ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE | WEBINAR SERIES

ESMO GUIDELINES: REAL WORLD CASES WEBINAR

RENAL CELL CARCINOMA

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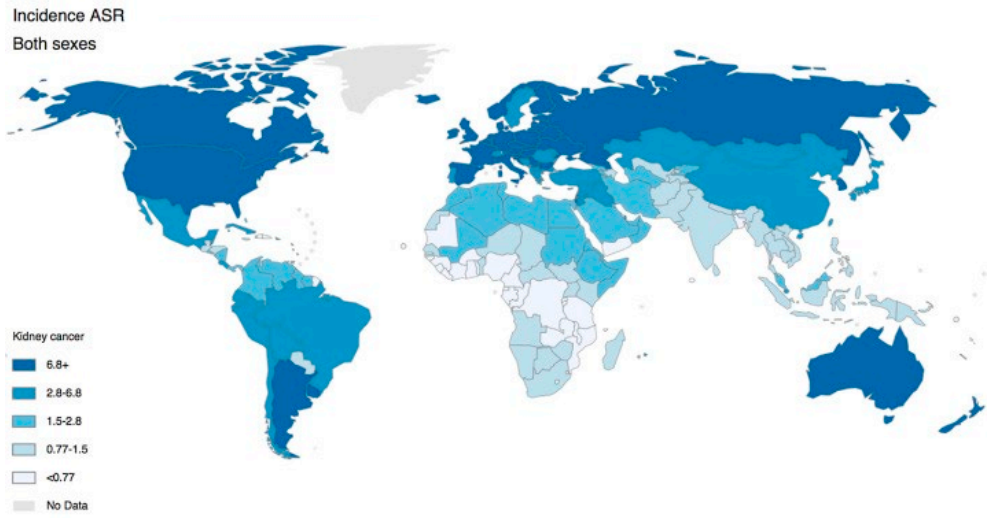
TUMOUR TOPIC, PRESENTATION OF EPIDEMIOLOGY, MOLECULAR PATHOLOGY FROM THE ESMO CPG

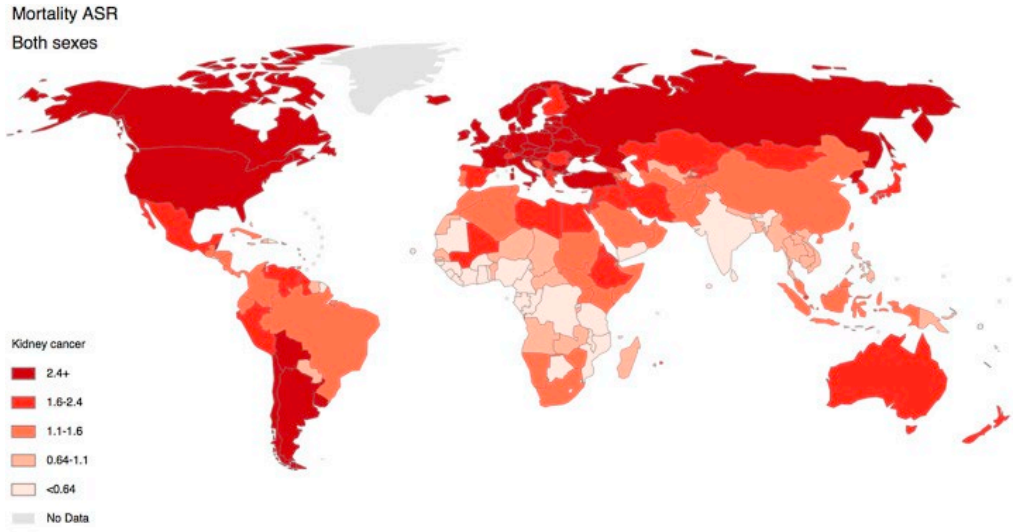
Camillo Porta
University of Bari «A. Moro» and A.O.U. Consorziale Policlinico di Bari, Bari, Italy

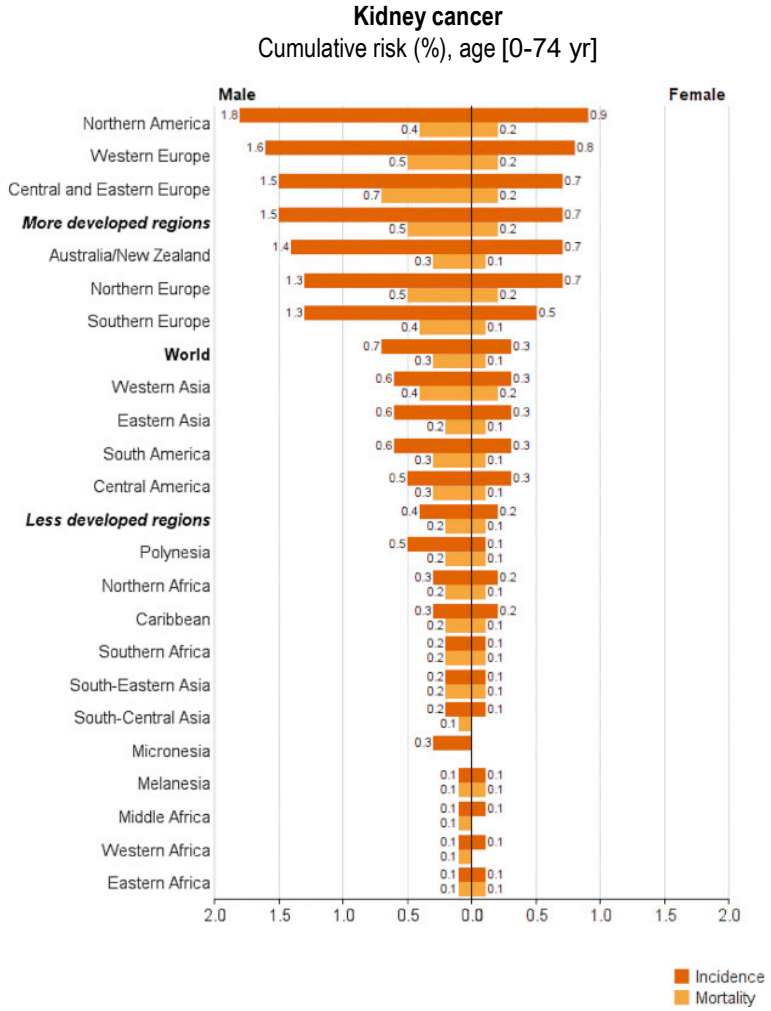
Kidney Cancer Epidemiology (I)

Incidence



Mortality





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Ferlay J, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: *IARC CancerBase* No. 11. Lyon, France: International Agency for Research on Cancer; 2013

Kidney Cancer Epidemiology (II)

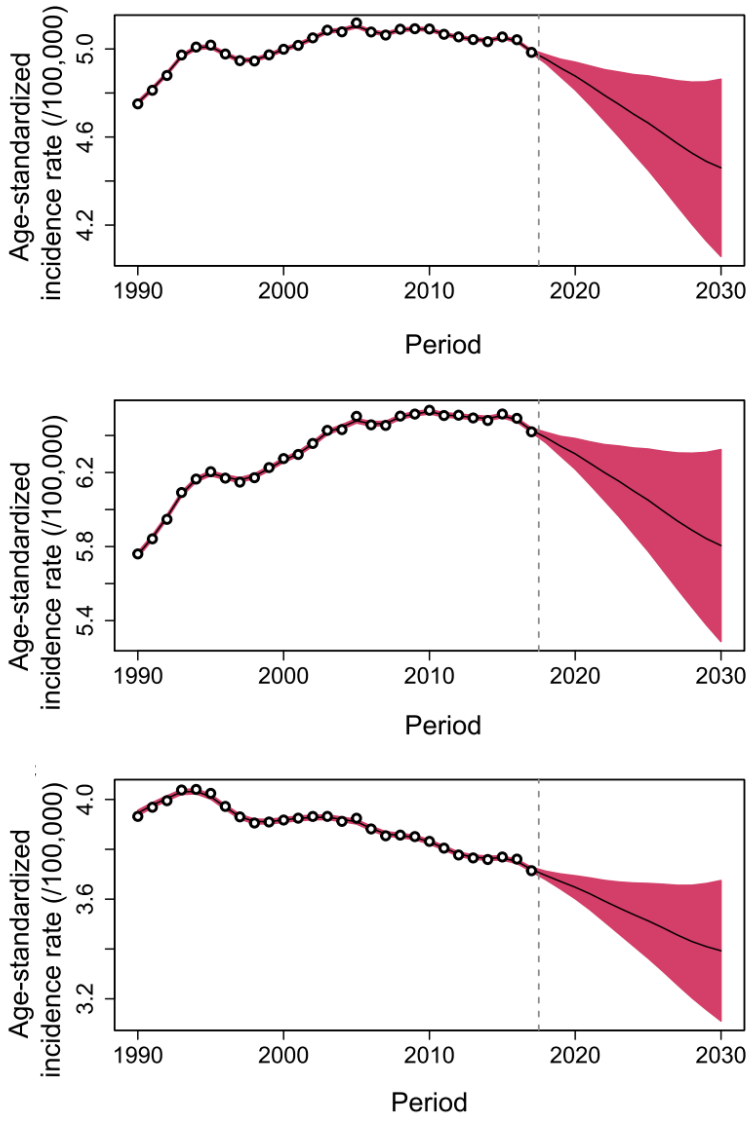
Du *et al. Biomarker Research* (2020) 8:16
https://doi.org/10.1186/s40364-020-00195-3

Biomarker Research

RESEARCH Open Access

Trends and projections of kidney cancer incidence at the global and national levels, 1990–2030: a Bayesian age-period-cohort modeling study

Zhebin Du[1†], Wei Chen[1†], Qier Xia[2†], Oumin Shi[3] and Qi Chen[1*]



Kidney cancer incidence is predicted to decrease in the next decade, but this predicted decrease will mainly be observed in developed, but not in undeveloped, countries

Du Z, et al. *Biomarker Res* 2020;8:16.

Kidney Cancer: Risk Factors and Clinical Presentation

LIFESTYLE FACTORS
Smoking • Obesity

MEDICAL CONDITIONS
Hypertension • Chronic Kidney Disease • Long-term Hemodyalisis

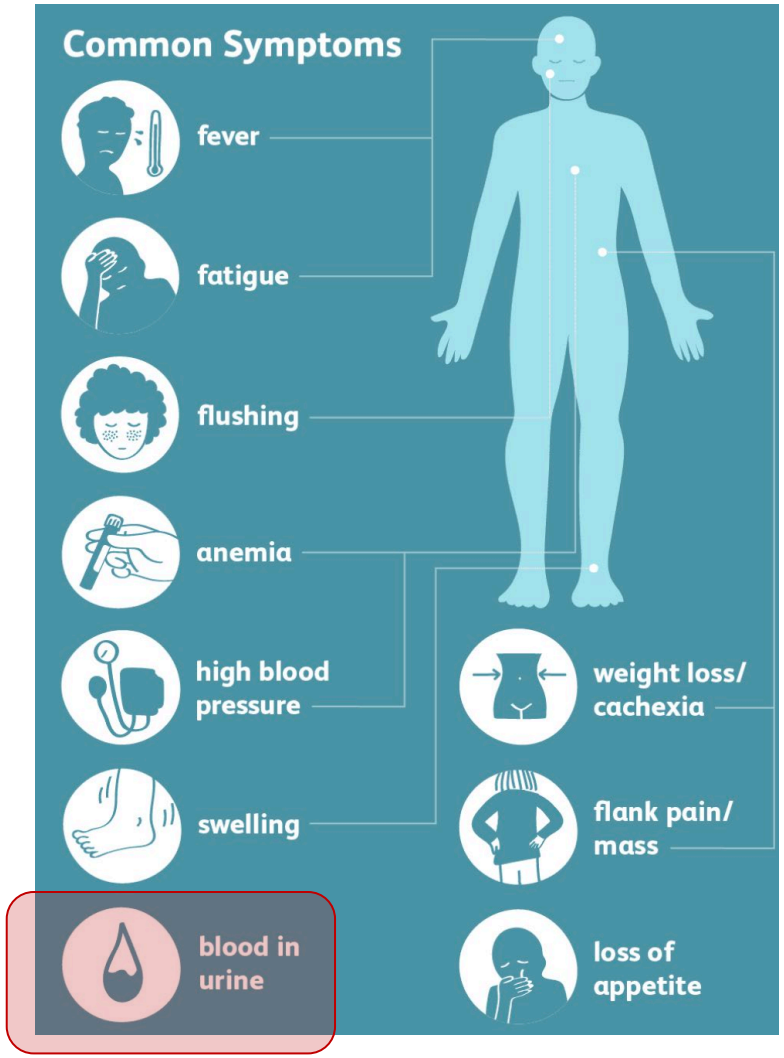
OCCUPATIONAL EXPOSURE
Chemicals such as Trichloroethylene • (Asbestos)

Modifiable

GENETIC FACTORS
Family History of Kidney Cancer • Hereditary Syndromes, e.g. von Hippel-Lindau (VHL), Birt-Hogg-Dube, and others

BIOLOGICAL FACTORS
Male gender • Age 60+

Not modifiable



Today, the classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (<10%)

Shephard E et al. *Br J Gen Pract* 2013;63:e250-5.

WHO/ISUP 2022 Histopathologic Classification

Clear cell renal tumours
- Clear cell renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential

Papillary renal tumours
- Renal papillary adenoma
- Papillary renal cell carcinoma

Oncocytic and chromophobe renal tumours
- Oncocytoma of the kidney
- Chromophobe renal cell carcinoma
- Other oncocytic tumours

Collecting duct tumours
- Collecting duct carcinoma

Other renal tumours
- Clear cell papillary renal cell tumour
- Mucinous tubular and spindle cell carcinoma
- Tubulo-cystic renal cell carcinoma
- Acquired cystic disease-associated renal cell carcinoma
- Eosinophilic solid and cystic renal cell carcinoma
- Renal cell carcinoma NOS

Molecularly defined renal carcinomas
- *TEF3*-rearranged renal cell carcinoma
- *TFEB*-rearranged renal cell carcinoma
- *ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma
- Fumarate hydratase-deficient renal cell carcinoma
- Succinate dehydrogenase-deficient renal cell carcinoma
- *ALK*-rearranged renal cell carcinoma
- *SMARCB1*-deficient renal medullary carcinoma

Moch H, et al. *Eur Urol* 2022;82:458-68.

