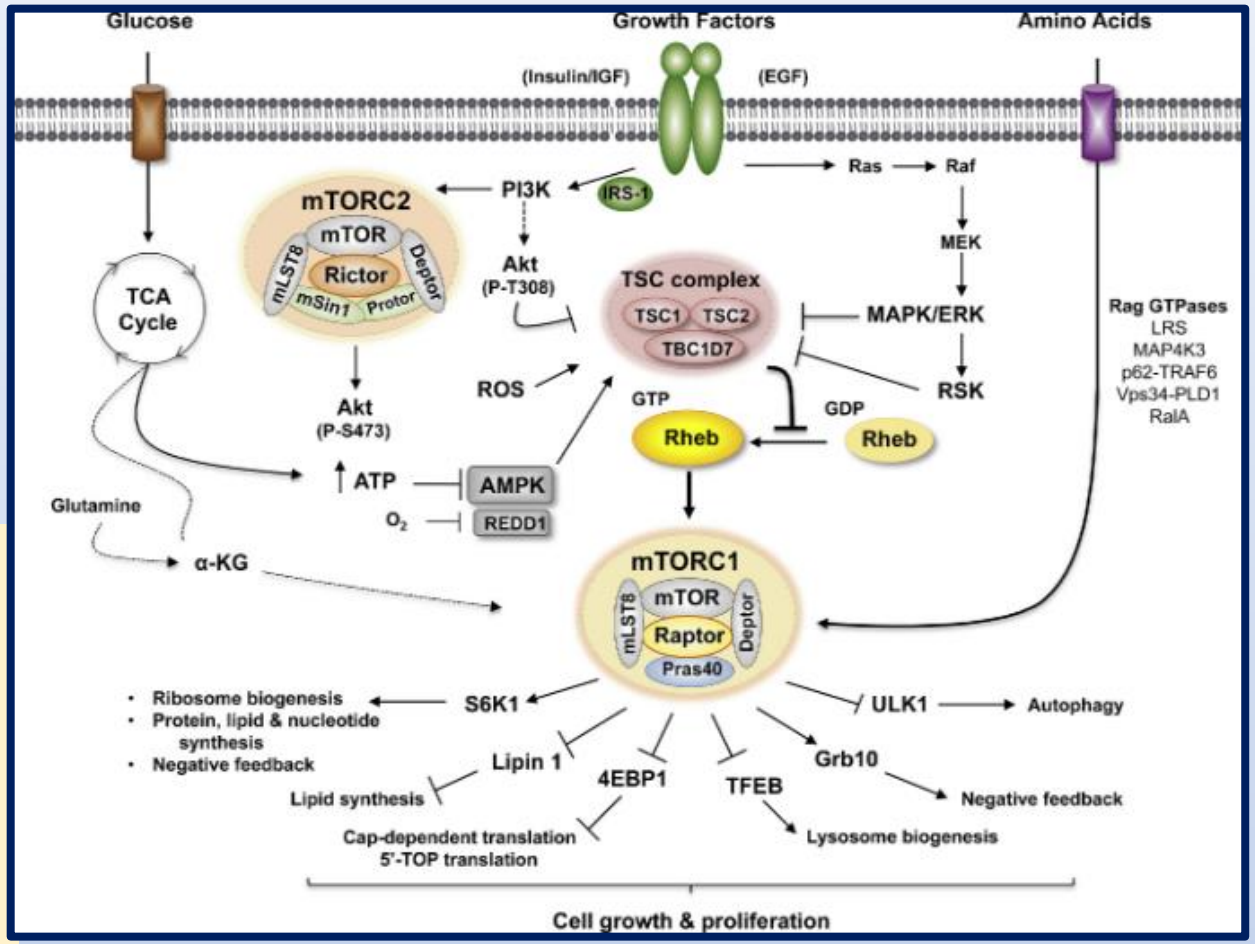
Rapamycin was discovered from *streptococcus hydroscopicus* in soil of Rapa Nui, aka Easter Island, 1964 METEI (Medical Expedition to Easter Island).

Powers T. The origin story of rapamycin: systemic bias in biomedical research and cold war politics. Mol Biol Cell. 2022 Nov 1;33(13):pe7

mTOR=

- Mammalian
- Target
- of
- Rapamycin

Huang K, Fingar DC. Growing knowledge of the mTOR signaling network. Semin Cell Dev Biol. 2014 Dec;36:79-90



mTOR in kidney cancer therapy

mTOR medications

- ORR rate: low
- PFS, OS: improved

Everolimus

- 10 mg/d monotherapy (inferior to nivolumab)
- 5 mg everolimus with 18 mg/d lenvatinib

Temsirolimus

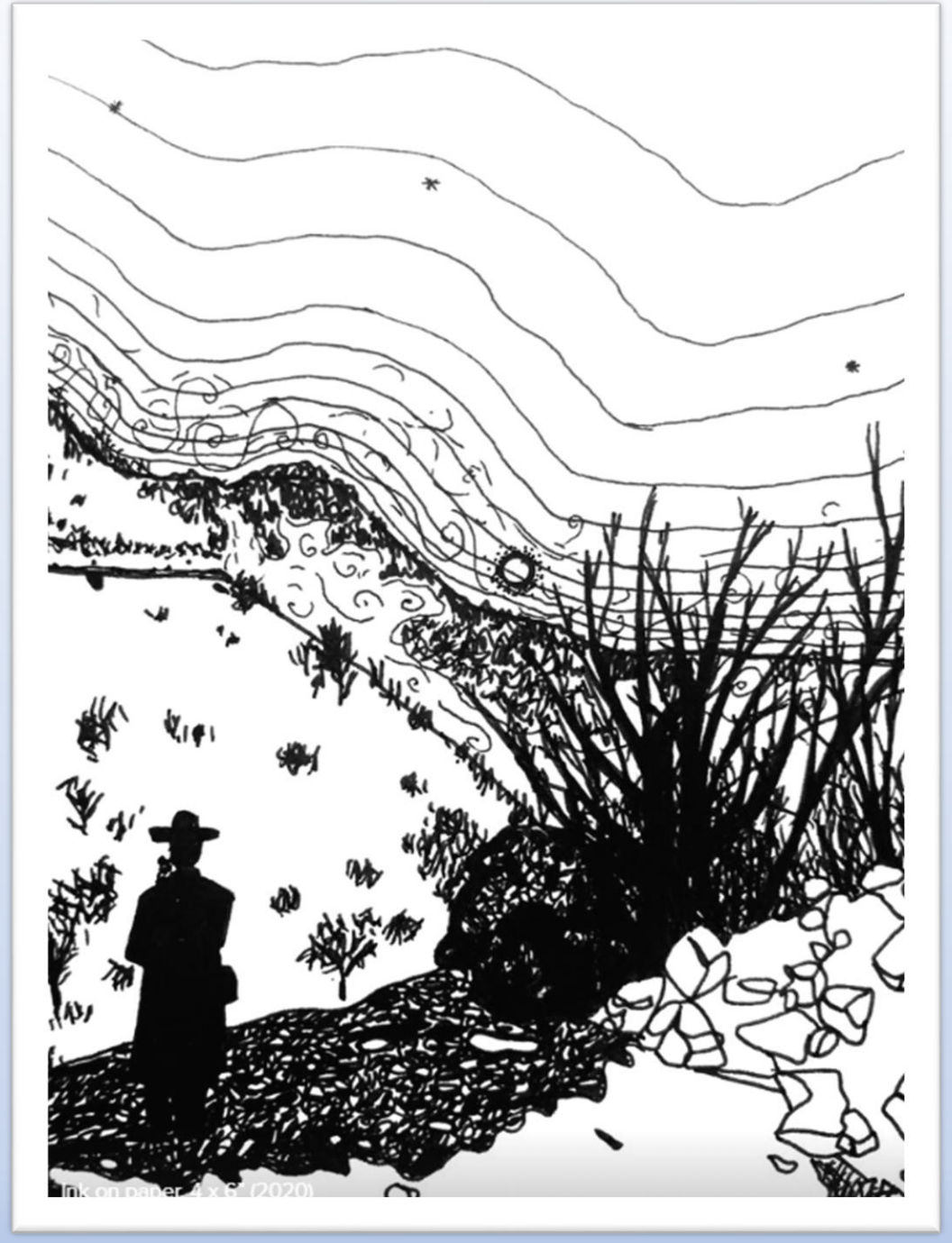
- 25 mg IV weekly, in high risk patients

Rare subtype:

Malignant perivascular epithelioid cell tumors (PEComas)

- rare malignant mesenchymal neoplasms TSC1 or TSC2 mutations (leading to mTOR activation)
- Treated with sirolimus; or nab-sirolimus

Meredith, L., Chao, T., Nevler, A. *et al.* A rare metastatic mesenteric malignant PEComa with *TSC2* mutation treated with palliative surgical resection and nab-sirolimus: a case report. *Diagn Pathol* **18**, 45 (2023)

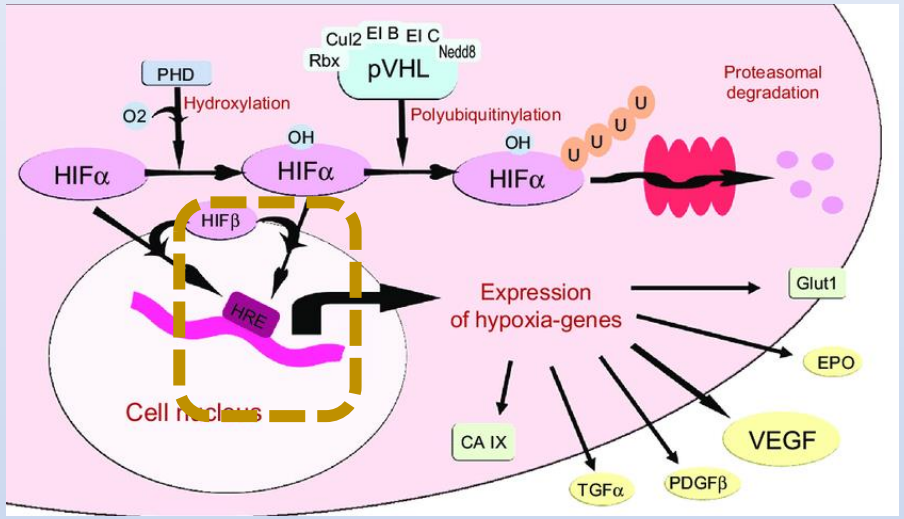


HIF2

Hypoxia inducible factor

Targeting HIF-2 alpha:Belzutifan

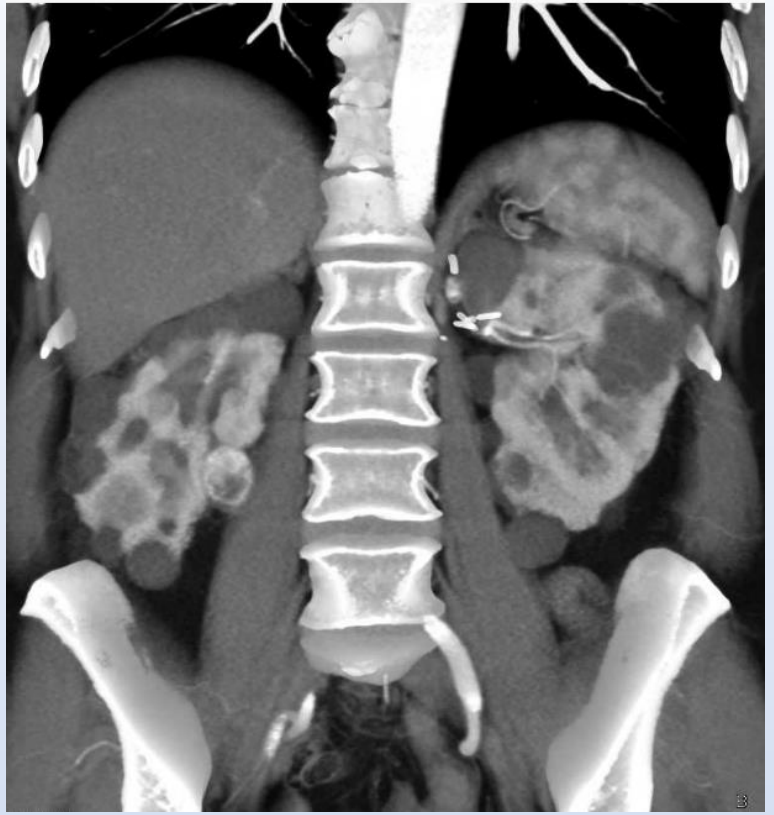
- On label for inherited VHL syndrome
- Off label for post-VEGF RCC
- Many studies, including adjuvant treatment