WHO/ISUP 2022 Histopathologic Classification

Clear cell renal tumours
- **Clear cell renal cell carcinoma (a)**
- Multilocular cystic renal neoplasm of low malignant potential

Papillary renal tumours
- Renal papillary adenoma
- **Papillary renal cell carcinoma (b)**

Oncocytic and chromophobe renal tumours
- **Oncocytoma of the kidney (c)**
- **Chromophobe renal cell carcinoma (d)**
- Other oncocytic tumours

Collecting duct tumours
- Collecting duct carcinoma

Other renal tumours
- Clear cell papillary renal cell tumour
- Mucinous tubular and spindle cell carcinoma
- Tubulo-cystic renal cell carcinoma
- Acquired cystic disease-associated renal cell carcinoma
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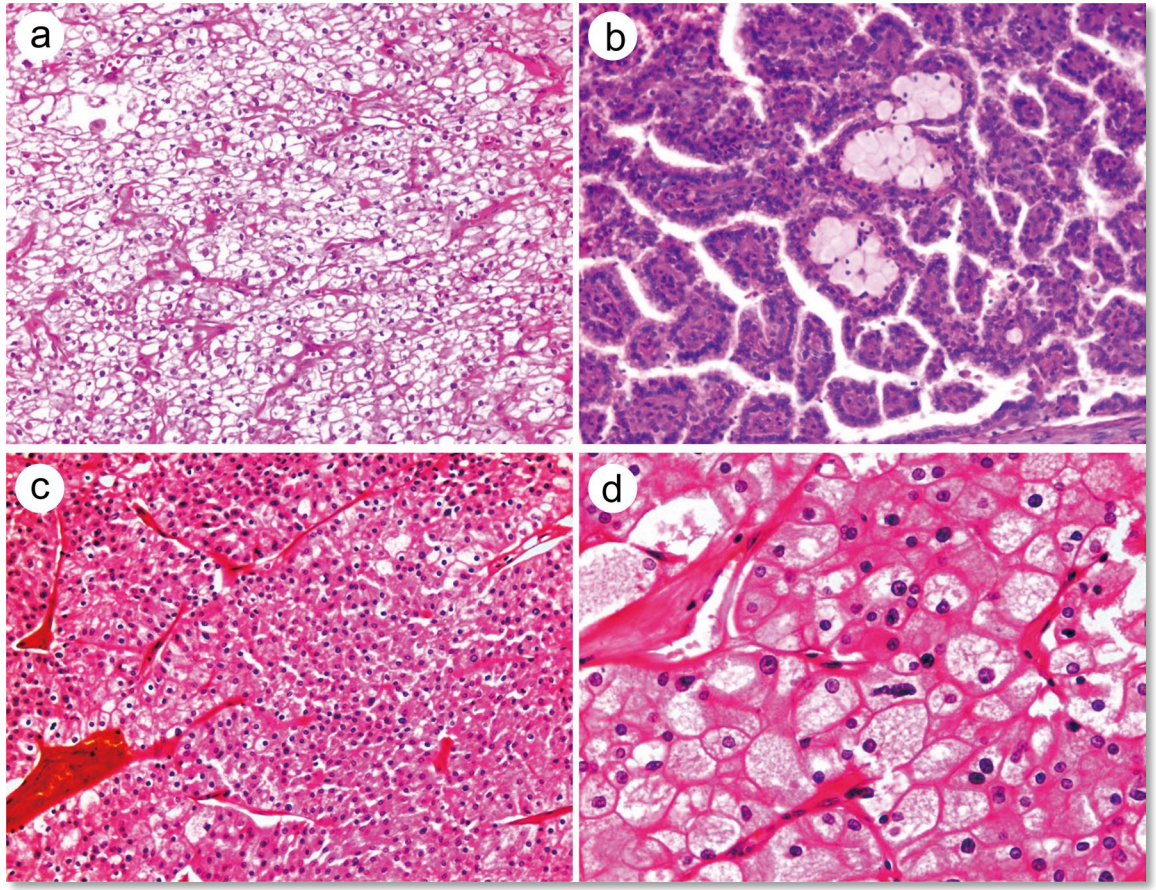
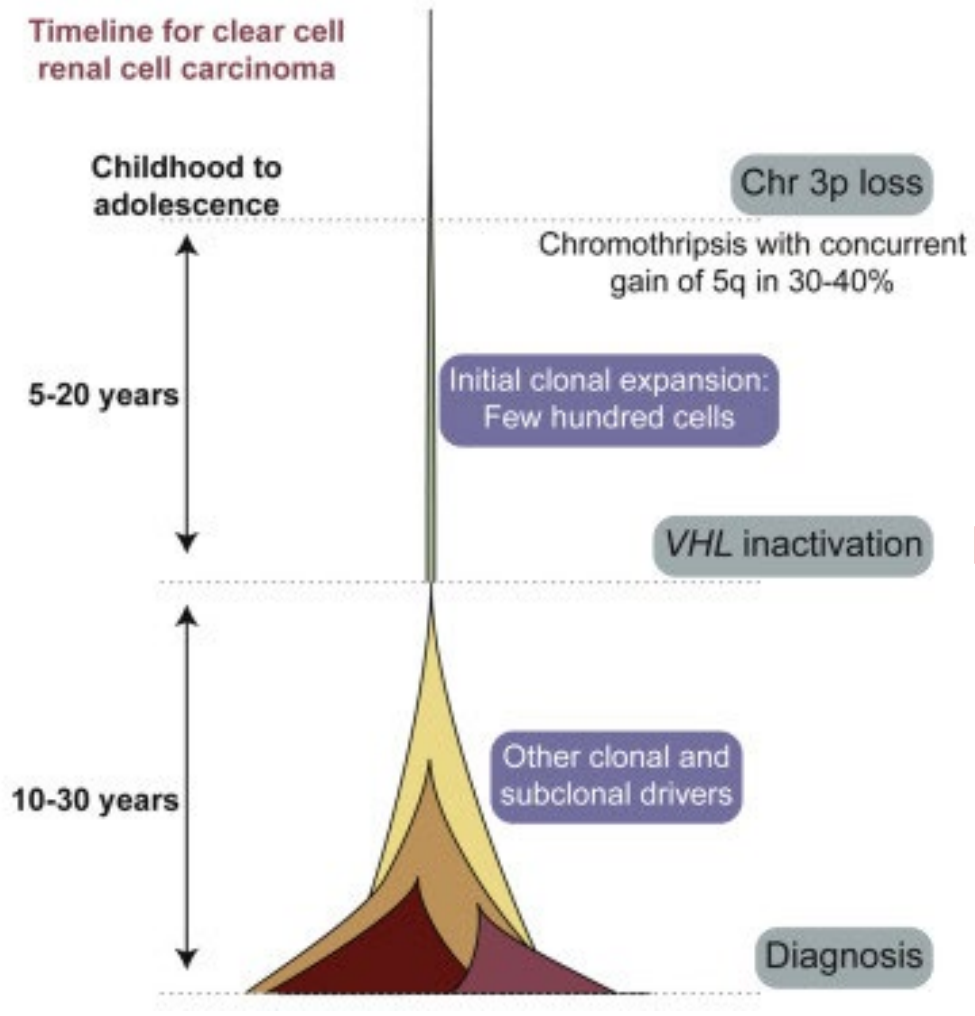


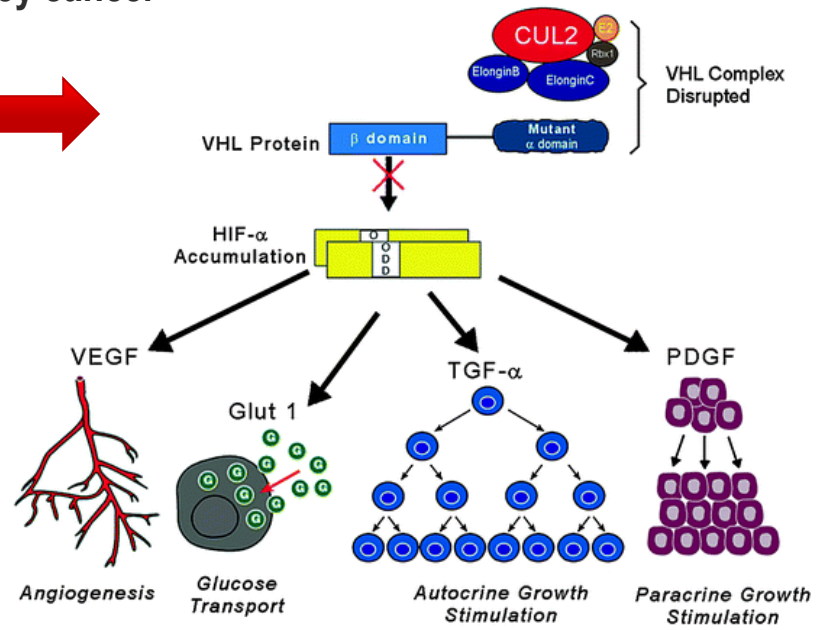
Moch H, et al. *Eur Urol* 2022;82:458-68; Mubarak M & Rashid R. *J Clin Transl Pathol* 2024;4:70-5; Rizzo M, et al. *Cancer Treat Rev* 2023;116:102558.

Clonal Evolution of clear cell Renal Cell Carcinoma



Clear cell renal cell carcinoma is characterized by near-universal loss of the short arm of chromosome 3, deleting several tumor suppressor genes (mainly *VHL*, but also *PBRM1*, *BAP1* and *SETD2*); in 36% of the cases, simultaneous 5q gain is observed. These events occurs in childhood or adolescence, generally as the initiating event that precedes emergence of the tumor's most recent common ancestor by years to decades

VHL gene inactivation is the key pathogenic event in sporadic clear cell kidney cancer



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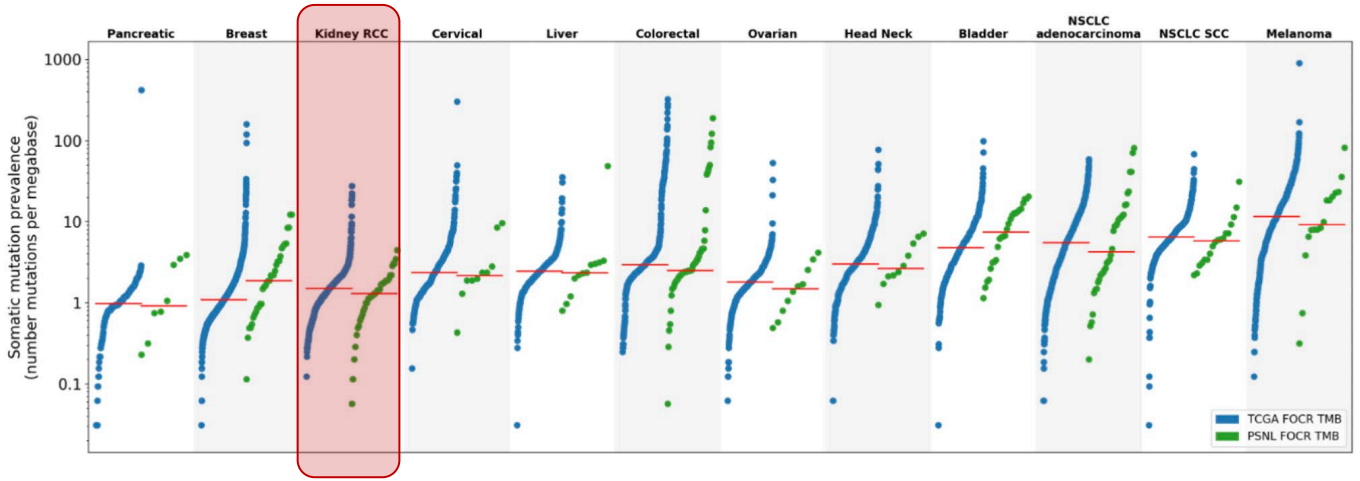
Mitchell TJ, et al. *Cell* 2018;173:P611-23.E17.

Renal Cell Carcinoma: an Immunogenic Tumour

The presence of neoantigen-specific T cells is a hallmark of solid tumours with a high mutagenic burden, which typically have abundant tumour-specific antigen owing to non-synonymous single nucleotide variations within the genome. These tumors tend to respond better to ICIs-based immunotherapy



Each dot represents a single patient sample. The horizontal red lines indicate the median number of mutations in each respective cancer and cohort. The vertical axis (log-scaled) shows the number of mutations per megabase, segregated by the various cancer types investigated. The estimation of TMB was determined utilizing the FOCR 'Uniform TMB Calculation Method' (Merino et al. 2020).

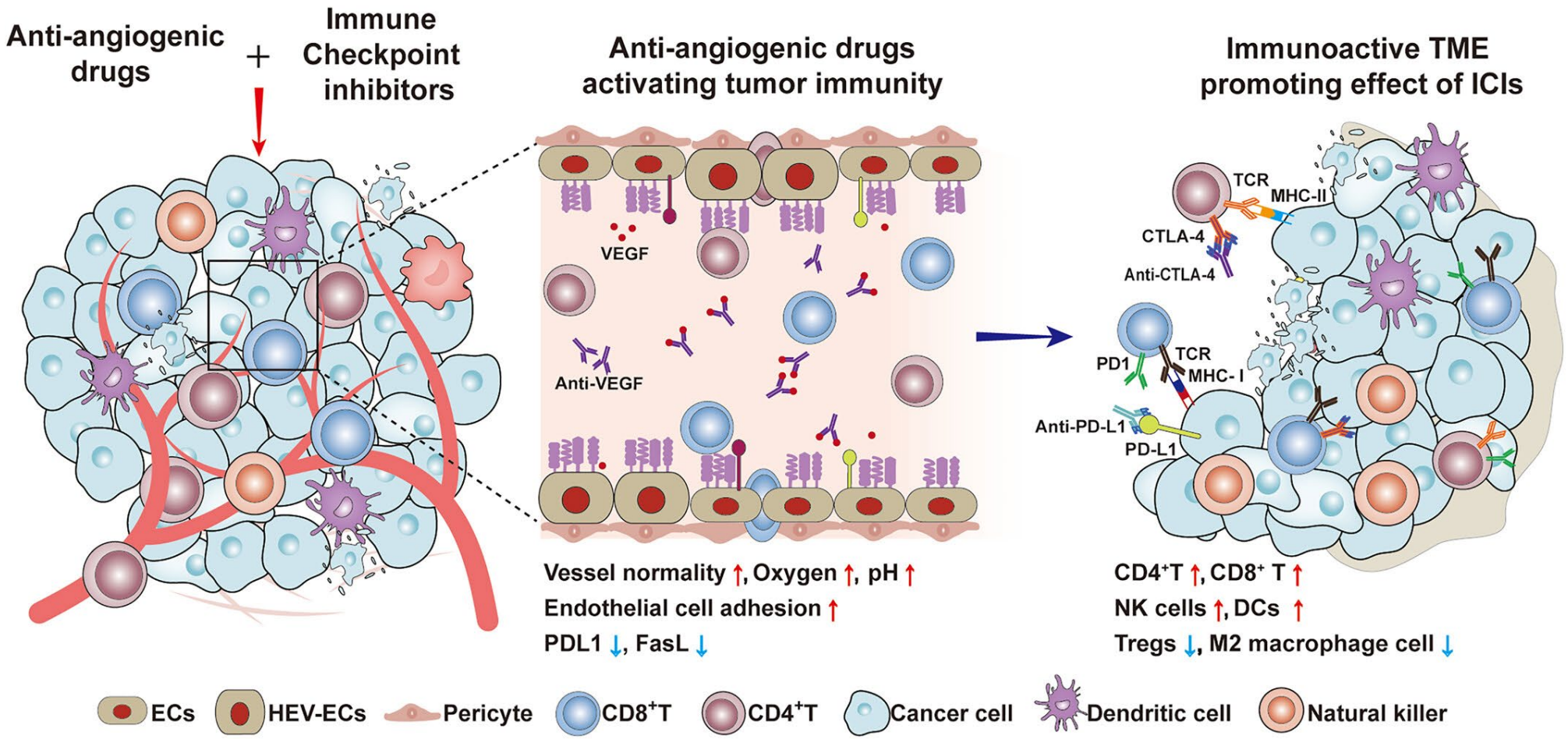
- **Cohorts**:
  - FOCR Exome-derived TMB from TCGA samples (from Merino et al. 2020)
  - NeXT Exome-derived TMB using Personalis NeXT DB samples

RCC exhibits high cytotoxic T cell reactivity despite only having an intermediate non-synonymous single nucleotide variation mutational burden. Instead, RCC tumours have a high pan-cancer proportion of insertions and deletions (INDEL) frameshift mutations, and coding frameshift INDELs are associated with high immunogenicity.

Moreover, in RCC cytotoxic T cells seem to recognize tumour-specific endogenous retrovirus epitopes (often of avian origin), whose presence has been well documented, and proved to be associated with clinical responses to immune checkpoint inhibitors

https://www.personalis.com/tumor-mutational-burden-a-continually-evolving-biomarker-for-immunotherapy/; Wolf MM, et al. *Nat Rev Nephrol* 2023;19:440-50.

Combining Antiangiogenics and Immune Checkpoint Inhibitors



Li A-Q & Fang J-H. *Interdiscip Med* 2024;2:e20230025.

THANK YOU FOR YOUR KIND ATTENTION !

camillo.porta@gmail.com

ESMO GUIDELINES:
REAL WORLD CASES

CASE PRESENTATION

Renal cell carcinoma

Dr. Regina Barragan-Carrillo, MD

Department of Medical Oncology and Experimental Therapeutics

City of Hope Comprehensive Cancer Center (United States)

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CLINICAL CASE

Patient presentation

52 YO male patient

- **PHx**: hypertension, receiving treatment with losartan BID.
- **PSHx**: appendectomy (1992).
- **FH**: Mother was diagnosed with ovarian cancer in her early 60s.
- **SHx**: Born and raised in Southern California. Softball coach (very active lifestyle). Denies tobacco use. Reports consumption of 2–3 standard alcoholic drinks per week. Married with 2 children in college.

CLINICAL CASE

History of present illness

Stage III clear cell renal carcinoma

Hepatic steatosis work-up

Abdominal US:
7.5 cm lobulated solid mass in the left upper renal pole

Staging CT CAP:
No sites of metastatic disease

Left hand-assist radical nephrectomy (several surgical complications)

Pathology:
6.8cm ccRCC with negative margins and no sarcomatoid or rhabdoid features, Grade 2 with renal sinus extension (pT3aNx).

CLINICAL CASE

History of present illness

Stage III clear cell renal carcinoma

CLINICAL CASE

History of present illness

Stage III clear cell renal carcinoma

Hepatic steatosis work-up

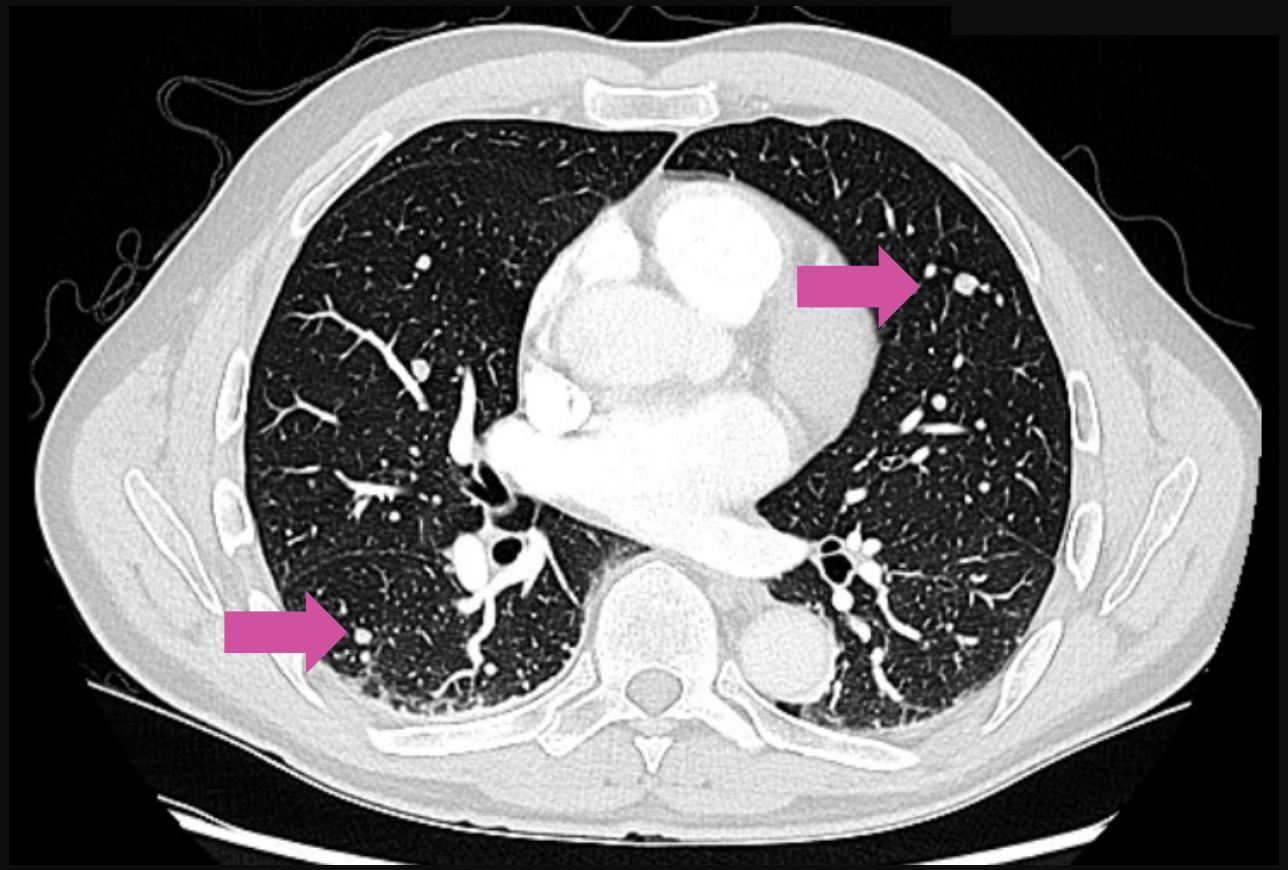
Consultation with Medical Oncology (11 weeks)

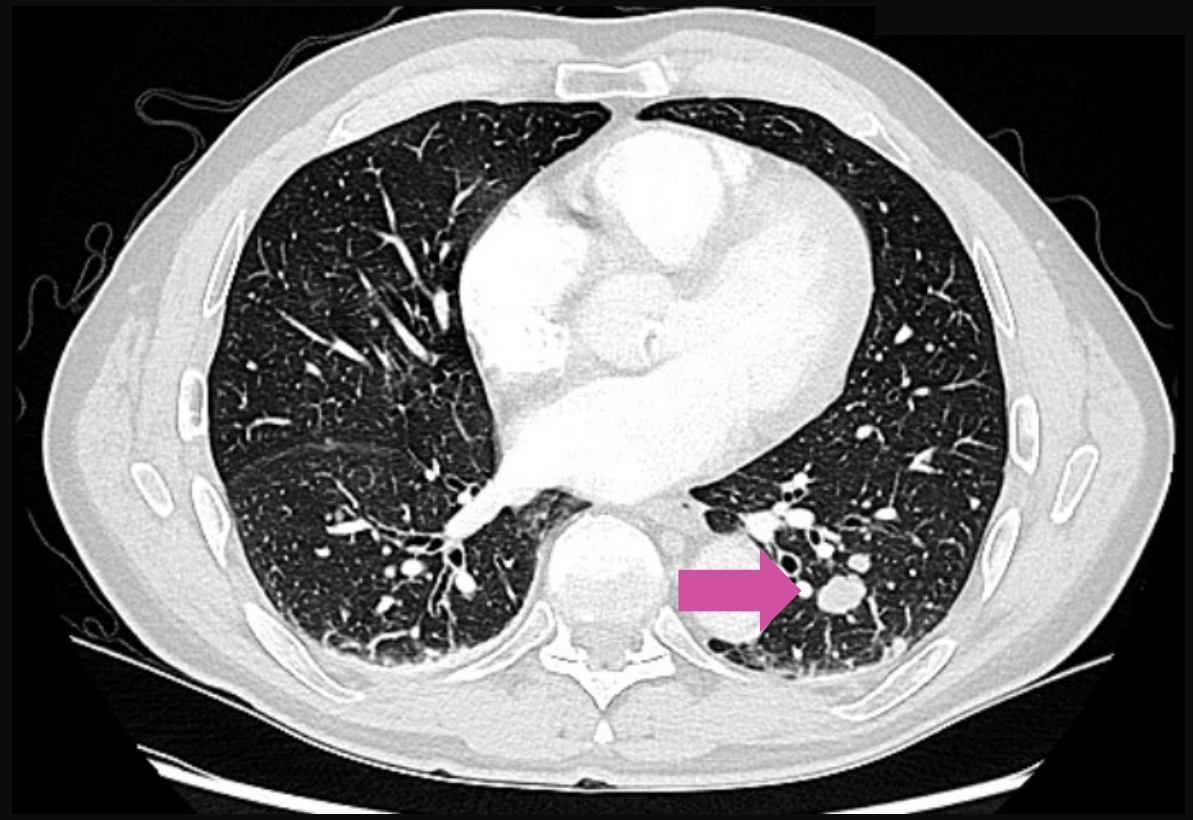
Follow up with Medical Oncology (13 months)

Follow-up CT CAP:
Several new lung lesions

Laboratory work-up:
Hb 11 g/dL, Platelets 560 k

Left hand-assist radical nephrectomy (several surgical complications)

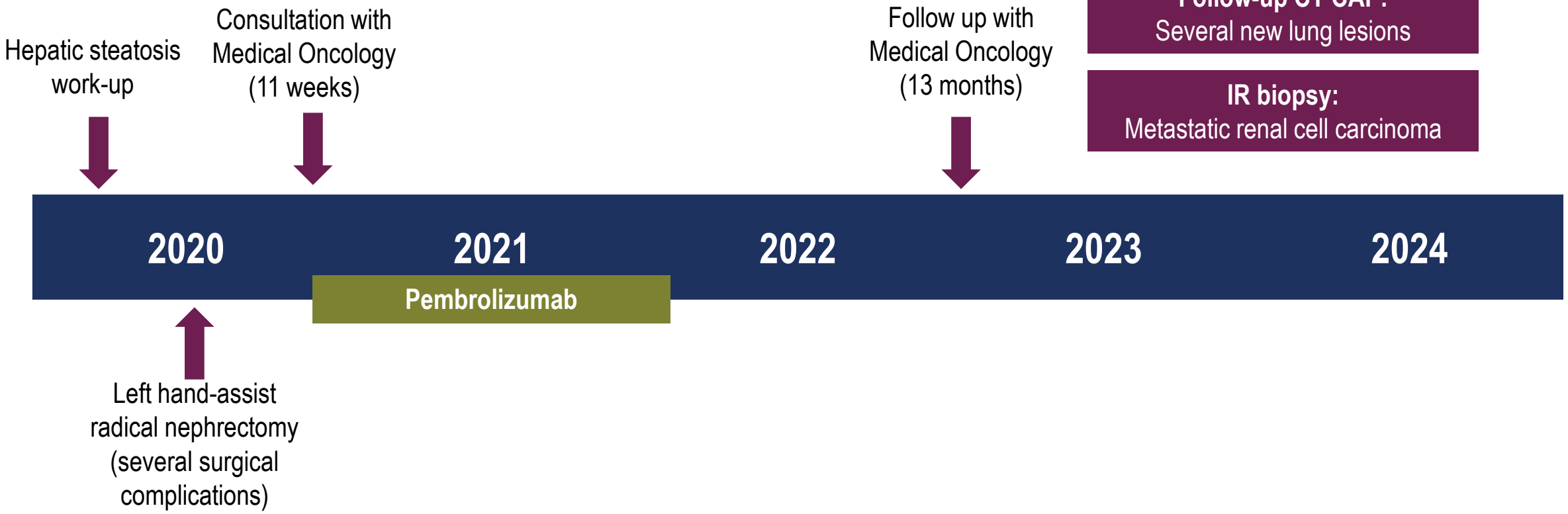




CLINICAL CASE

History of present illness

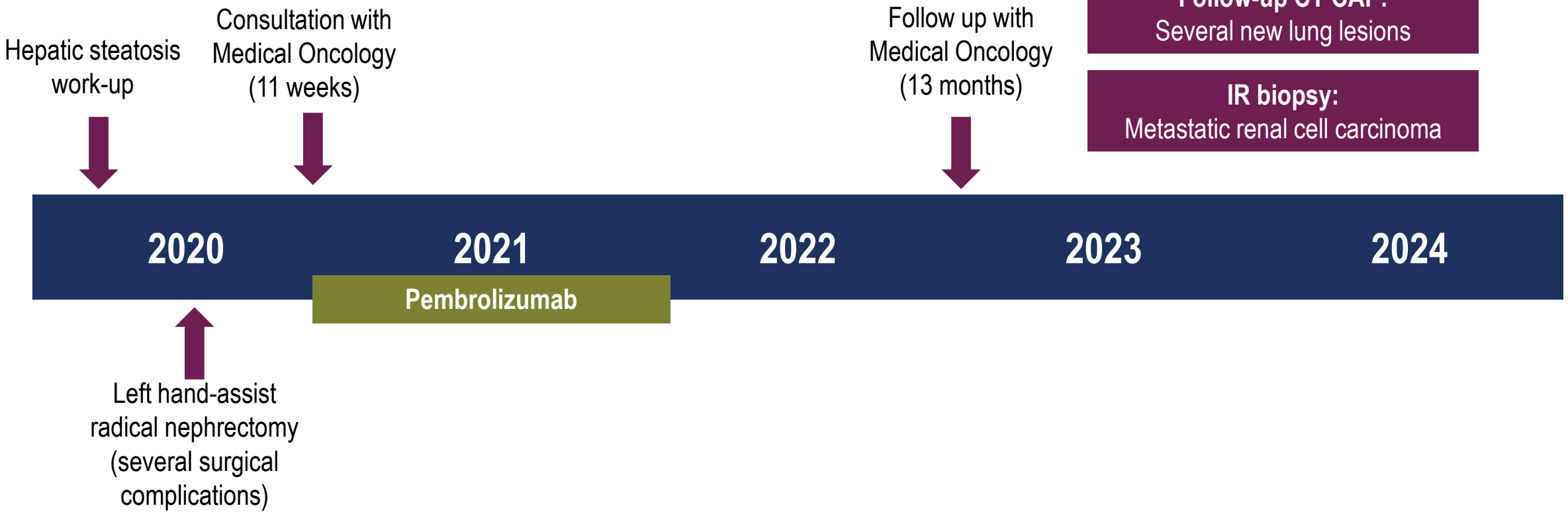
Stage III clear cell renal carcinoma



CLINICAL CASE

History of present illness

Intermediate risk metastatic clear cell renal carcinoma (IMDC 2 points)