Belzutifan

120 mg/d

40 mg tablets



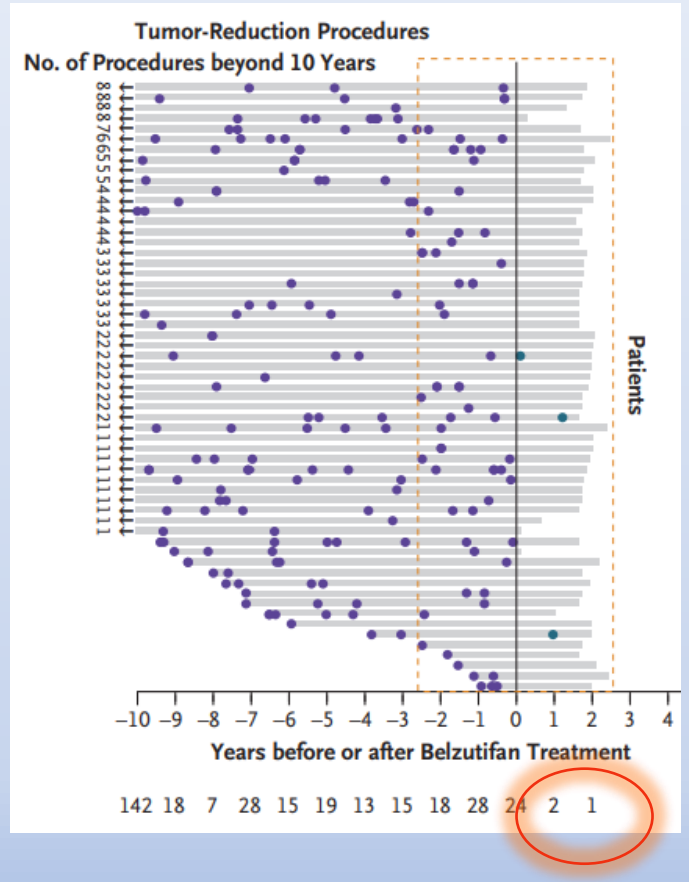
Multiple bilateral tumors
CT reconstruction view.

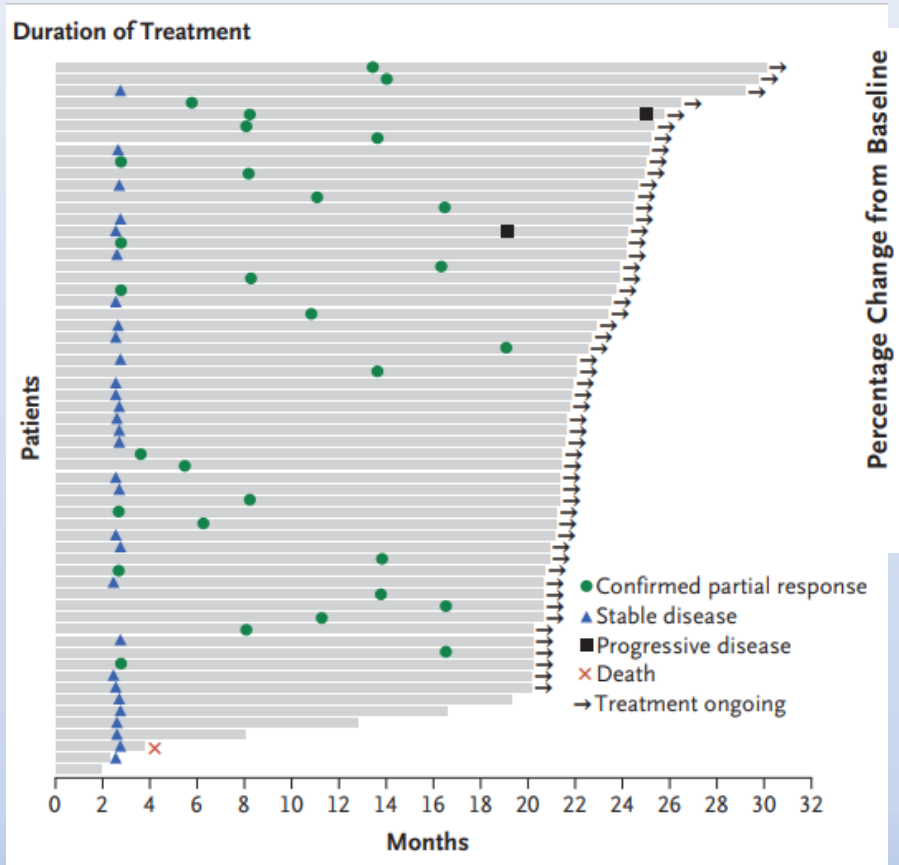
https://www.ctisus.com/teachingfiles/kidney/339265
(Case 6825)

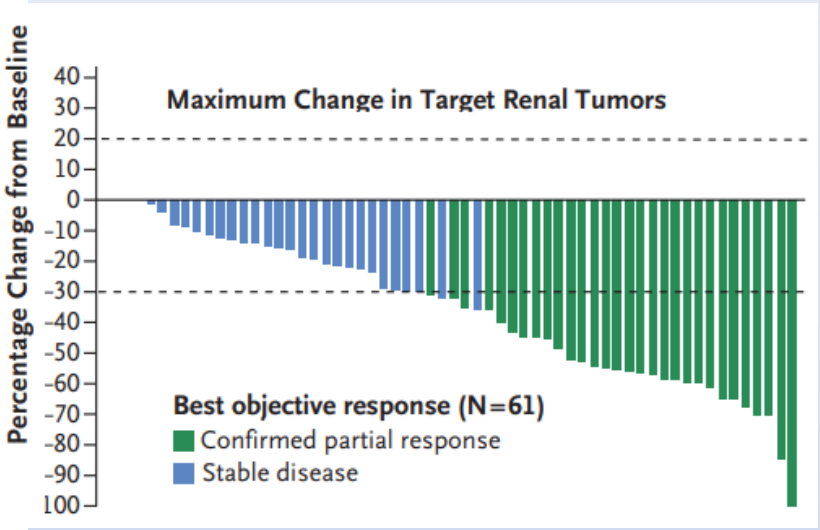
Targeting HIF-2 alpha:Belzutifan

- Smaller tumors
- Fewer procedures

Jonasch E, Donskov F, Iliopoulos et al. MK-6482-004 Investigators.
Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease.
N Engl J Med. 2021 Nov 25;385(22):2036-2046



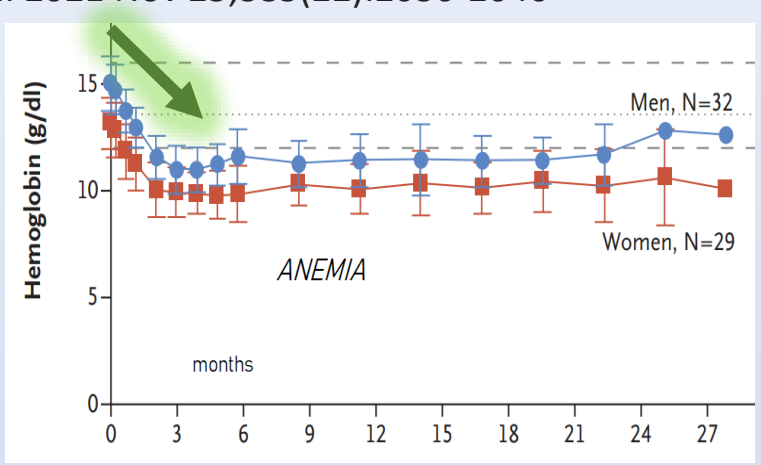




Targeting HIF-2 alpha:Belzutifan

- Frequent moderate anemia
- Rare high-grade problems

Jonasch E, Donskov F, Iliopoulos et al. MK-6482-004 Investigators. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med. 2021 Nov 25;385(22):2036-2046



Event	number (percent)			
Most frequent adverse events	Any Grade	Grade 1	Grade 2	Grade 3
Anemia	55 (90)	24 (39)	26 (43)	5 (8)
Fatigue	40 (66)	29 (48)	8 (13)	3 (5)
Headache	25 (41)	20 (33)	5 (8)	0
Dizziness	24 (39)	20 (33)	4 (7)	0
Nausea	21 (34)	15 (25)	6 (10)	0
Dyspnea	14 (23)	13 (21)	0	1 (2)
Arthralgia	12 (20)	10 (16)	2 (3)	0
Constipation	12 (20)	10 (16)	2 (3)	0
Myalgia	12 (20)	9 (15)	2 (3)	1 (2)

A few B-based RCC trials:

- B monotherapy
- B + lenvatinib
- B + pablociclib*

  [* not approved in RCC]

ALL ARE INVESTIGATIONAL COMBINATIONS

- Cabozantinib vs B + lenvatinib
- Adjuvant pembrolizumab +/- B
- Lenvantinib/pembrolizumab

  Alone [on-label]

  vs +B,

  vs + Quavonlimab*

  [* investigational CTLA4 medication]