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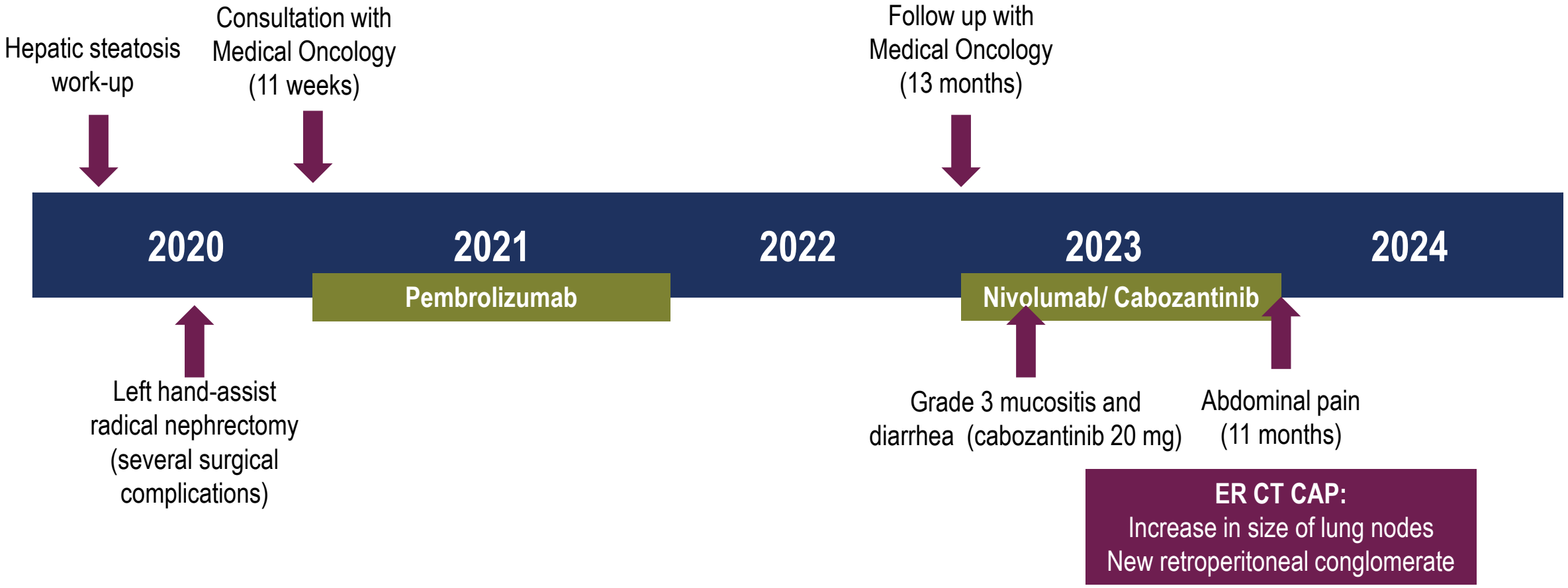

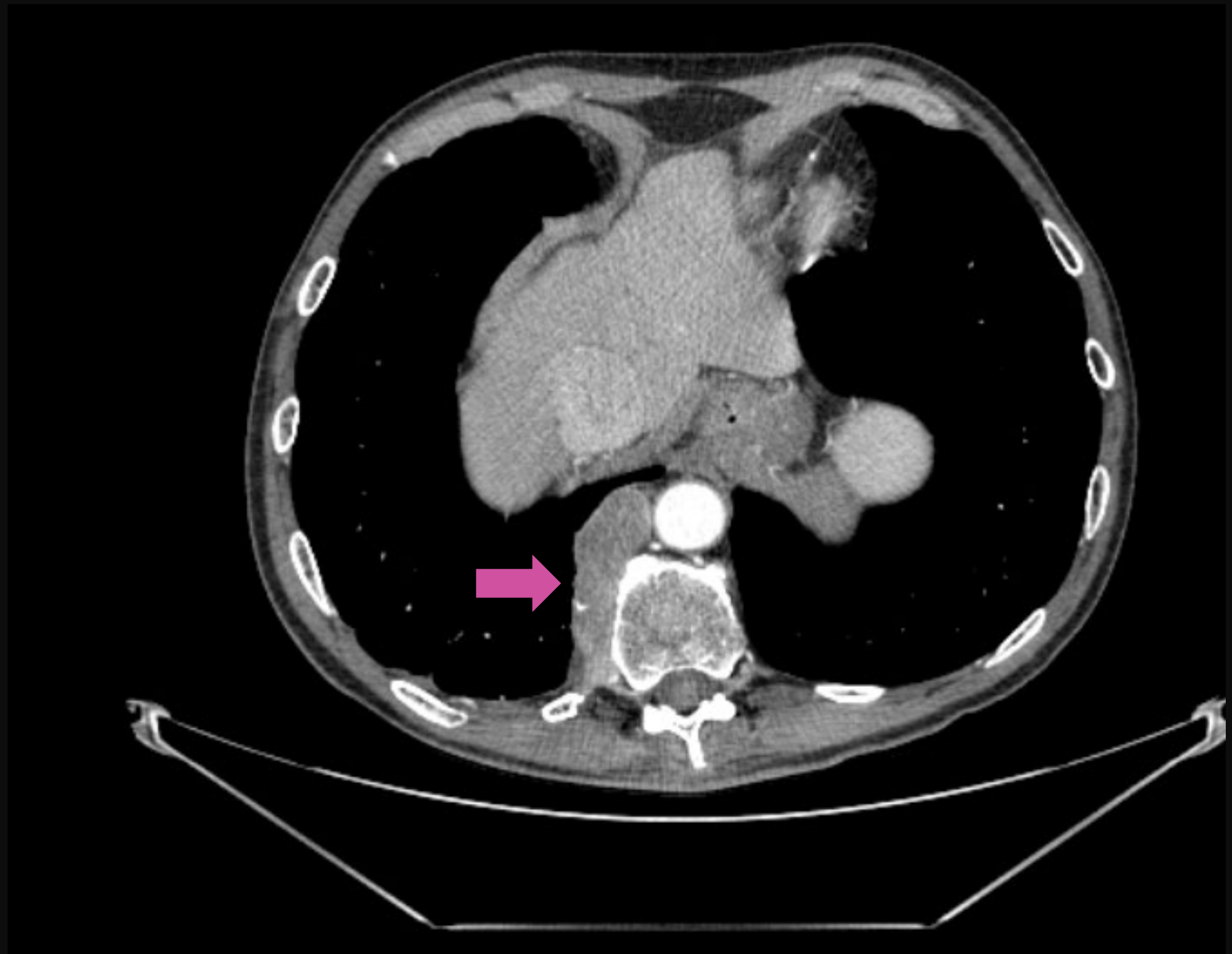

CLINICAL CASE

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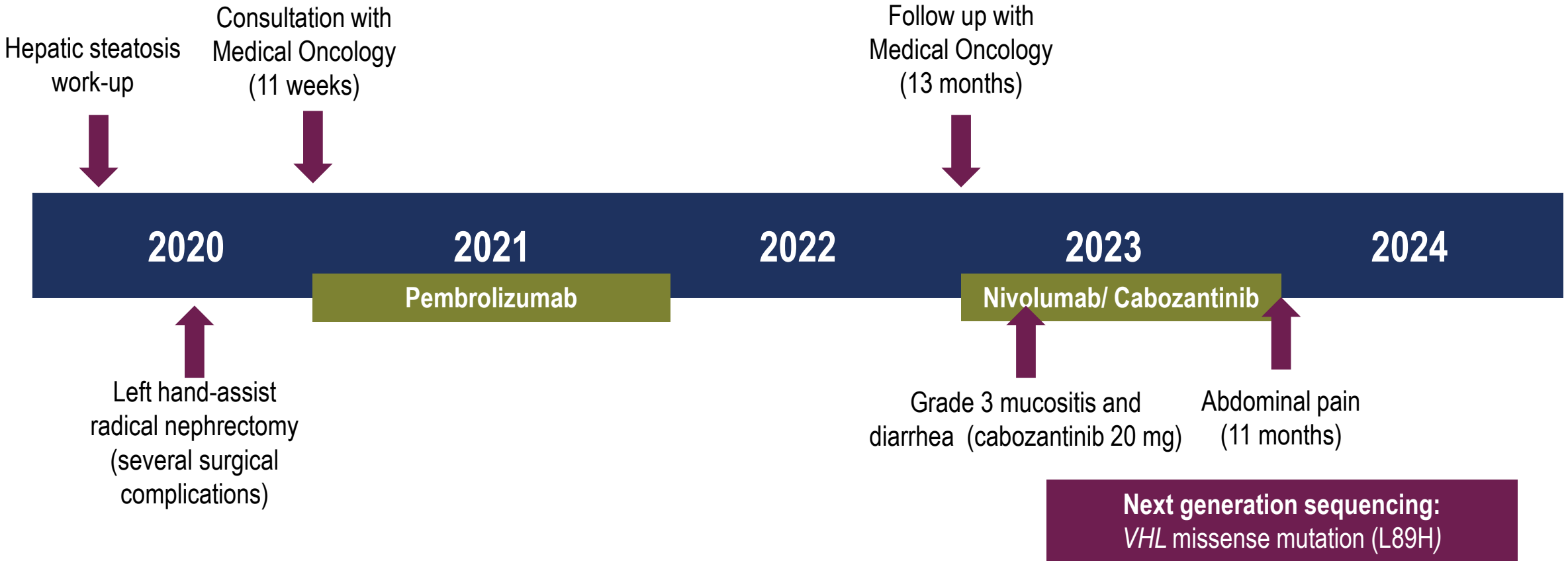
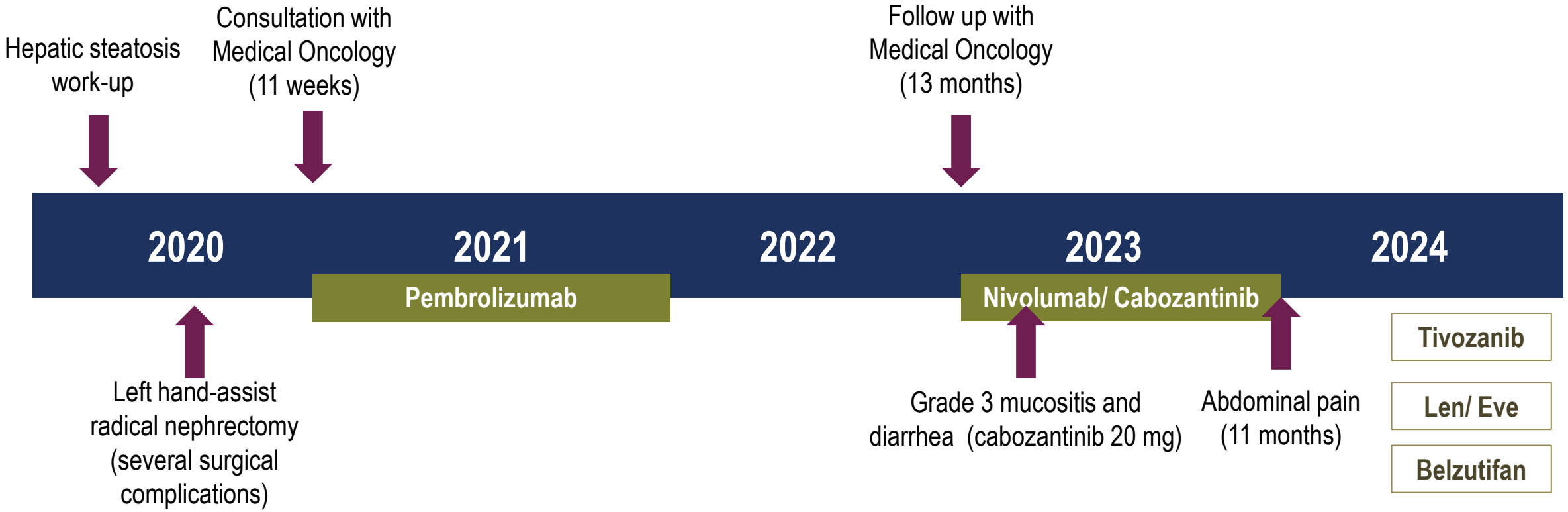


Next generation sequencing:
VHL missense mutation (L89H)

CLINICAL CASE

History of present illness

Intermediate risk metastatic clear cell renal carcinoma (IMDC 2 points)



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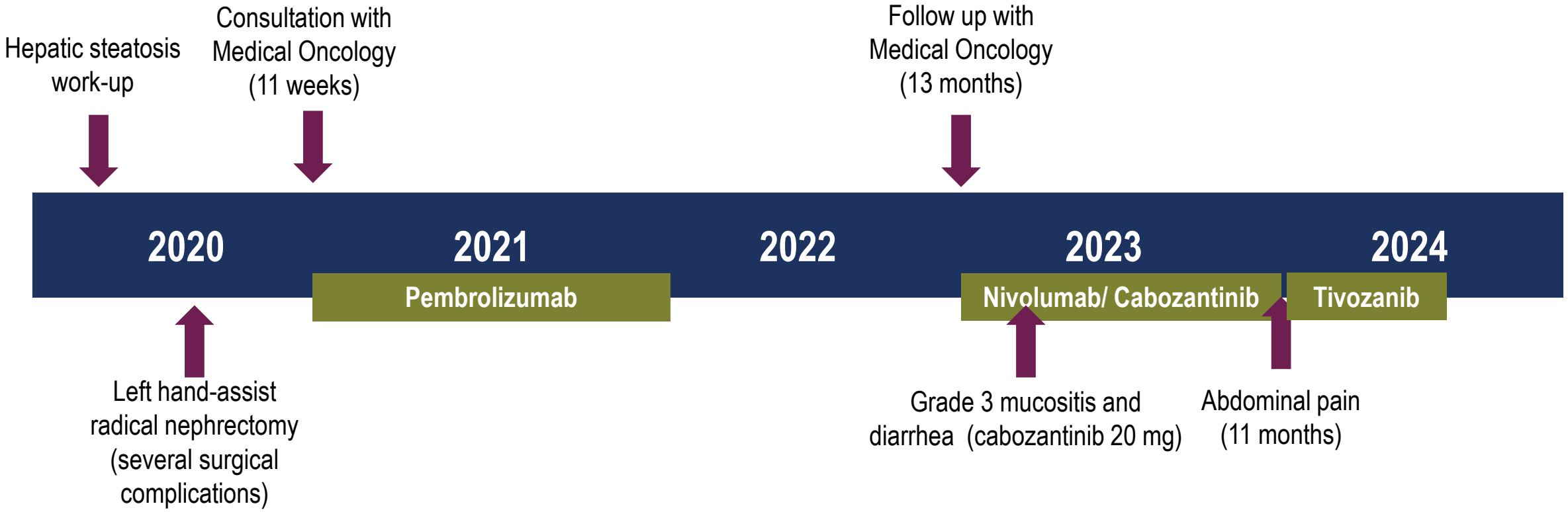

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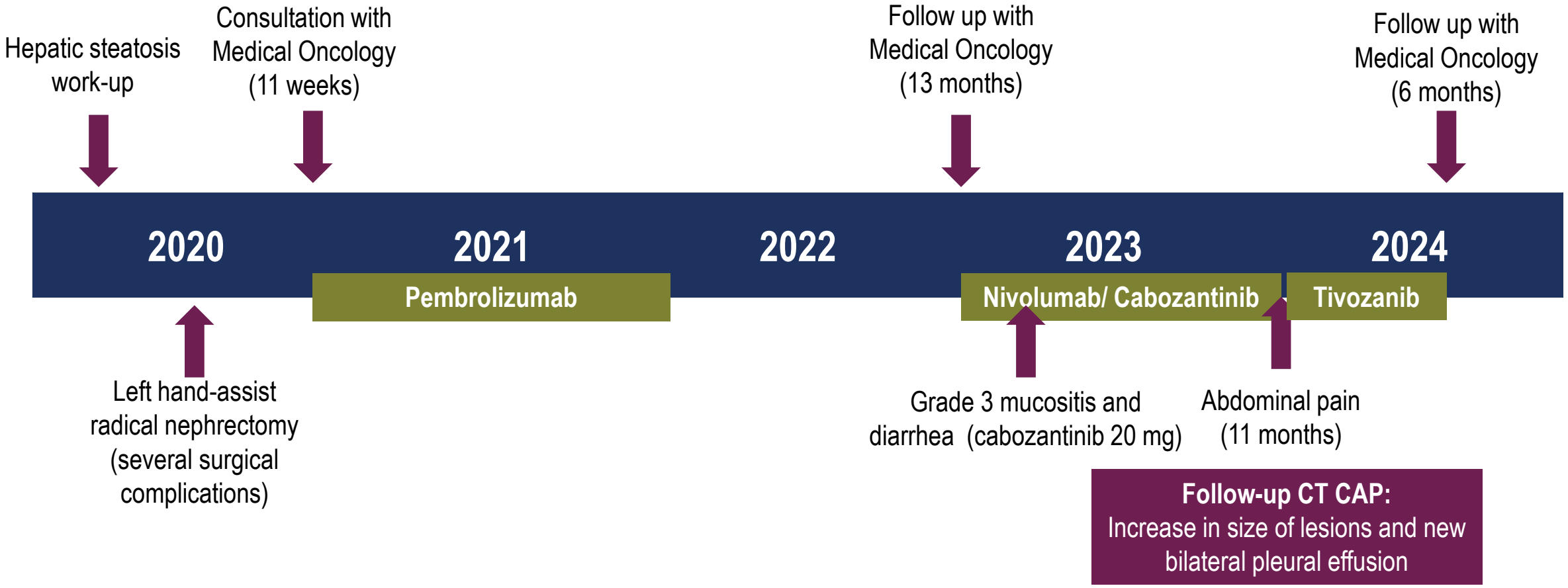