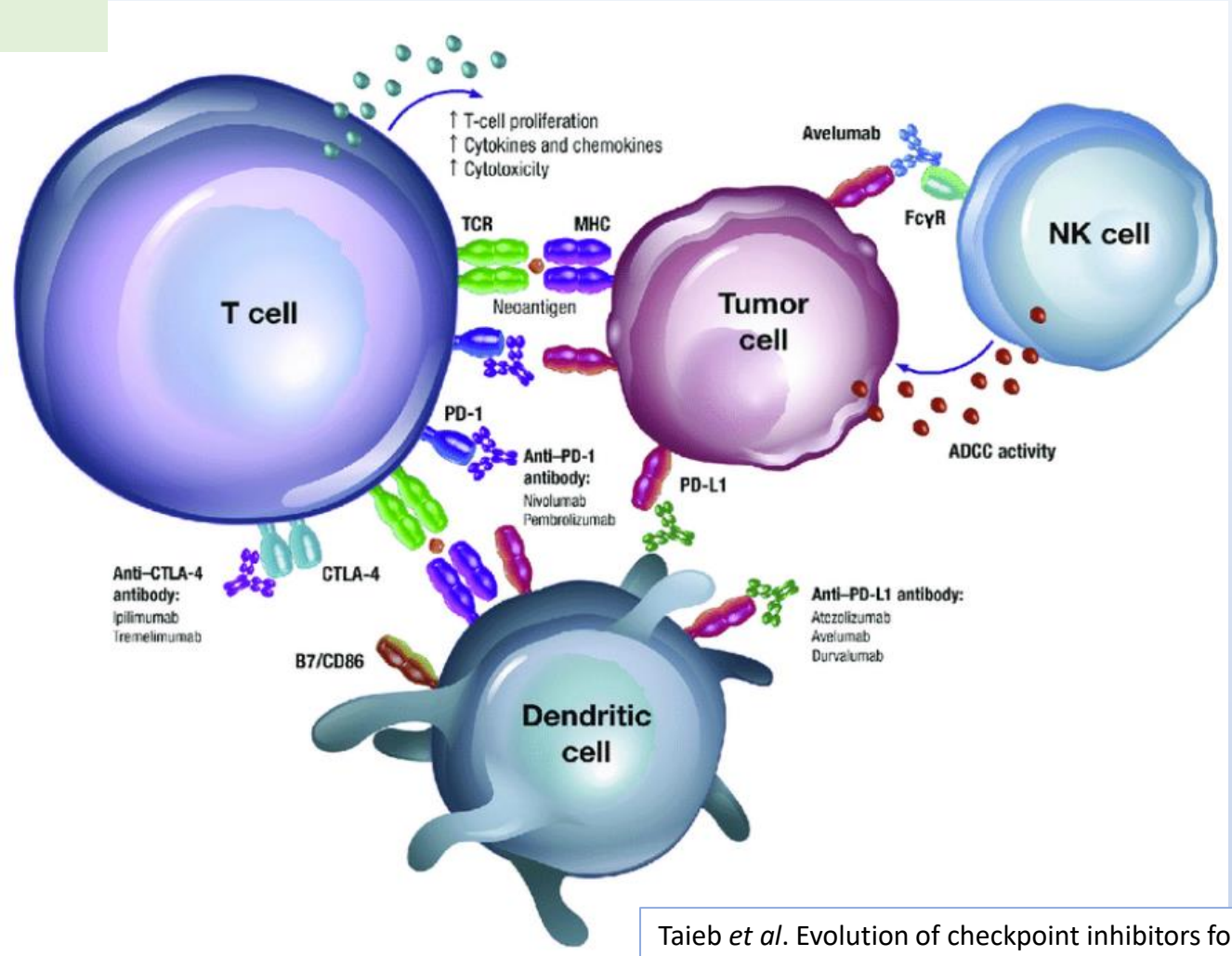
Checkpoint inhibitors

Checkpoint inhibitors

IL2 receptor:
low affinity : T-effector
high affinity : T-reg; NK

PD-1: on lymphocyte
PD-L1: on target cell

CTLA-4: on lymphocyte
interacts with dendritic cell



Taieb *et al*. Evolution of checkpoint inhibitors for the treatment of metastatic gastric cancers: Current status and future perspectives. *Cancer Treatment Reviews. April 2018*.

"RCC ipi-nivo 1-3":
ipi 1 mg/kg/dose, nivo 3 mg/kg/dose x 4
"melanoma ipi-nivo 3-1"
ipi 3 mg/kg/dose, nivo 1 mg/kg/dose x 4
… and then nivolumab monotherapy

Immune checkpoint inhibitor side effects.

	Nivolumab plus Ipilimumab	
	Any Grade	Grade 3 or 4
	number of patients (percent)	
All events	509 (93)	250 (46)
Fatigue	202 (37)	23 (4)
Pruritus	154 (28)	3 (<1)
Diarrhea	145 (27)	21 (4)
Rash	118 (22)	8 (1)
Nausea	109 (20)	8 (1)
Increased lipase level	90 (16)	56 (10)
Hypothyroidism	85 (16)	2 (<1)
Decreased appetite	75 (14)	7 (1)
Asthenia	72 (13)	8 (1)
Vomiting	59 (11)	4 (<1)
Anemia	34 (6)	2 (<1)
Dysgeusia	31 (6)	0

All PD-1 therapies – across all diagnoses:
Risks, with early or delayed latency:

Every organ system is at risk

<u>Respiratory:</u>
- *Pneumonitis*
- *Respiratory depression*

<u>GI:</u>
- *Diarrhea, colitis, GI bleeding*
- *Jaundice, nausea, vomiting*
- *Constipation*
- *Abdominal pain*
- *Pancreatitis*

<u>Endocrine</u>
- *Thyroiditis*
- *Hypopituitary*
- *Hypoadrenal*
- *Testosterone*

<u>Renal</u>
- *Creatinine elevation*
- *Nephritis*

<u>Skin</u>
- *Dry rash*
- *Itching*
- *Blistering rash*

<u>Central nervous system</u>
- *Headache*
- *RPLS*

<u>Musculoskeletal</u>
- *Myasthenia-like syndrome*
- *Arthritis*
- *myositis*

<u>Cardiac</u>
- *Carditis*
- *Heart-conduction*
- *Tachycardia*

Chatzkel J, Schell MJ, Chahoud J, Zhang J, Jain R, Swank J, Ludlow S, Lombardi K, Lucas Y, Croft C, Rembisz J, Jameel G, Fishman M. Coordinated Pembrolizumab and High Dose IL-2 (5-in-a-Row Schedule) for Therapy of Metastatic Clear Cell Renal Cancer. *Clin Genitourin Cancer.* 2022 Jun;20(3):252-259.

CLINICAL RESULTS: Phase 2 trial result pembrolizumab and IL-2 (not on-label)

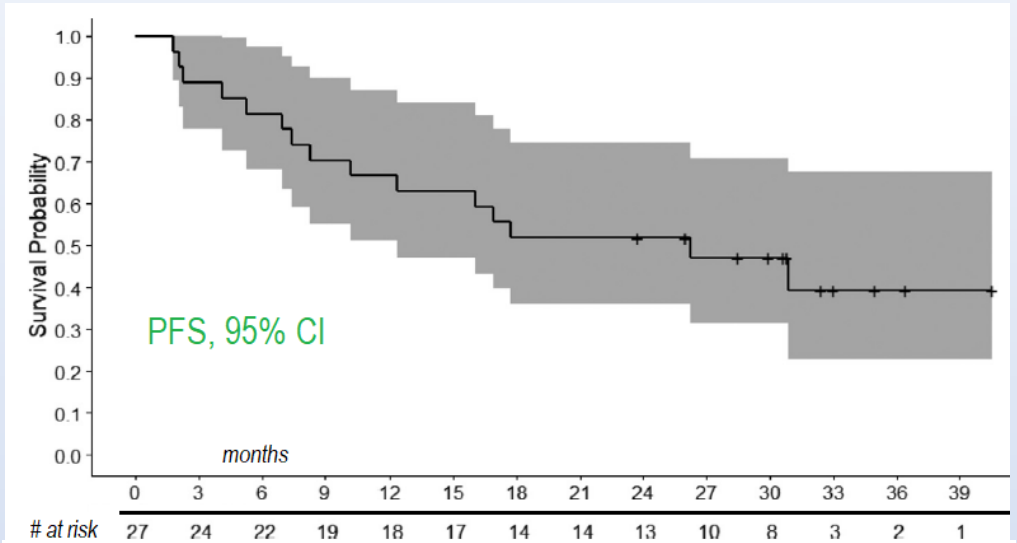
Demographics and baseline characteristics (N=27)	
Age	
Median (range) – years	60
<65 y - number (%)	17 (63)
Men sex - number (%)	22 (81)
IMDC prognostic risk - number (%)	
Favorable	10 (37)
Intermediate	16 (59)
Poor	1 (4)
Number with tumor at specific sites:	
Kidney	5
Renal bed	2
Lung or pleura	17
Liver	3
Bone	2
Adrenal	3
Any LN	14
Mediastinal LN	12
Other LN	7
Other*	7

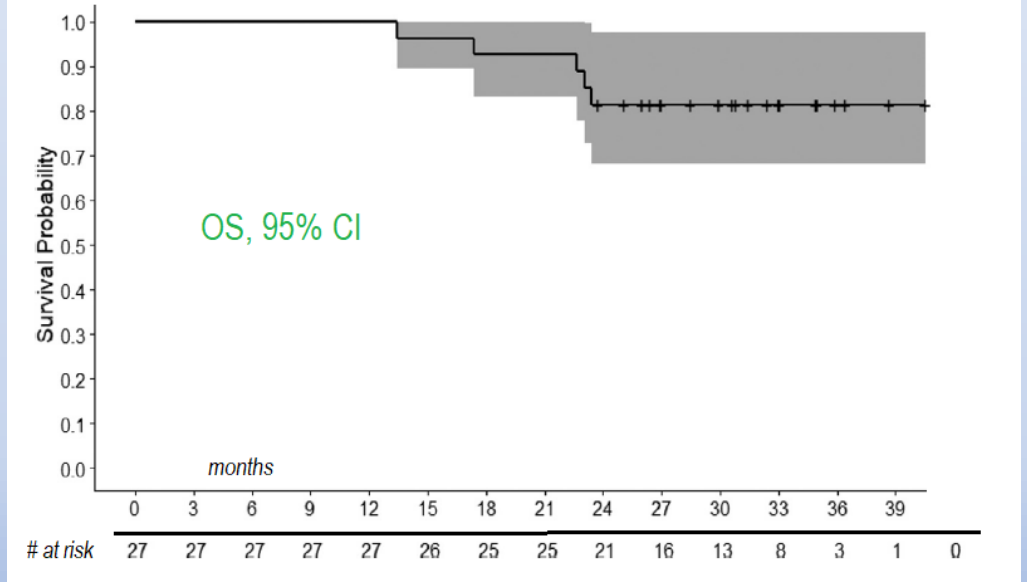
[1] One each: Brain; pancreas; chest wall; gluteal; paraspinal; soft tissue of hip; retroperitoneum.