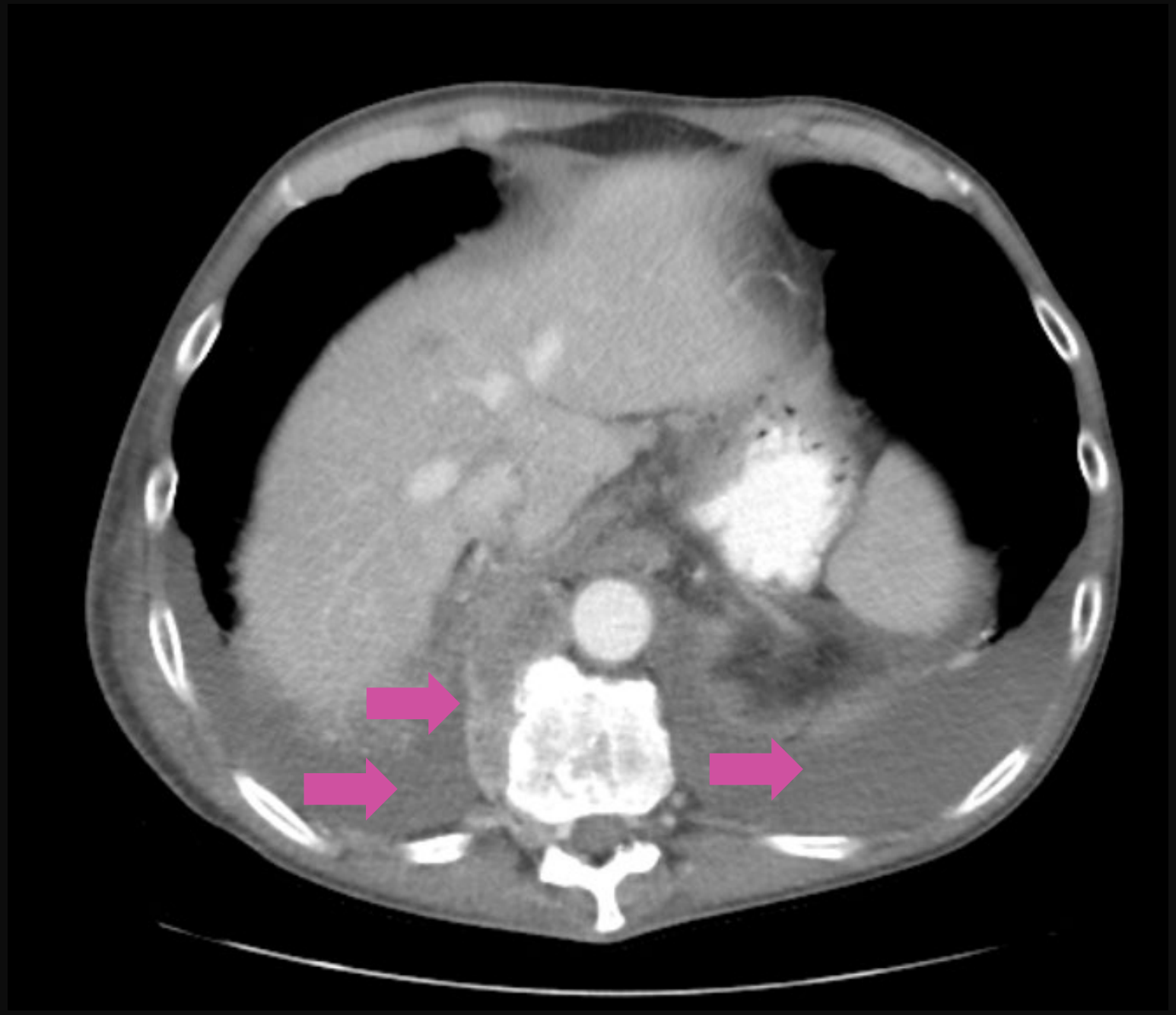

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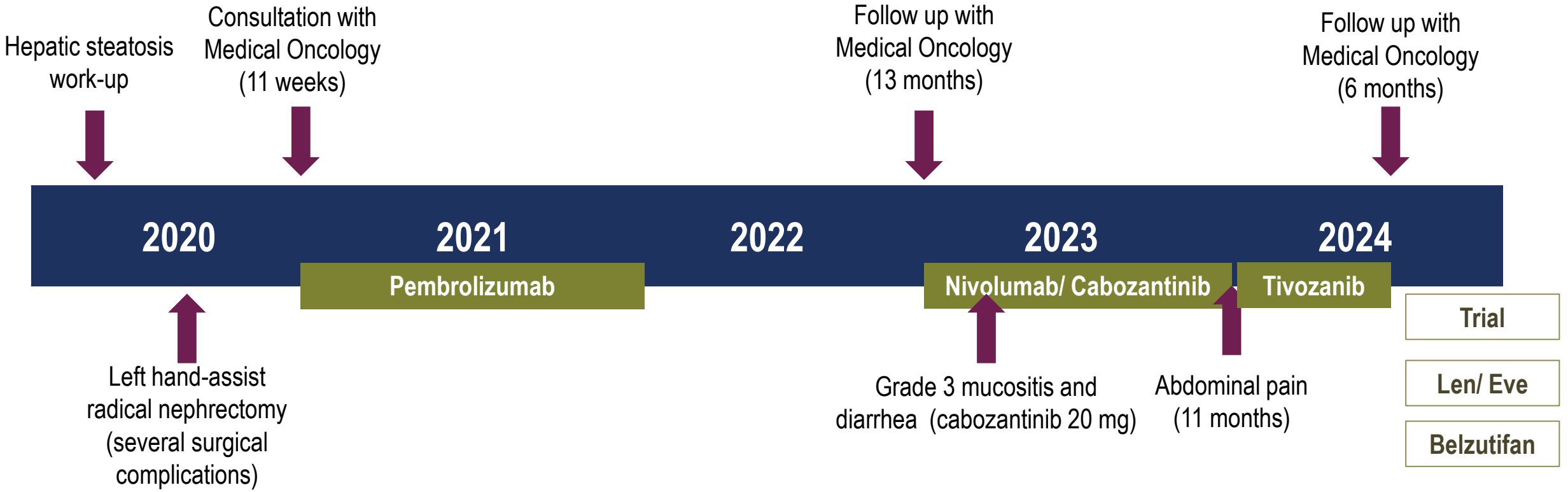

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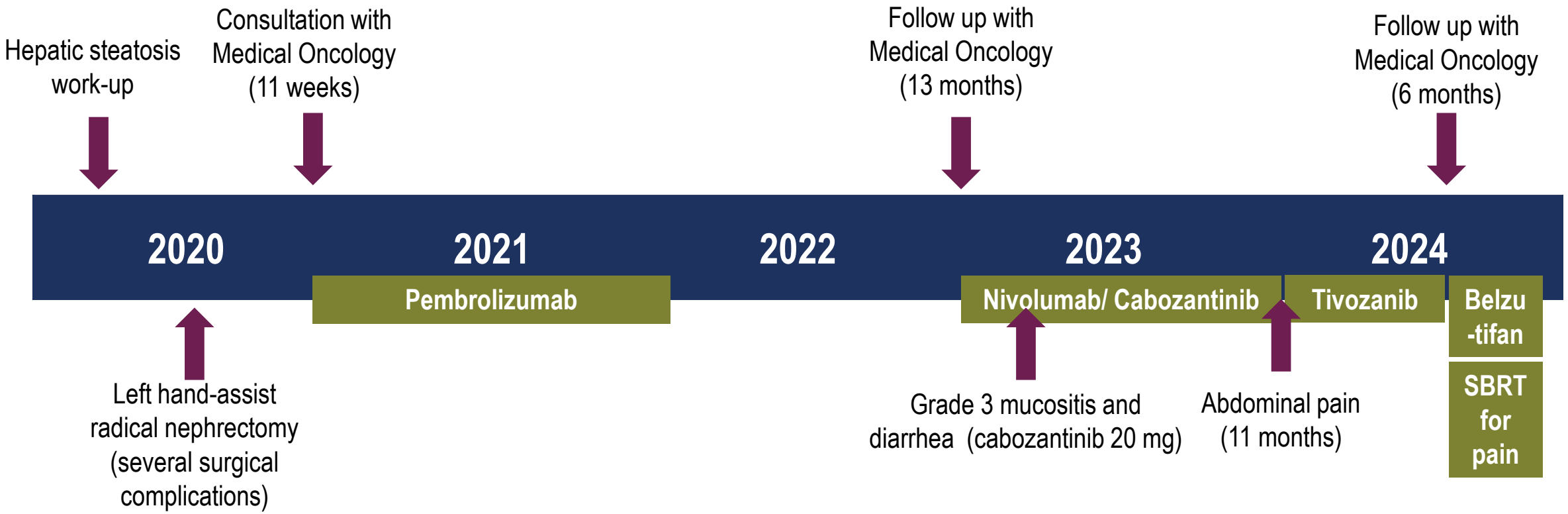

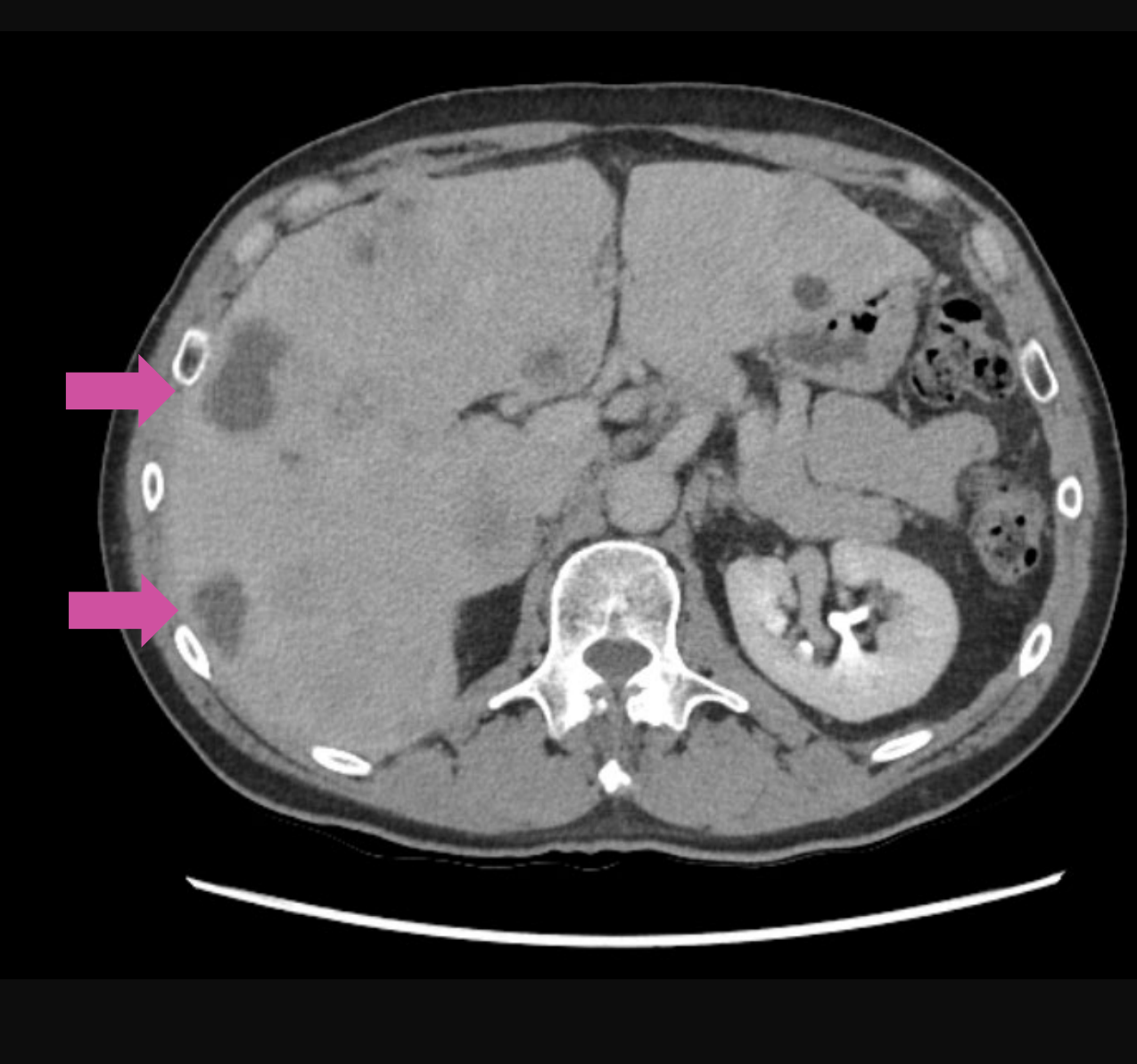

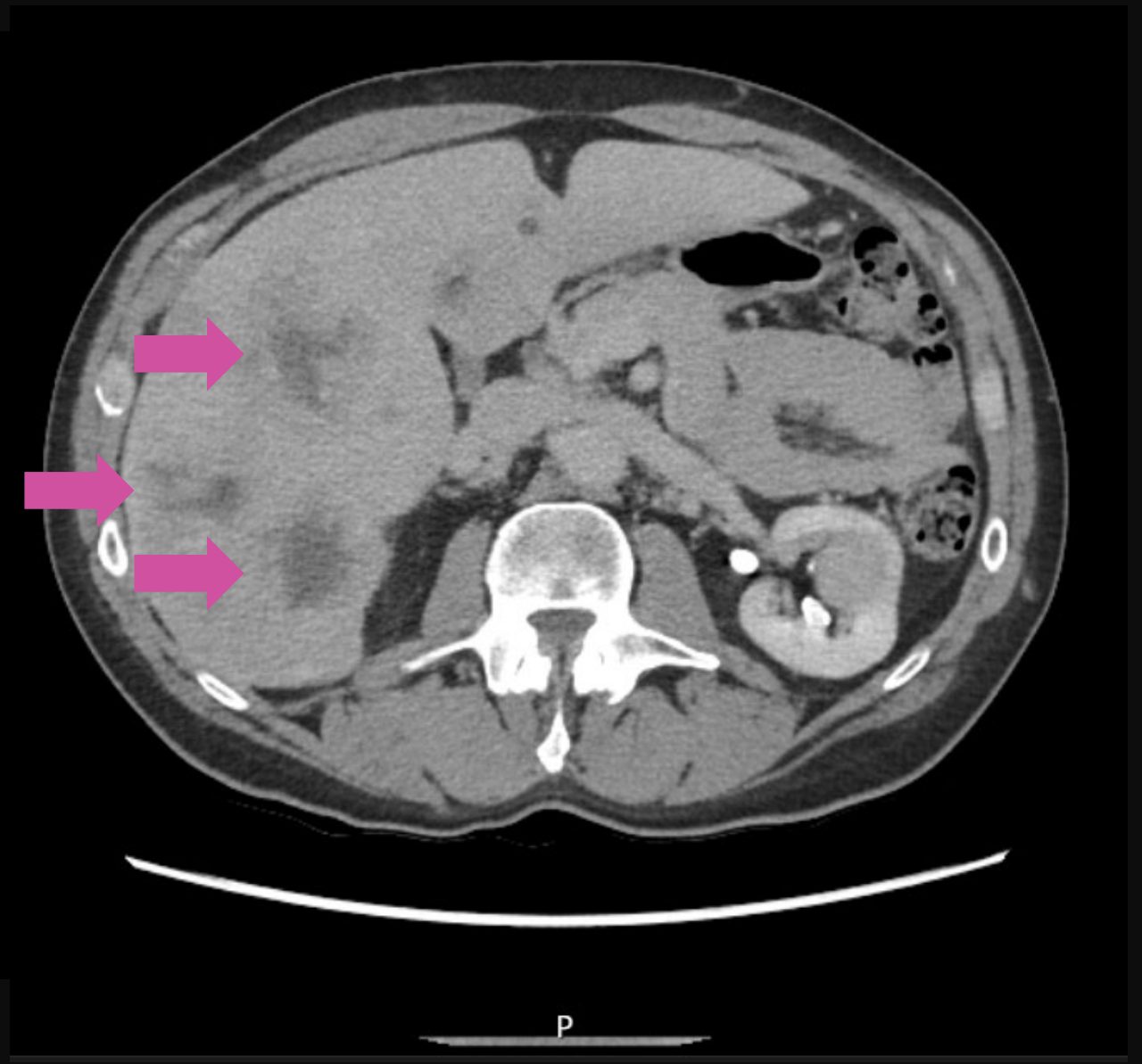
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CLINICAL CASE

History of present illness

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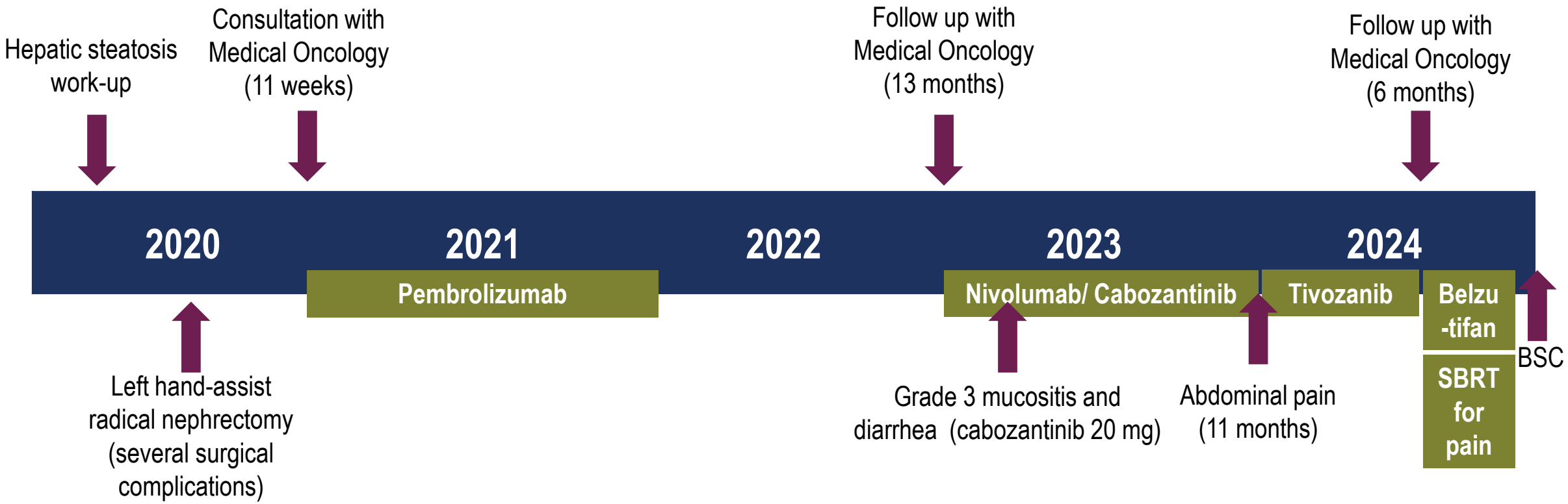

ESMO GUIDELINES: REAL WORLD CASES

CASE PRESENTATION

Renal cell carcinoma

Dr. Regina Barragan-Carrillo, MD
regina.barragan.carrillo@gmail.com

X: @reginabarcar

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

An ESMO tour of renal cancer.

Thomas Powles
Director of Barts Cancer Center.
Professor of Urology Cancer, Barts Cancer Institute.




DISCLOSURES

Research funding/honoraria/travel costs:

MSD, Merck-Serono, Pfizer, GSK, Novartis, Roche, AZ, BMS, Exelexis, Ipsen, Seagen, Astellas, Jansen, Eisai, Mashup, Genentech, Natera, FMI, Takeda.

Disclaimer

- This session may refer to medicines that are not TGA indicated in Australia for use in renal cell carcinoma.

- Clinical guidance discussed throughout this presentation are based on Prof Powles' opinion and experience, and may not necessarily reflect Eisai view.

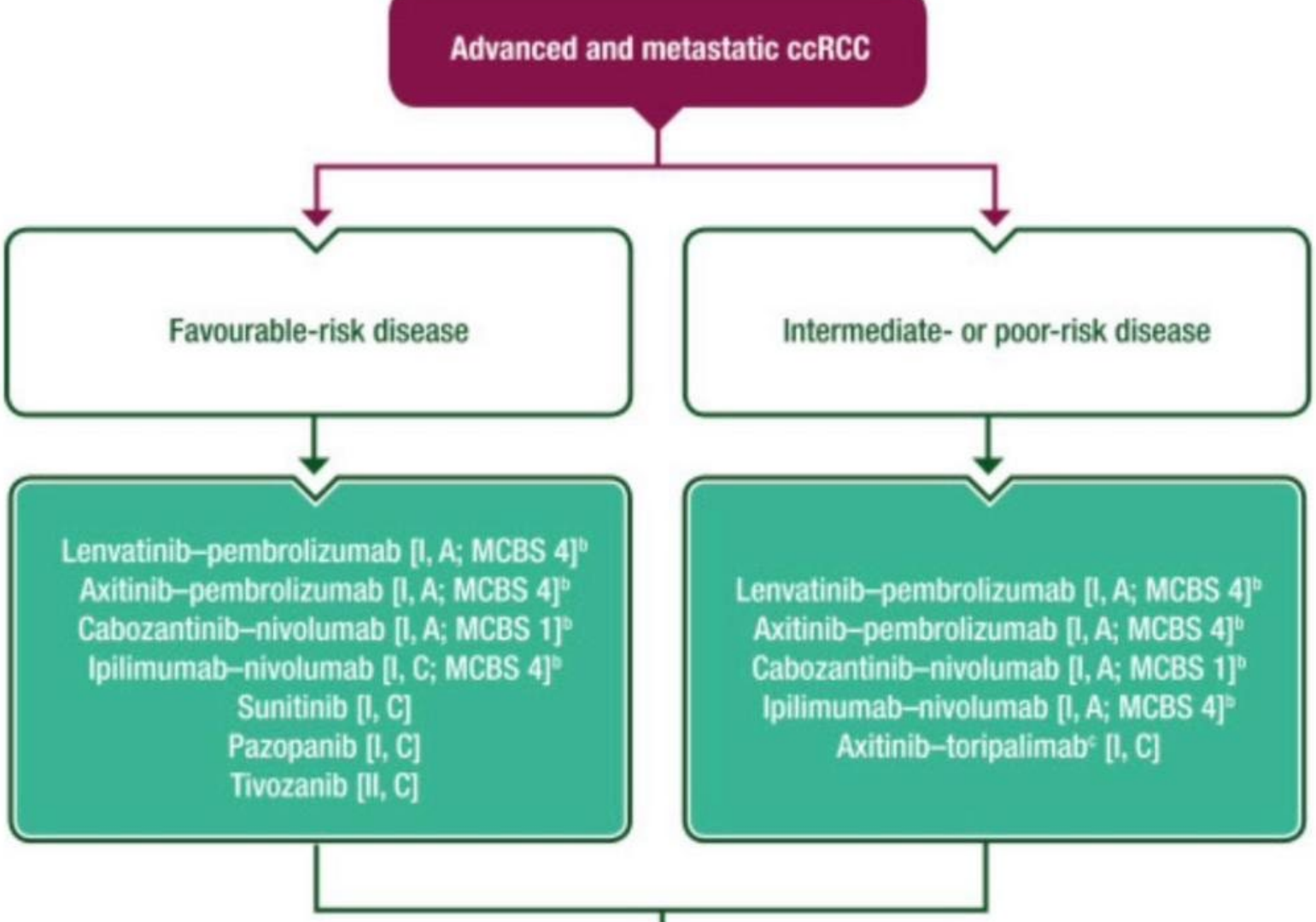
The widespread success in advanced disease has not occurred in the adjuvant setting

Advanced disease (1st line vs sunitinib)	ICI	PFS	OS
Ipilimumab and nivolumab	PD1		
Axitinib and pembrolizumab	PD1		
Axitinib and avelumab	PDL1		
Bevacizumab and atezolizumab	PDL1		
Cabozantinib and nivolumab	PD1		
Lenvatinib and pembrolizumab	PD1		
Cabozantinib/ipi/nivolumab	combo		
PEG-IL2 and Nivolumab*	PD1		

Perioperative disease	ICI	PFS	OS
pembrolizumab	PD1		
Nivolumab (perioperative)	PD1		
atezolizumab	PDL1		
nivolumab	PD-1		
Ipilimumab and nivolumab	combo		

The adjuvant VEGF TKI story was not the same.

ESMO guidelines



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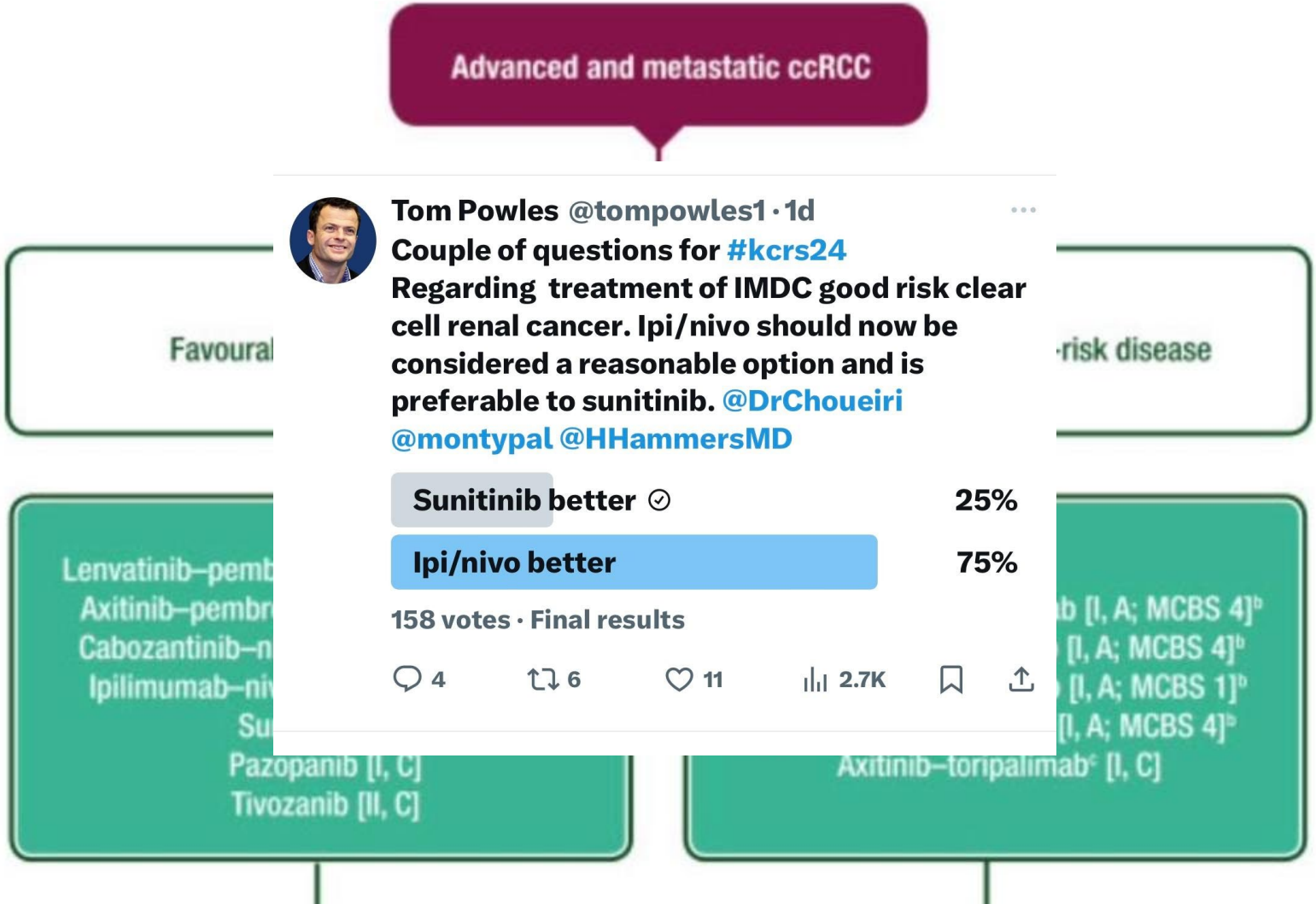
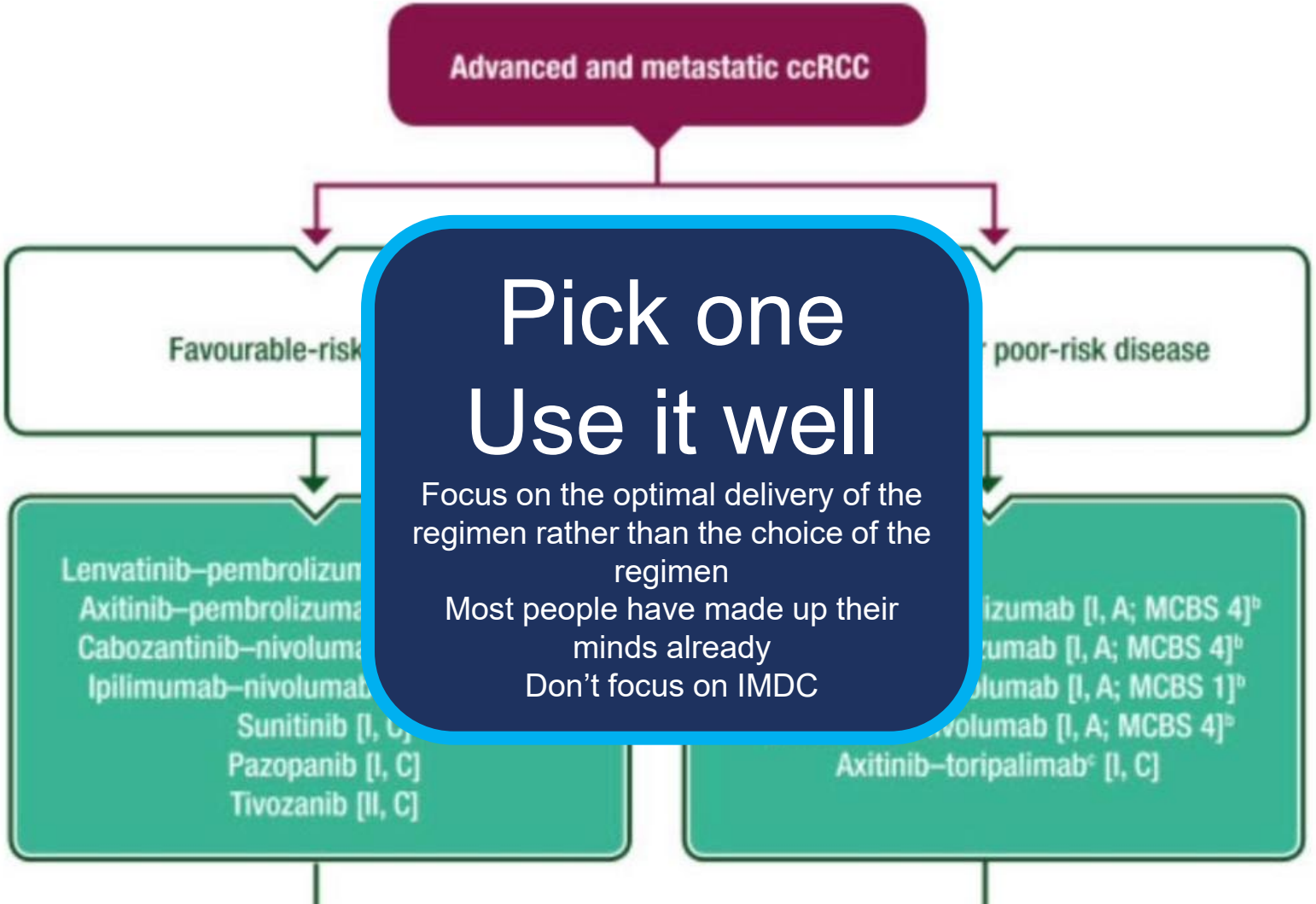