Summary of Objective Responses	
Objective response rate	19 (70)
Best objective response - number (%)	
Complete Response	5 (19)
Partial Response	14 (52)
Stable disease	5 (19)
Progressive disease	2 (7)
Not Assessed	1 (4)*

* One patient did not receive any study treatment after baseline imaging was obtained

Null hypothesis <45% ORR



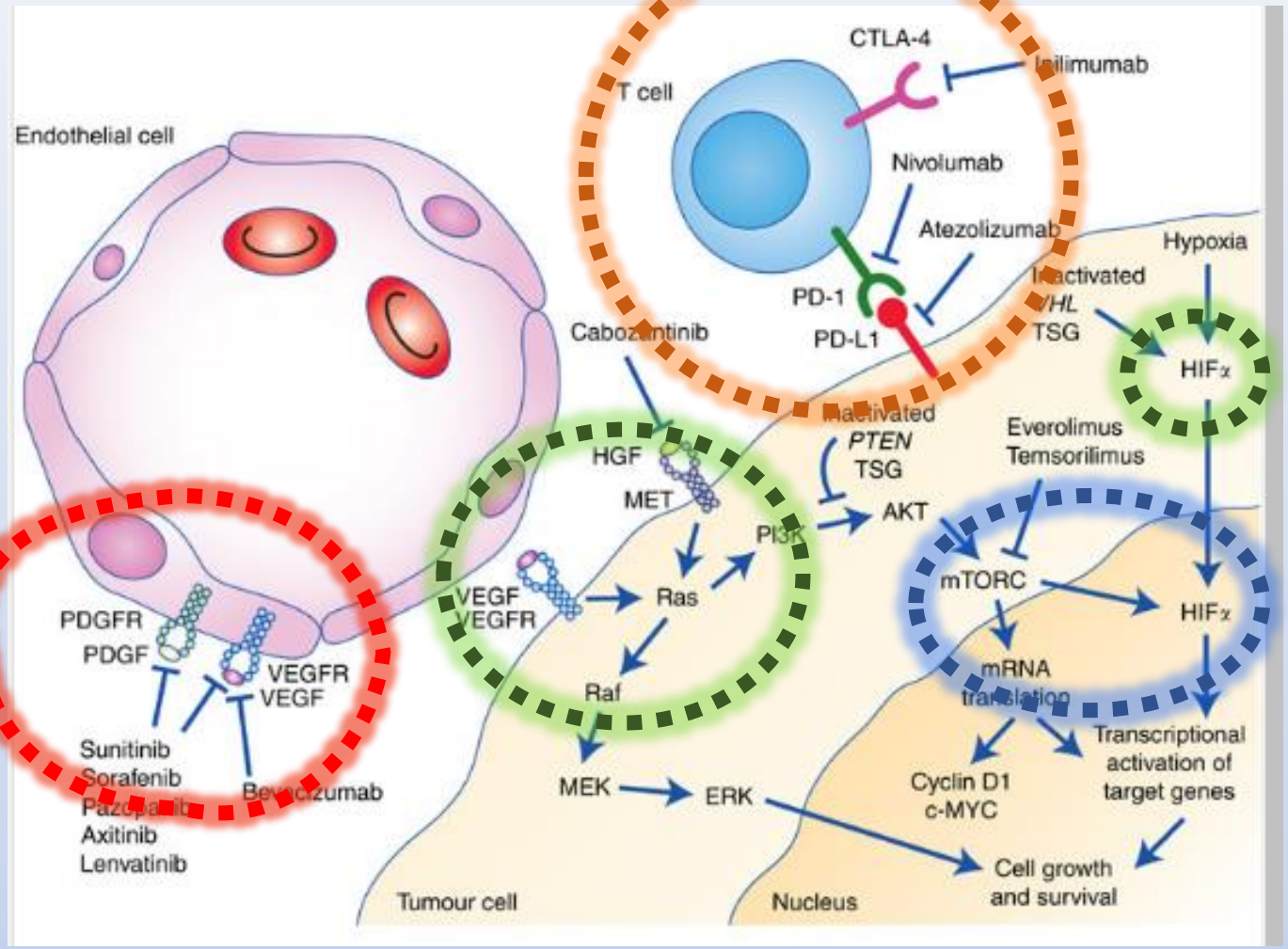


Summary mechanisms

Medical treatment of renal cancer: new horizons

British Journal of Cancer (2016) 115, 505–516 | doi: 10.1038/bjc.2016.230

Basma Greef*,1 and Tim Eisen2



ANGIOGENESIS

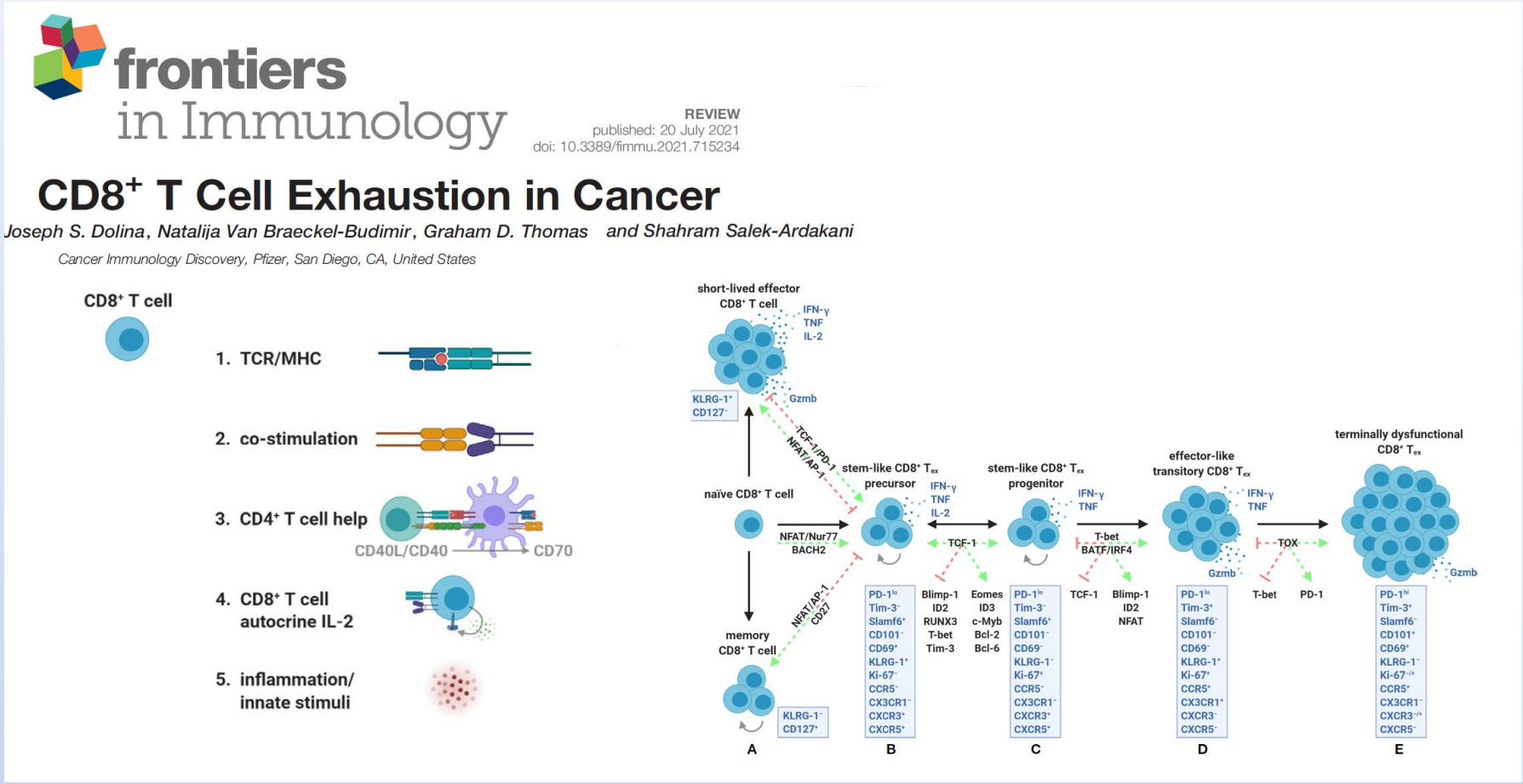
GROWTH STIMULATION

TUMOR METABOLISM

IMMUNE ACTIVATION

Building on immunotherapy

Breaking T cell exhaustion:

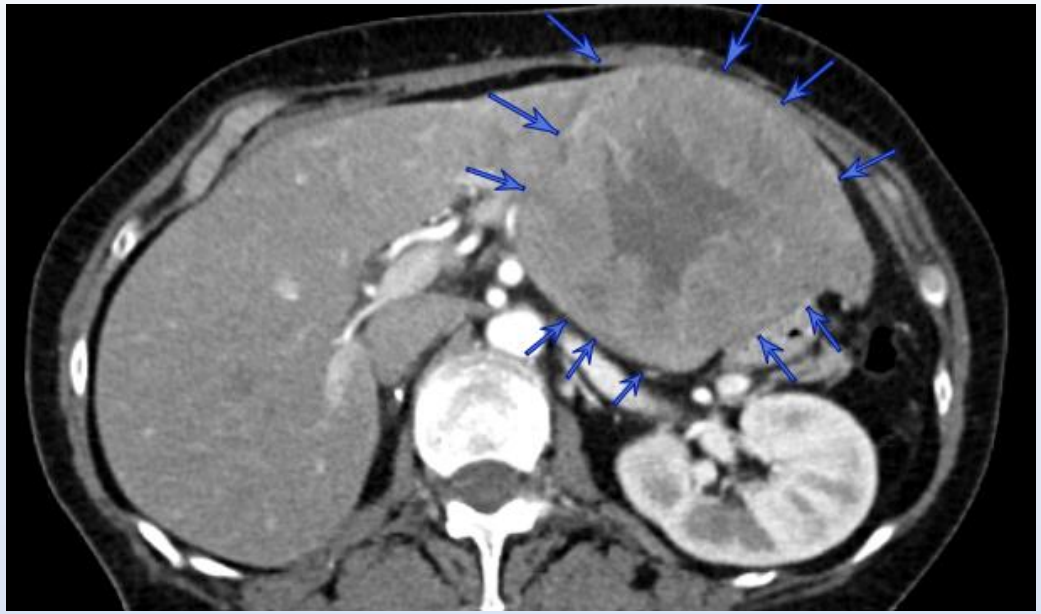


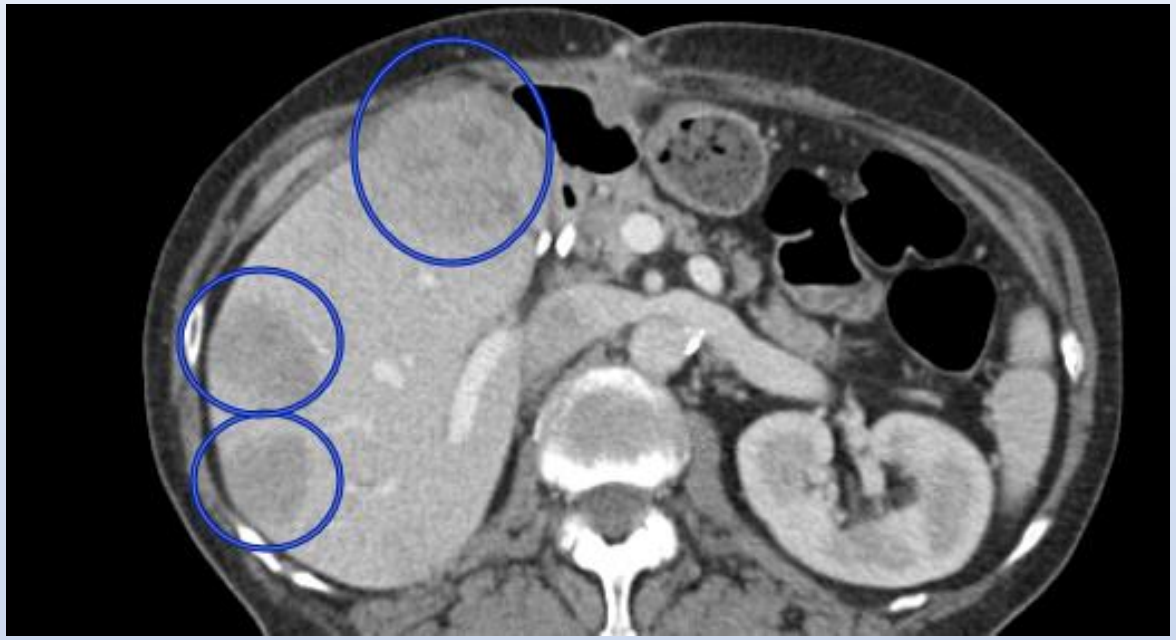
Nephrectomy decisions

Now

Maybe later

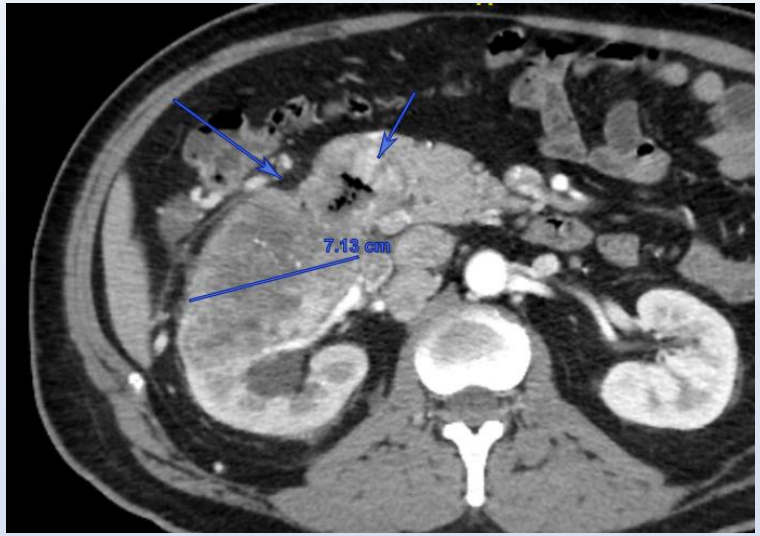
Maybe never

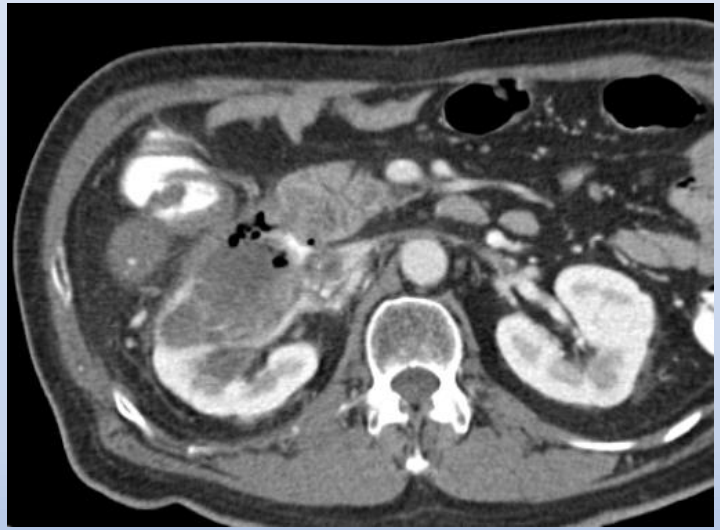




- Papillary type 2
- Liver dominant

T4 (duodenal invasion)

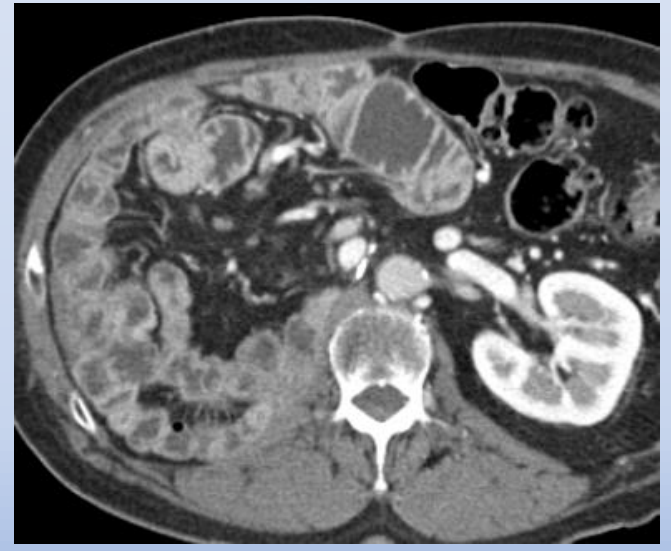




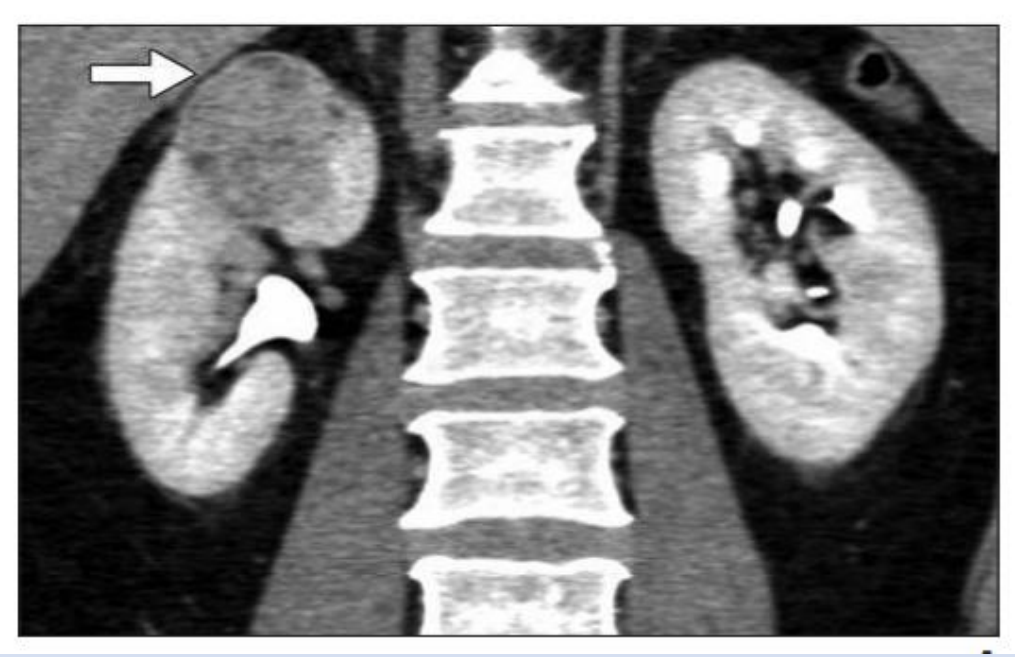
- Bleeding 1-3 units/week

- XRT (kidney too)
- Neoadjuvant sunitinib
- Surgery

- Off treatment
- NED + 19 months



Nephrectomy Now?



Athina C. Tsili[1]
Maria I. Argyropoulou[1]
Anna Gousia[2]
John Kalef-Ezra[3]
Nikolaos Sofikitis[4]
Vasiliki Malamou-Mitsi[2]
Konstantinos Tsampoulas[1]

Renal Cell Carcinoma: Value of Multiphase MDCT With Multiplanar Reformations in the Detection of Pseudocapsule

AJR Online August 2012 p 380 -387

- ✔ Projected reserve of remaining kidney is good.
  - Creatinine level
  - Differential renal scan
- ✔ No general medical contraindication to surgery
  - Recent MI; new stents
  - Pulmonary reserve
- ✔ No other identifiable dominant disease
  - COPD
  - Dementia
- ✔ No evident other disease: Going for cure
- ✔ Possible partial nephrectomy?

Nephrectomy *maybe* later?

Survival evaluations

Resectable primary

+ metastatic disease

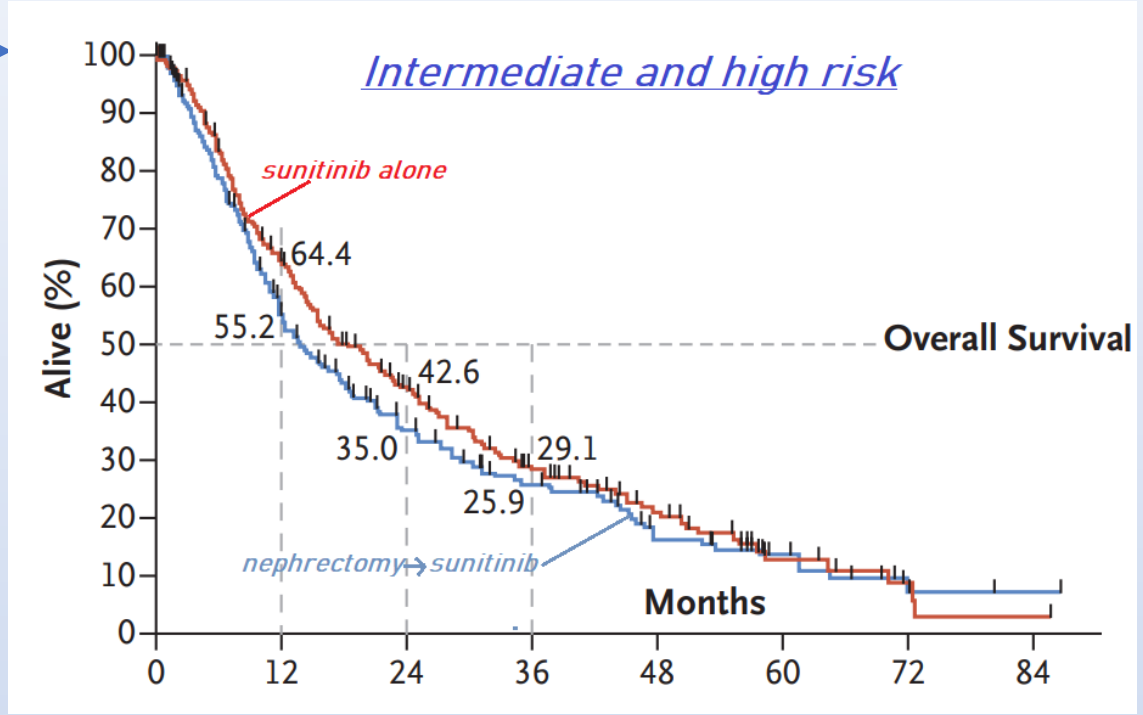
(2009-2017)
N= 450

Randomize

nephrectomy → sunitinib

sunitinib → nephrectomy

nephrectomy
sometimes (17%)



CARMENA trial:
55% intermediate
45% high-risk

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma *N Engl J Med 2018;379:417-27*

A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, C. Beisland, M. Aitchison, S. Oudard, J.-J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.-C. Bernhard, L. Albiges, M.-O. Timsit, T. Lebret, and B. Escudier

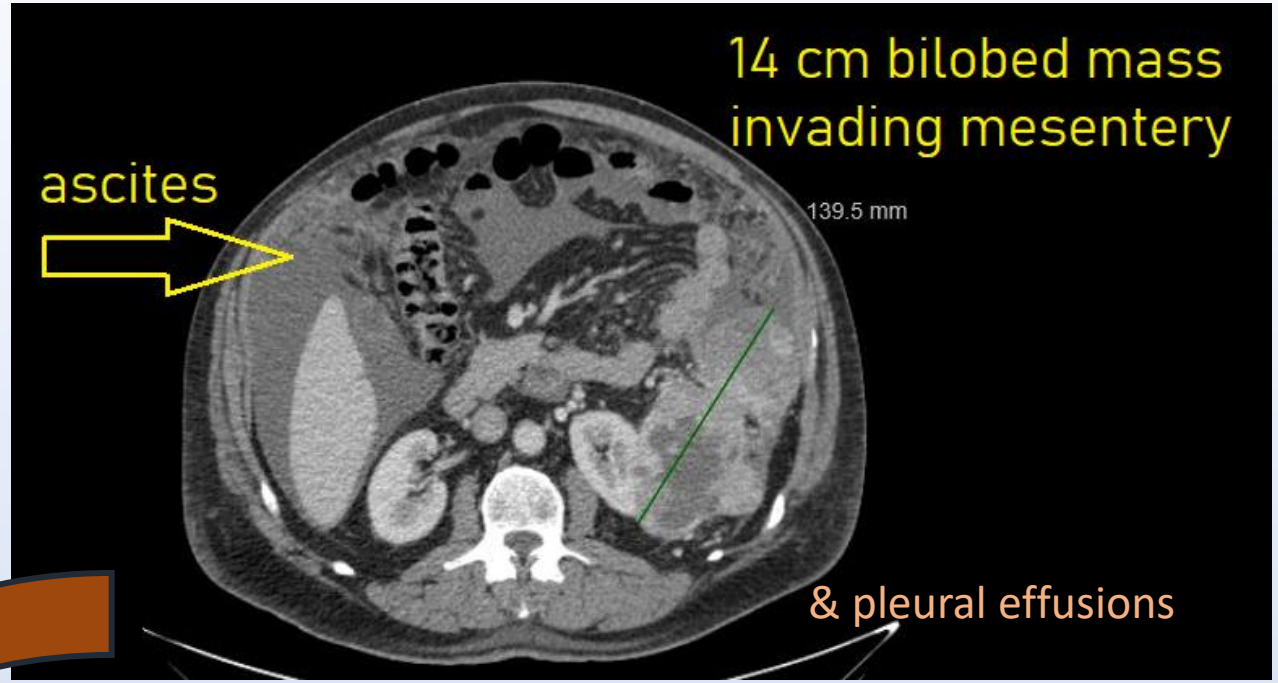
Conclusion: Not much advantage to up-front nephrectomy.
… and then sunitinib lost about 6 consecutive trials.

(vs lenvatinib/everolimus, vs cabozanitinb, vs ipilumimab-nivolumab, vs cabozantinib-nivolumab, vs axitinib-pembrolizumab, vs lenvatinib/pembrolizumab)

Nephrectomy later?

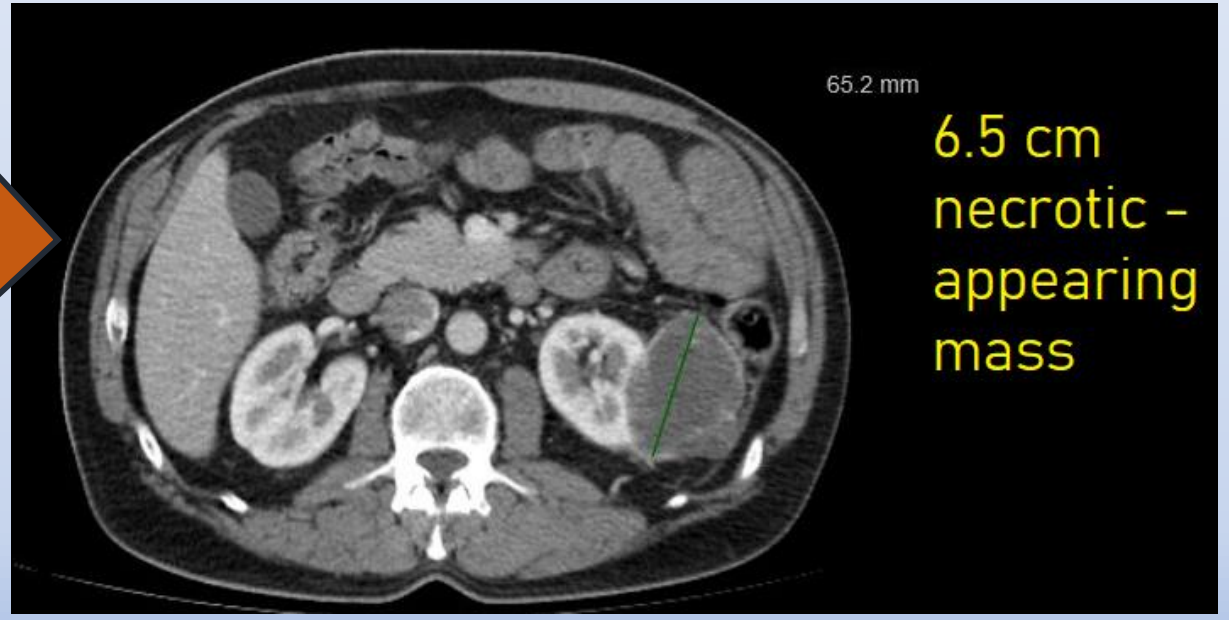
✔ Extent of other disease:

Balance of renal *vs* extrarenal tumor burden after up-front medical therapy



8 months treatment:
cabozantinib
& nivolumab

& 3 months more, then nephrectomy (and partial colectomy, and lymphadenecgtomy): No extrarenal disease on scan or in specimen. No remaining visible disease.



Nephrectomy, maybe never?

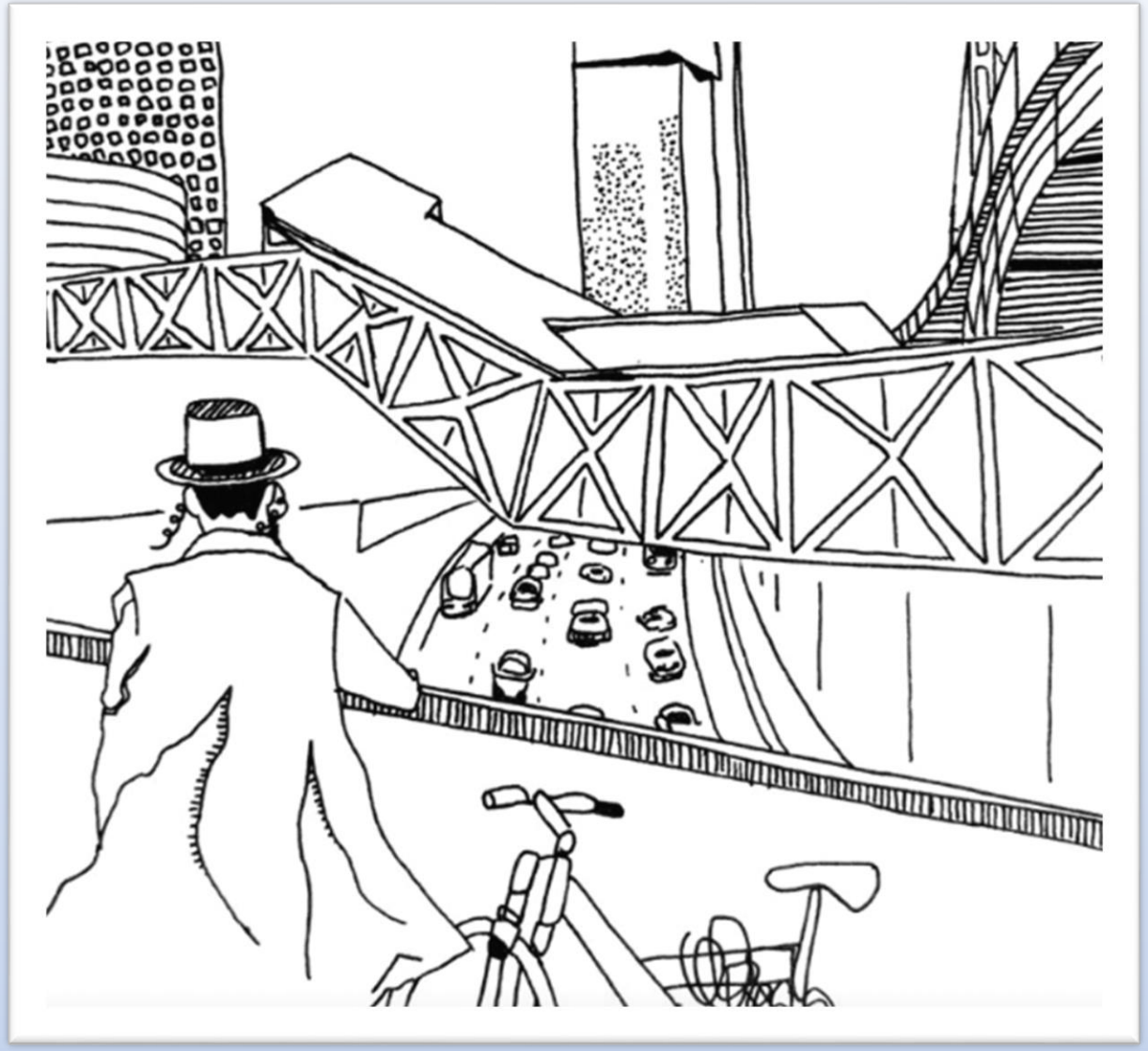
- ✔ Projected reserve of remaining kidney is good.
  - Creatinine level
  - Differential renal scan
- ✔ Low (under 80%) fractional debulking; balance of renal *vs* extrarenal tumor burden after up-front medical therapy
- ✔ Age of patient vs size of mass, natural growth rate.
  - Cardiac, pulmonary reserve
  - Pulmonary reserve
- ✔ Downstage to a cryotherapy or partial nephrectomy?

Adjuvant treatments

Successes

Trials with no benefit

Ongoing trials



Adjuvant treatments

Successes

Trials with no benefit

Ongoing trials

Yes (PFS): (no OS)

S-TRAC

Sunitinib 12mo vs *NOT*

Yes (OS, PFS)

Keynote 564

Pembroizumab x12 mo vs *NOT*

NO:

Vaccines (several: Reniale; Vitespen)

Interferon

Interleukin-2

Interferon with IL-2

Cytokines with 5-FU

Sunitinib (ASSURE)

Sorafenib (ASSURE)

Pazopanib (PROTECT)

Axitinib (ATLAS)