Advanced and metastatic ccRCC
Favoural
risk disease
Lenvatinib–pemb
Axitinib–pembr
Cabozantinib–n
Ipilimumab–niv
Su
Pazopanib [I, C]
Tivozanib [II, C]
b [I, A; MCBS 4]b
[I, A; MCBS 4]b
[I, A; MCBS 1]b
[I, A; MCBS 4]b
Axitinib–toripalimabc [I, C]
Tom Powles @tompowles1 · 1d
Couple of questions for #kcrs24
Regarding treatment of IMDC good risk clear cell renal cancer. Ipi/nivo should now be considered a reasonable option and is preferable to sunitinib. @DrChoueiri @montypal @HHammersMD
Sunitinib better
25%
Ipi/nivo better
75%
158 votes · Final results
4
6
11
2.7K

ESMO

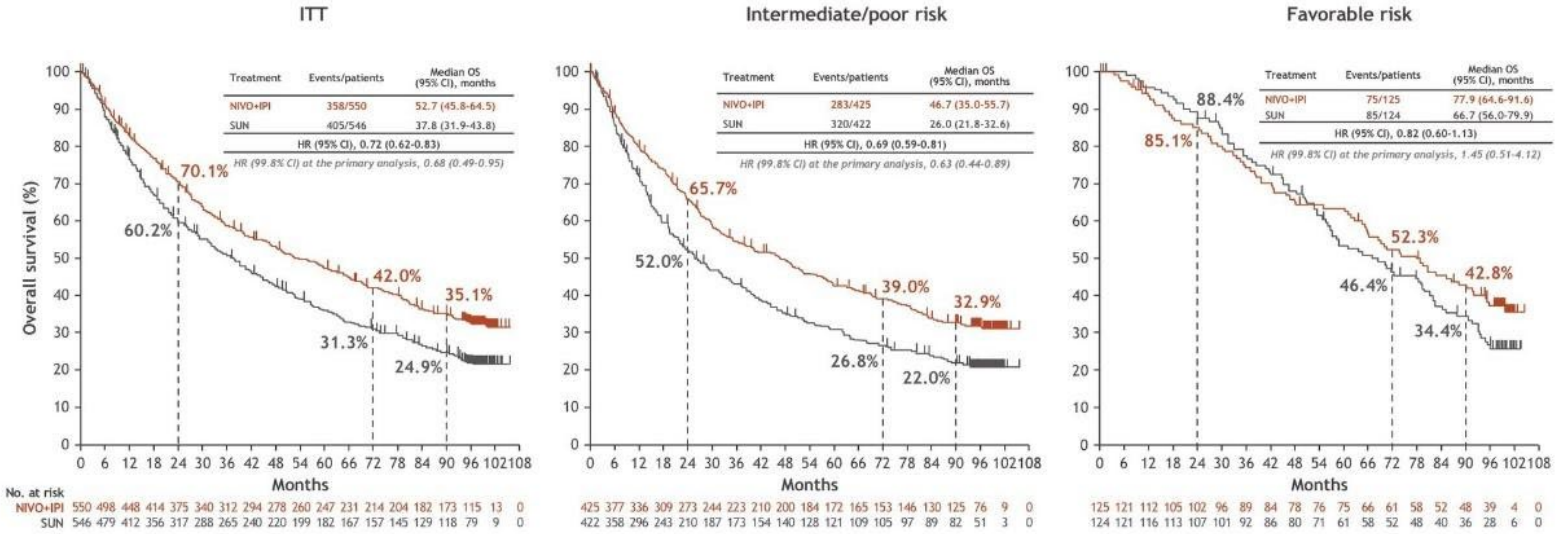

Advanced and metastatic ccRCC
Favourable-risk
poor-risk disease
Lenvatinib–pembrolizumab
Axitinib–pembrolizumab
Cabozantinib–nivolumab
Ipilimumab–nivolumab
Sunitinib [I, C]
Pazopanib [I, C]
Tivozanib [II, C]
izumab [I, A; MCBS 4]b
umab [I, A; MCBS 4]b
lumab [I, A; MCBS 1]b
volumab [I, A; MCBS 4]b
Axitinib–toripalimabc [I, C]
Pick one
Use it well
Focus on the optimal delivery of the regimen rather than the choice of the regimen
Most people have made up their minds already
Don't focus on IMDC

The ipilimumab/nivolumab data looks as good as an other combination across all IMDC groups

CheckMate 214

Overall survival

- The HR for OS has been stable over 8 years of median follow-up in ITT and intermediate/poor-risk patients and has improved over time in favorable risk patients



Symbols represent censored observations. Stratified Cox proportional hazards model.

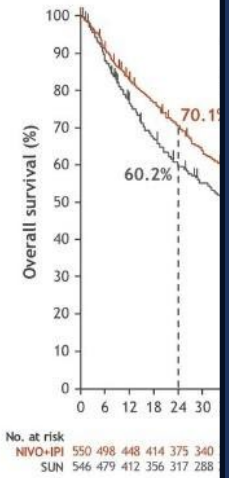
1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290.

The ipilimumab/nivolumab data looks as good as an other combination across all groups

CheckMate 214

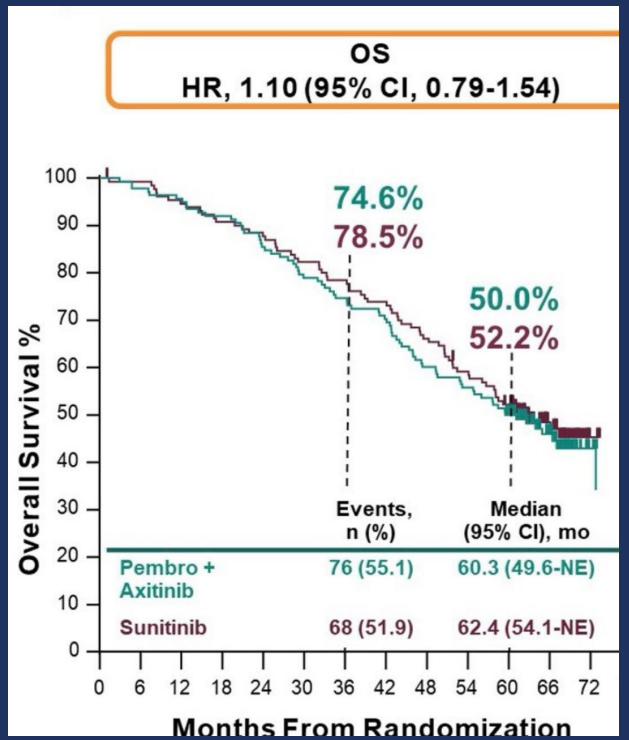
Overall su

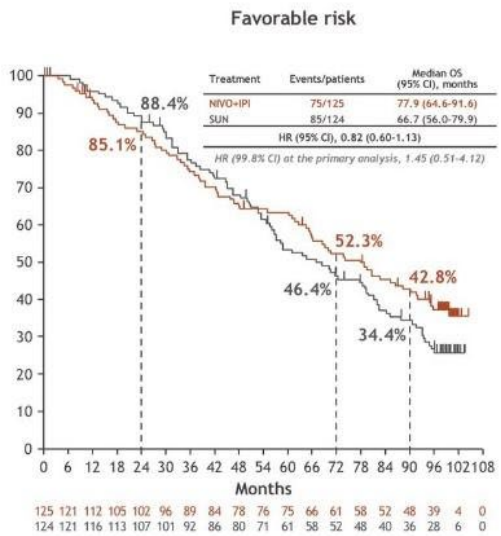
- The HR for OS h … favorable risk pa … poor-risk patients and has improved over time in



Symbols represent censored
1. Motzer RJ, et al. *N Engl J*

Axi/pembro OS in good risk

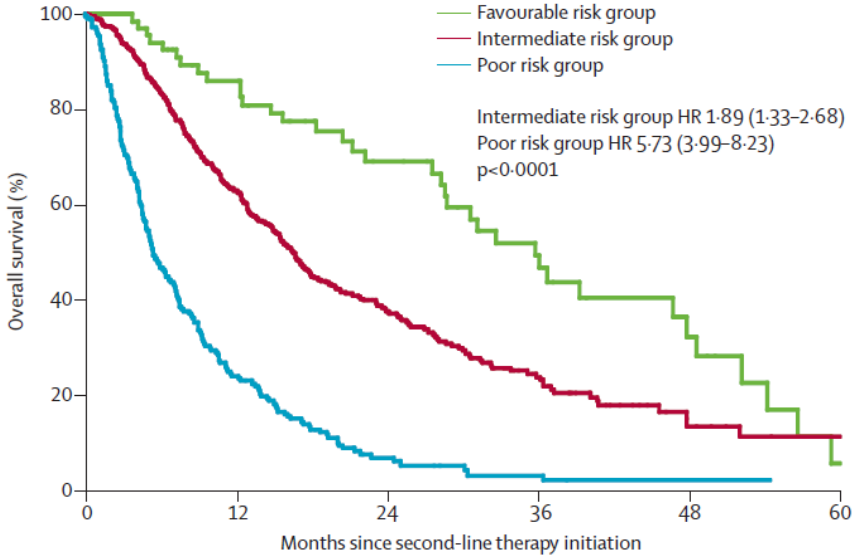




The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study

Jenny J Ko, Wanling Xie*, Nils Kroeger, Jae-Lyun Lee, Brian I Rini, Jennifer J Knox, Georg A Bjarnason, Sandy Srinivas, Sumanta K Pal, Takeshi Yuasa, Martin Smoragiewicz, Frede Donskov, Ravindran Kanesvaran, Lori Wood, D Scott Ernst, Neeraj Agarwal, Ulka N Vaishampayan, Sun-young Rha, Toni K Choueiri†, Daniel Y C Heng†*

The CM214 trial led to IMDC classification being used as a predictive biomarker.
VEGF for good risk and PD-1 bases therapy for the rest.



Tom Powles @tompowles1 · 1d

What is the role of IMDC classification for 1st line metastatic RCC . @DrChoueiri @montypal @HHammersMD

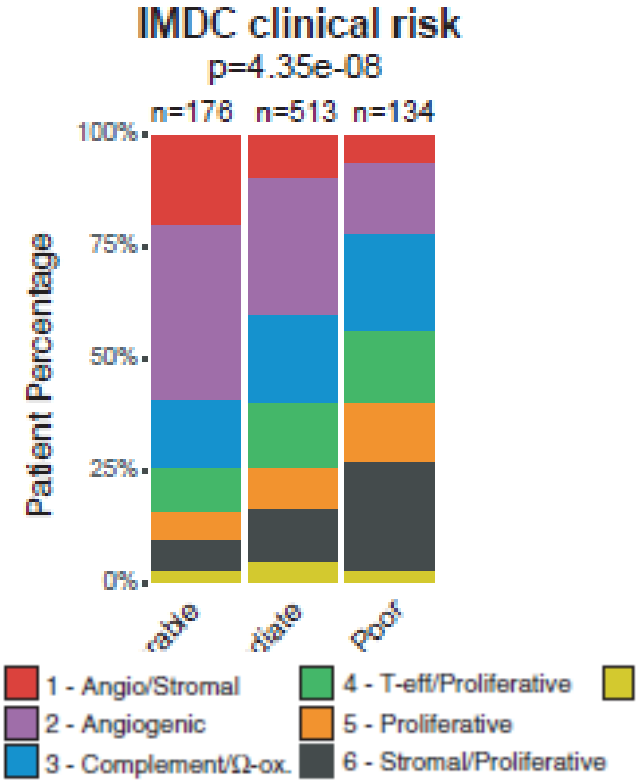
Treatment choice	48%
Prognosis only	48%
Neither	4%

122 votes · 19 hours 33 minutes left

3 4 1.2K

Lancet Oncology 2016

Is IMDC is holding us back?



The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study

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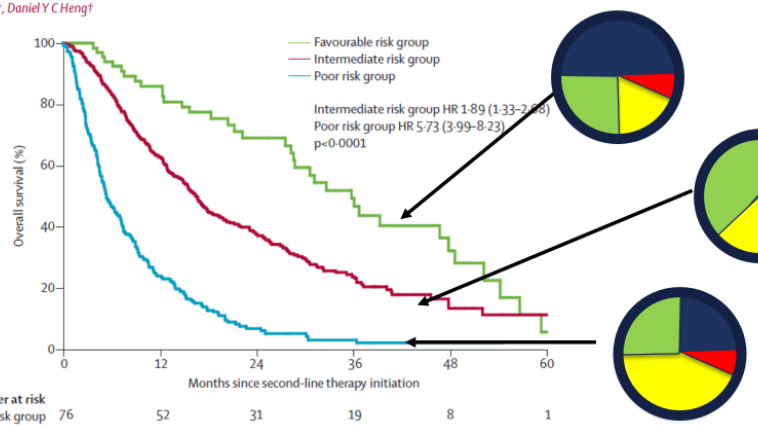
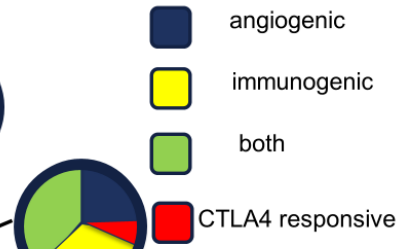




Which agent to stop and when: have we got this completely wrong?

VEGF TKI therapy

- Chronic toxicity[1]
- No cures[2]
- Evidence intermittent therapy is OK[3]

PD-1 based therapy

- Tolerated[4]
- Durable benefit[4]
- No evidence for duration of therapy[5]

It makes more sense to stop the VEGF therapy than the PD-1 therapy
Is it possible to complete the de-escalation trials asking these questions?

PD-1, programmed cell death protein; TKI, tyrosine inhibitors; VEGF, vascular endothelial growth factor

1. Grimm MO, *et al. J Clin Med.* 2020;9(2):565; **2.** McDermott DF, *et al. J Clin Oncol.* 2015;33(18):2013–20; **3.** Zahoor H, *et al. Oncotarget.* 2018;9(18):14036–14037; **4.** Schmidt EV. *Semi Immunopathol.* 2019;41(1):21–30; **5.** Pokorny R, *et al. J Immunother Cancer.* 2021;9(1):e001781.