Ipilumimab-nivolumab

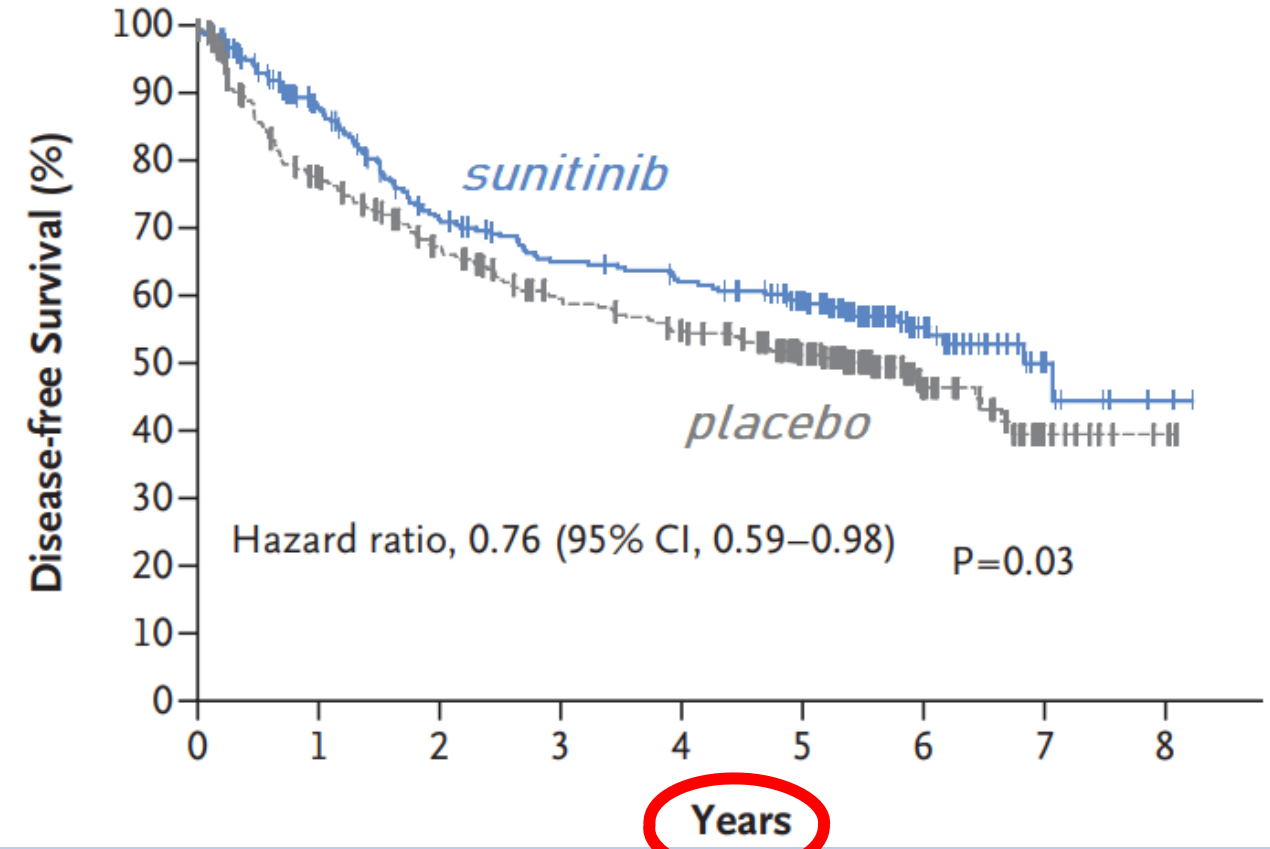
Atezolizumab

Yes (PFS): (no OS)
S-TRAC
Sunitinib 12mo vs *NOT*

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

N Engl J Med 2016;375:2246-54

A. Ravaud, R.J. Motzer, H.S. Pandha, D.J. George, A.J. Pantuck, A. Patel, Y.-H. Chang, B. Escudier, F. Donskov, A. Magheli, G. Carteni, B. Laguerre, P. Tomczak, J. Breza, P. Gerletti, M. Lechuga, X. Lin, J.-F. Martini, K. Ramaswamy, M. Casey, M. Staehler, and J.-J. Patard, for the S-TRAC Investigators*

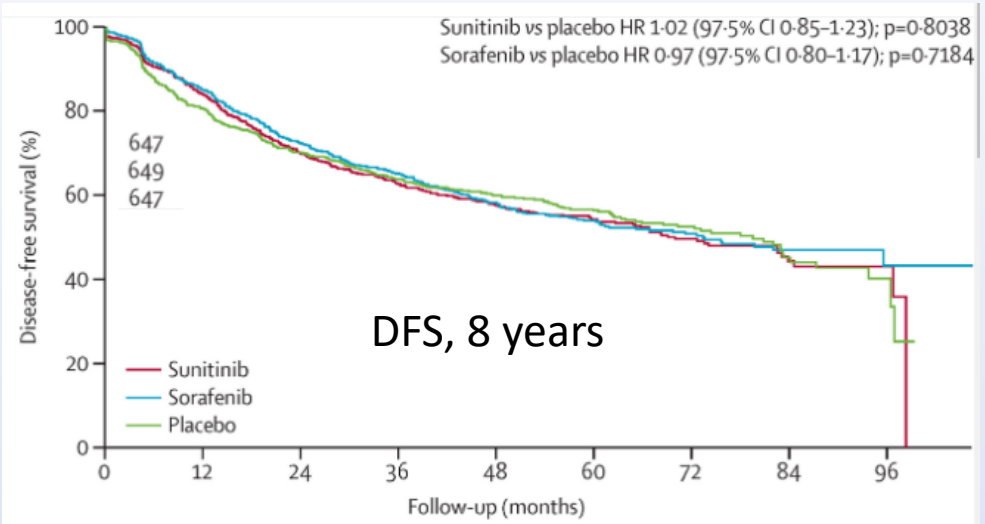


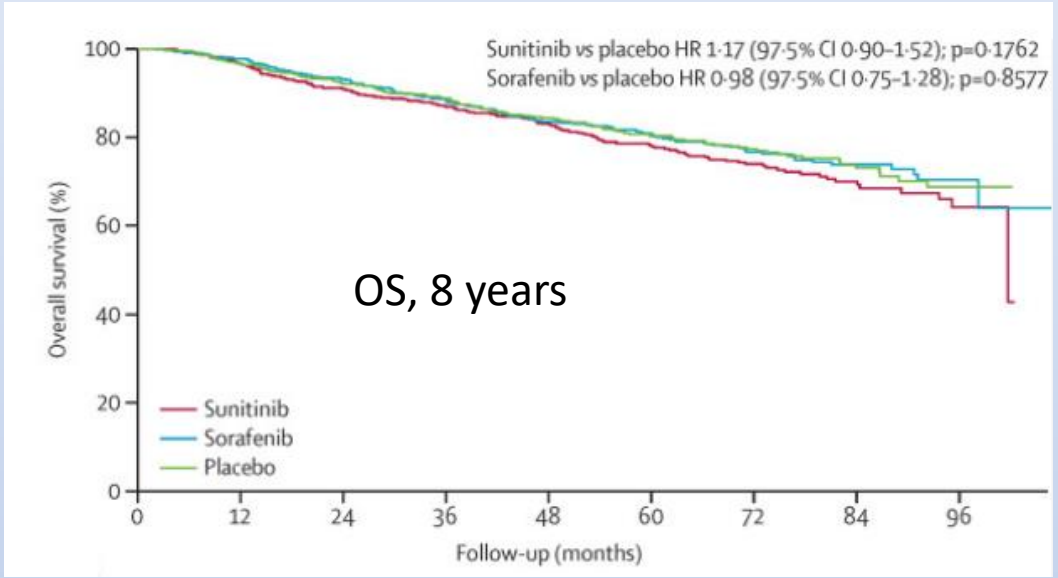
OS:
deaths reported:
64 patients sunitinib group
64 (20.9%) in placebo group

NO: ASSURE
Sunitinib vs placebo
Sorafenib vs placebo

1 year:

Sorafenib 400 mg po BID (+ placebo)
Sunitinib 50 mg/d (28 on/ 14 off) (+ placebo)
Placebo + placebo





N Haas et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. THE LANCET VOLUME 387, ISSUE 10032, P2008-2016, MAY 14, 2016

Yes (OS, PFS)

Keynote 564

Pembrolizumab x12 mo vs *NOT*

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Oncol 2022; 23: 1133–44

*Thomas Powles, Piotr Tomczak, Se Hoon Park, Balaji Venugopal, Thomas Ferguson, Stefan N Symeonides, Jaroslav Hajek, Howard Gurney, Yen-Hwa Chang, Jae Lyun Lee, Naveed Sarwar, Antoine Thiery-Vuillemin, Marine Gross-Goupil, Mauricio Mahave, Naomi B Haas, Piotr Sawrycki, Joseph E Burgents, Lei Xu, Kentaro Imai, David I Quinn, Toni K Choueiri, for the KEYNOTE-564 Investigators**

Type of nephrectomy		
Partial	37 (7%)	38 (8%)
Radical	459 (93%)	460 (92%)
Primary tumour stage		
T1	11 (2%)	15 (3%)
T2	27 (5%)	33 (7%)
T3	444 (90%)	437 (88%)
T4	14 (3%)	13 (3%)
Tumour nuclear grade		
1	19 (4%)	16 (3%)
2	153 (31%)	150 (30%)
3	219 (44%)	213 (43%)
4	103 (21%)	119 (24%)

Metastatic stage		
M0	467 (94%)	469 (94%)
M1 with no evidence of disease	29 (6%)	29 (6%)
Disease risk category		
M0 intermediate to high	427 (86%)†	433 (87%)
M0 high	40 (8%)	36 (7%)
M1 with no evidence of disease	29 (6%)	29 (6%)
Sarcomatoid features		
Present	52 (10%)	59 (12%)
Absent	414 (83%)	415 (83%)
Unknown	30 (6%)	24 (5%)
PD-L1 combined positive score†		
<1	124 (25%)	113 (23%)
≥1	365 (74%)	383 (77%)

Yes (OS, PFS)

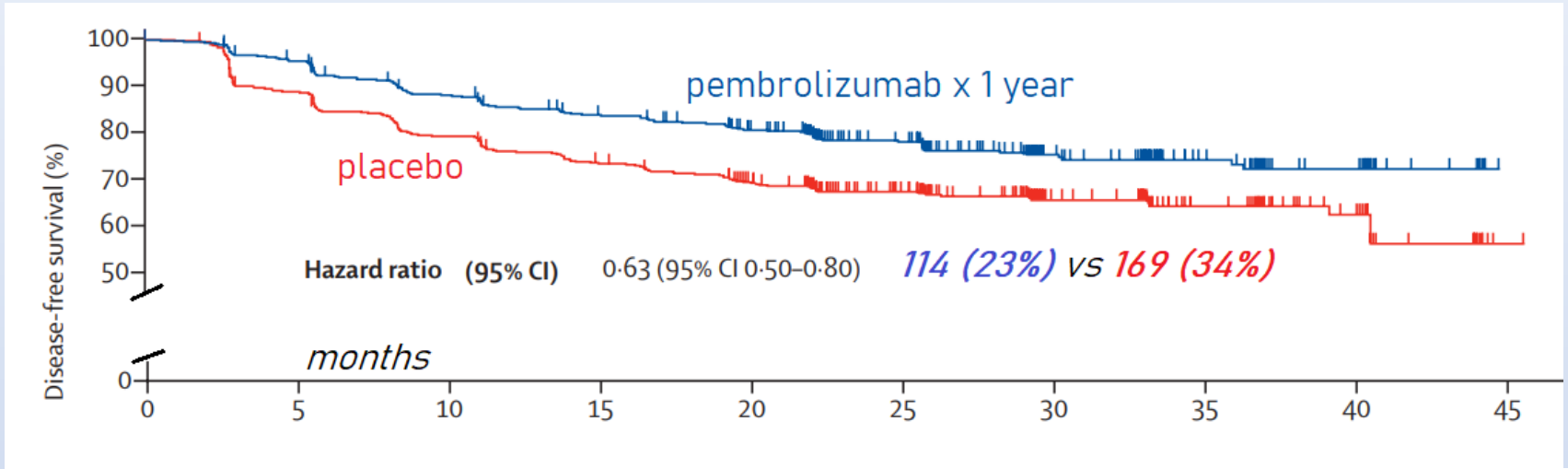
Keynote 564

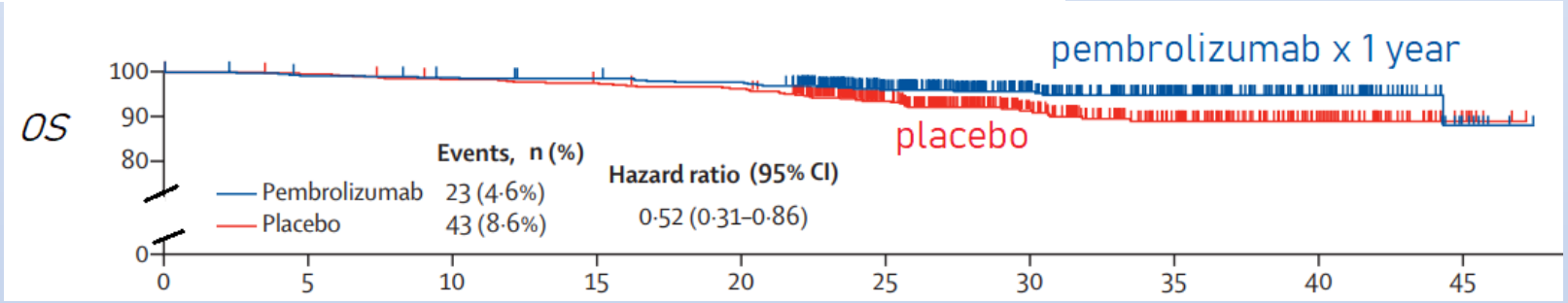
Pembroizumab x12 mo vs *NOT*

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Oncol 2022; 23: 1133–44

*Thomas Powles, Piotr Tomczak, Se Hoon Park, Balaji Venugopal, Thomas Ferguson, Stefan N Symeonides, Jaroslav Hajek, Howard Gurney, Yen-Hwa Chang, Jae Lyun Lee, Naveed Sarwar, Antoine Thiery-Vuillemin, Marine Gross-Goupil, Mauricio Mahave, Naomi B Haas, Piotr Sawrycki, Joseph E Burgents, Lei Xu, Kentaro Imai, David I Quinn, Toni K Choueiri, for the KEYNOTE-564 Investigators**





Adjuvant nivolumab and ipilimumab vs placebo (CheckMate 914)

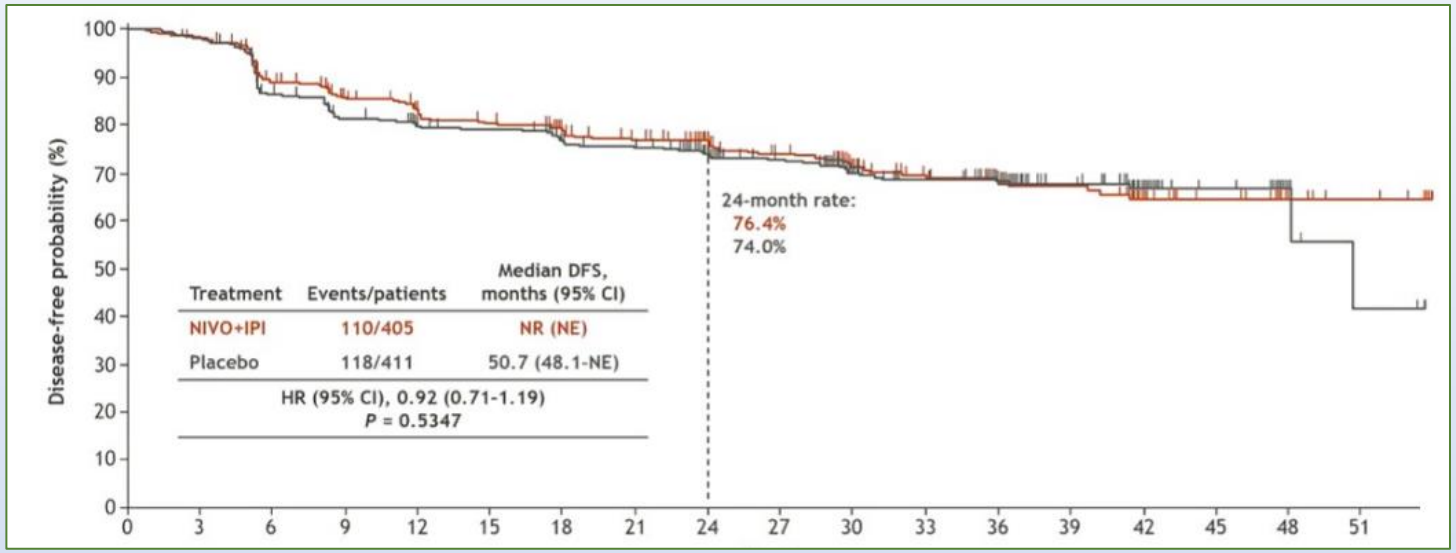
6 months :

nivolumab 240 q2 w + Ipilimumab 1 mg/kg/dose q6w (vs None)

- pT2a (G 3 or 4); *or*
- pT2b, pT3, pT4 ; N0M0; *or*
- pT (any) N1 M0

>>All were M0<<

- Adverse events:
  - G3+: 28.5% vs 2.0%



DFS was not met (HR, 0.92; 95% CI, 0.71–1.19; P = 0.5347)

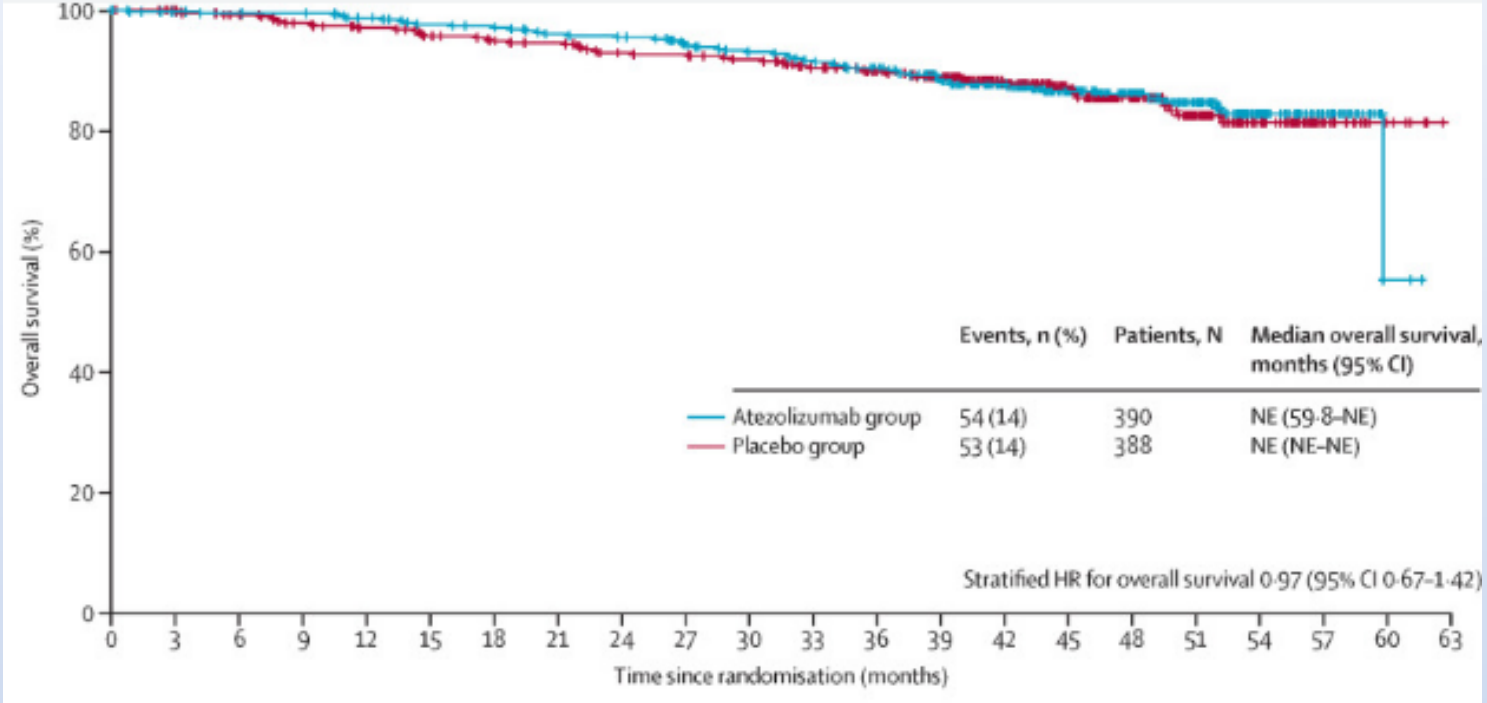
Motzer et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. *THE LANCET:* VOLUME 401, ISSUE 10379, P821-832, MARCH 11, 2023

Adjuvant atezolizumab vs placebo (IMmotion 010)

Atezolizumab 1200 mg, q3w x 1 year.

- T2 G4;
- T3a Gr 3/4;
- T3b/c or T4
- TxN+
- M1 resected with no evidence of disease

- Adverse events:
  - G3+: 27% vs 21%



Pal et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial

THE LANCET VOLUME 400, ISSUE 10358, P1103-1116, OCTOBER 01, 2022

DFS was not met (0.93, 95% CI 0.75-1.15, p=0.50)

Adjuvant conclusions:

Trials are long

Huge amount of resources

Disease are heterogenous

More studies: Same general format

>>>Use selectively <<<

Challenges in clinical practice

Challenges in practice:

A lot of issues are not covered in clinical trials:

Brain lesions

- At presentation vs at recurrence
- How often to scan
- Surgery or radiation immediately
- Medical treatment and close re-evaluation

Challenges in practice:

A lot of issues are not covered in clinical trials:

Restarting after good response

- Debulking nephrectomy
- Nephrectomy for cure after initial treatment
- Anatomically isolated site of progression– can it be resected, irradiated, embolized and then stay on the same treatments?

Challenges in practice:

A lot of issues are not covered in clinical trials:

Choosing which VEGF drug to take next

- Cabozantinib: Also targets C-MET, AXL
- Lenvatinib: Also targets FGFR
- Axitinib: Very short half life
- Tivozanib: Trial specific to third line treatment
- Bevacizumab: low intensity ascites control

Challenges in practice:

A lot of issues are not covered in clinical trials:

Histology factors

- Sarcomatoid: Better difference with ipilimumab-nivolumab
- Papillary: No specific trials
- Chromophobe: No specific trials; lenvatinib-everolimus appeared good in a part of a single-arm trial
- Rare subtypes –all extrapolations
- Nephrectomy decisions for not-clear-cell cases

Summary and what’s next?

Summary and future directions

- Trials emphasize first-line treatment two-part PD-1 combinations
  - Most people take these
  - No practical ranking among them

- Single agent therapies are active
  - Mulityear responses are a regular occurrence.

- PD-1 and lymphocyte target medications: Benefit for most
- VEGFR medications: Major contribution to RCC
- Belzutifan targeted therapy: Some differences to VEGF treatment; may be something to overlap; trials are in progress.

Summary and future directions

- Treatment decisions should be individualized
- Trials don’t seem to capture patient nuances

- Sequencing these remains largely a heuristic endeavor

- T cell function– many ways to affect it
  - Reversing exhaustion
  - T cell drugs
  - Microbiome factors

Thank you!