Which agent to stop and when: have we got this comp

Tom Powles @tompowles1 · 1d

How long should immune therapy + VEGF therapy be given in patients who complete 2 years of PD1/VEGF therapy having had an initial response (lung and LN disease) and ongoing stable disease but are not in CR. @DrChoueiri @montypal @HHammersMD

Continue VEGF only ✓	39%
Continue both	23%
Continue IO only	17%
Stop both	21%

114 votes · Final results

1 · 4 · 6 · 1.2K

VEGF TKI therapy

- Tolerated[4]
- Durable benefit[4]
- No evidence for duration of therapy[5]

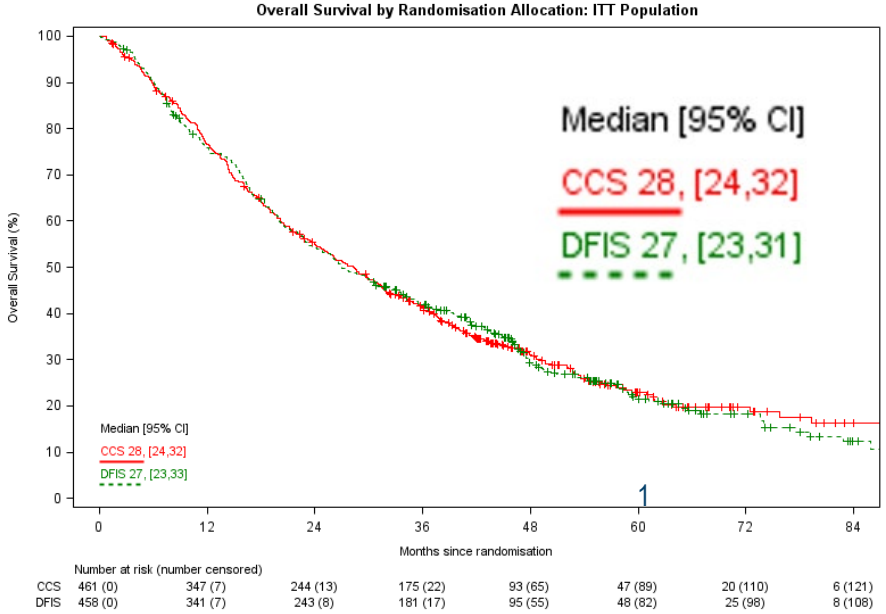
It makes
Is it pos

1 therapy
uestions?

PD-1, programmed cell death protein; TKI, tyrosine
1. Grimm MO, *et al. J Clin Med.* 2020;9(2):565; **2.** M
Immunopathol. 2019;41(1):21–30; **5.** Pokorny R, *e*

4037; **4.** Schmidt EV. *Semi*

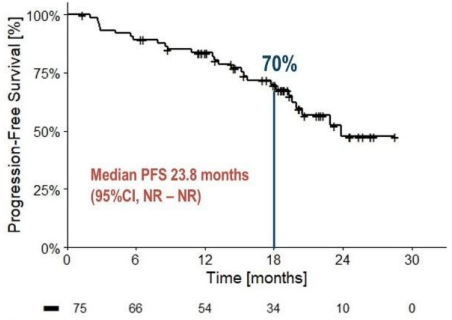
VEGF treatment breaks:



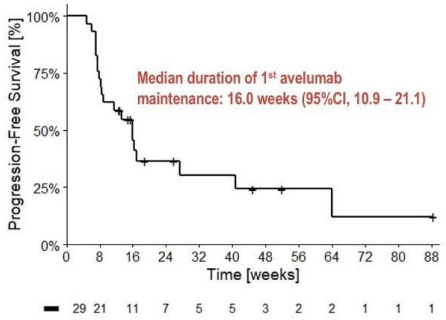
OS and PFS for the for TIDE study

Secondary & exploratory endpoints:

PFS and OS in the overall population:



Duration of 1st avelumab maintenance



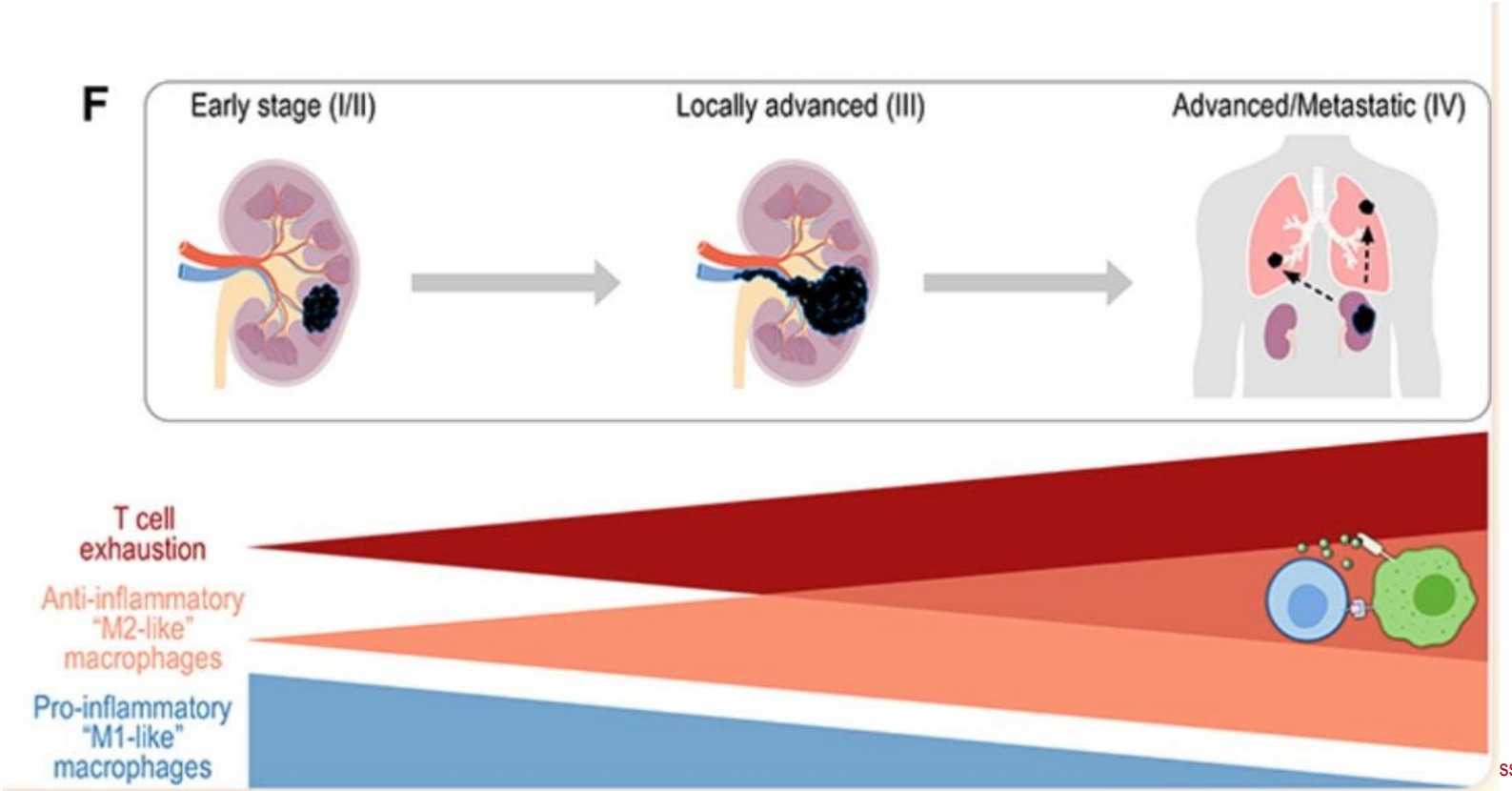
Median OS was not reached, the 18-months OS was 94%.

At cut-off date 27/75 patients progressed and 7/75 died. The median FU values were 19.3 months for PFS and 18.9 months for OS.

Prof Roberto Iacovelli – @DrIacovelli

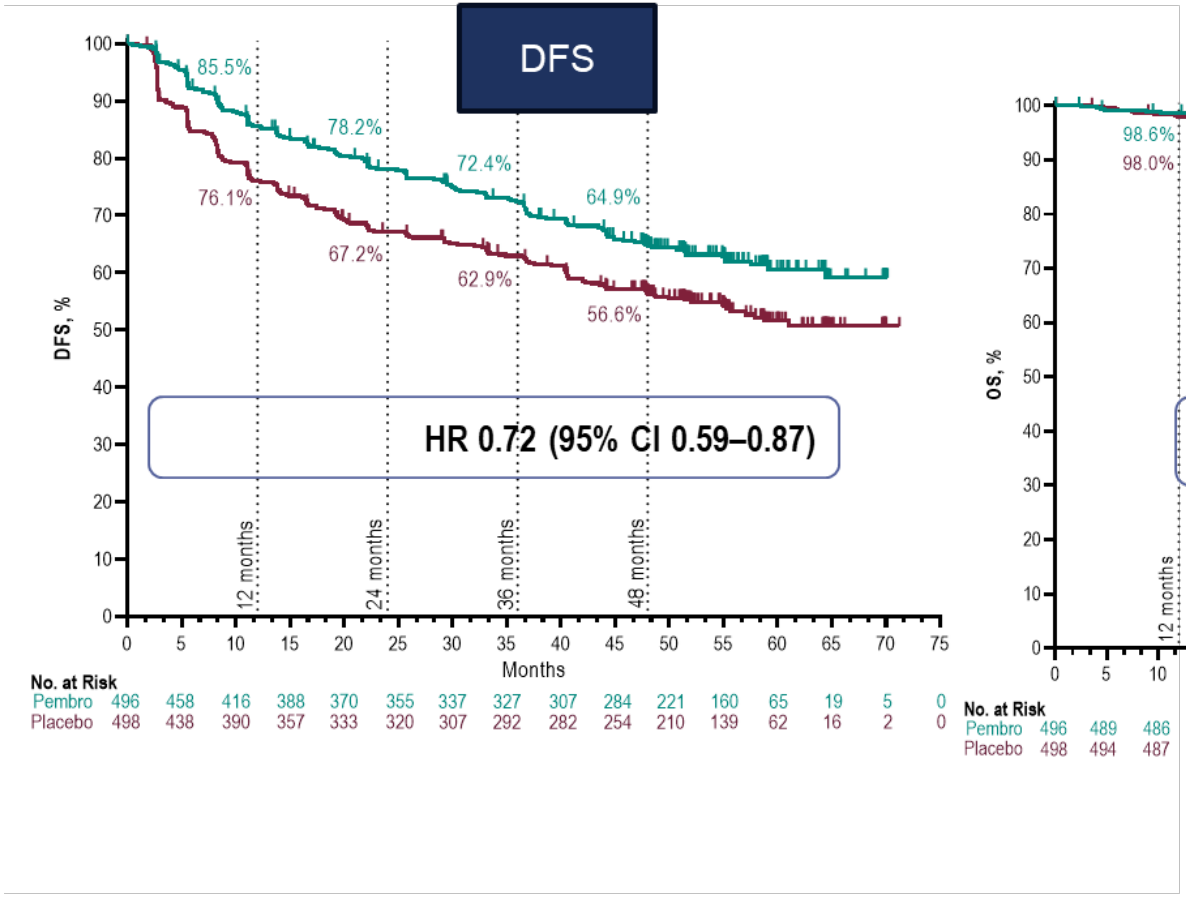
Stopping VEGF TKI in the frist 6 months is associated with quite rapid PD.
VEGF TKI is curing patients so why go on with it beyond 2 years?

Immune checkpoint inhibition is associated with cure in advanced disease and earlier intervention is likely to be better.



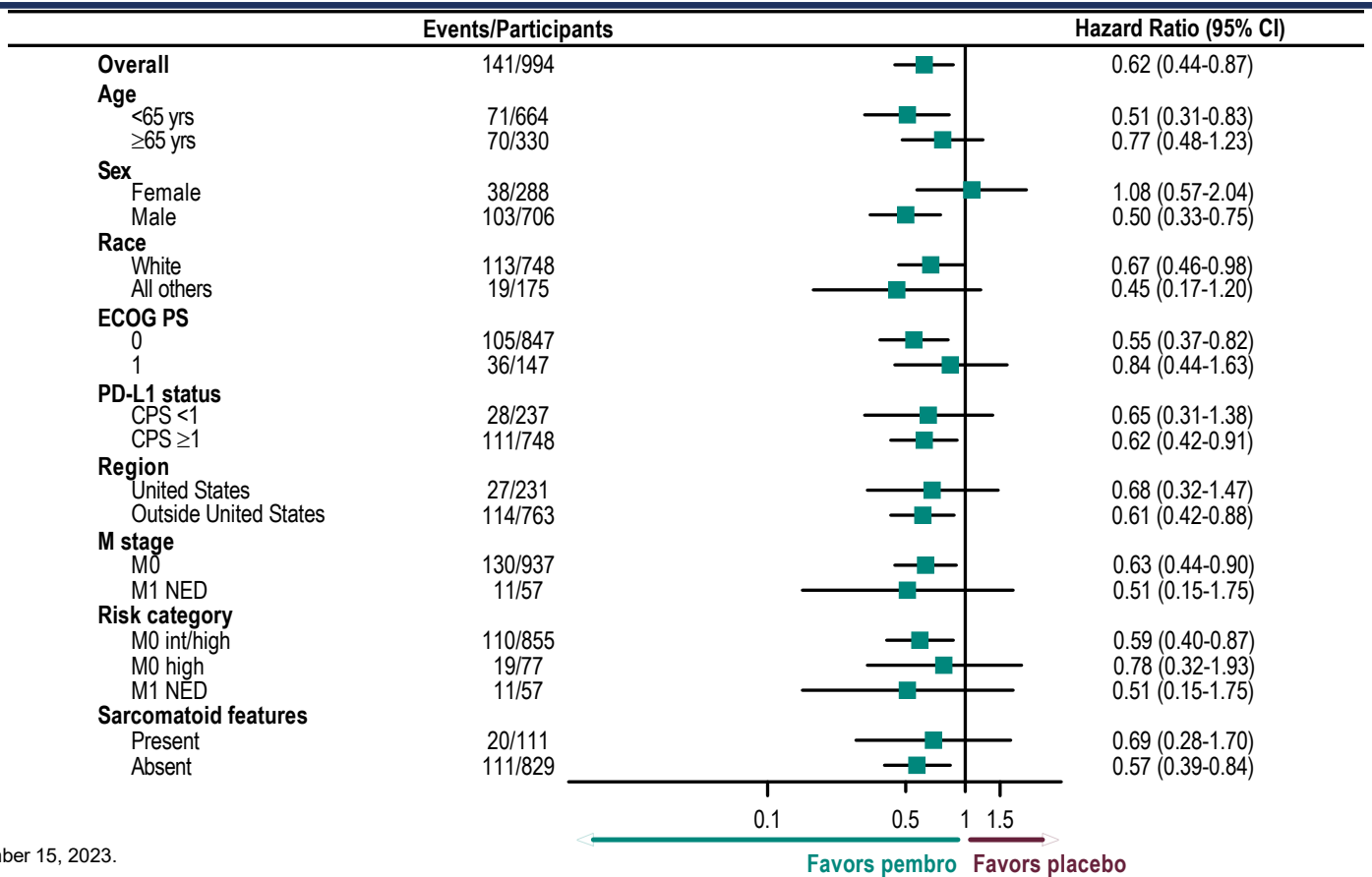
Braun
Cancer Cell

Adjuvant pembrolizumab in intermediate and high risk clear cell RCC



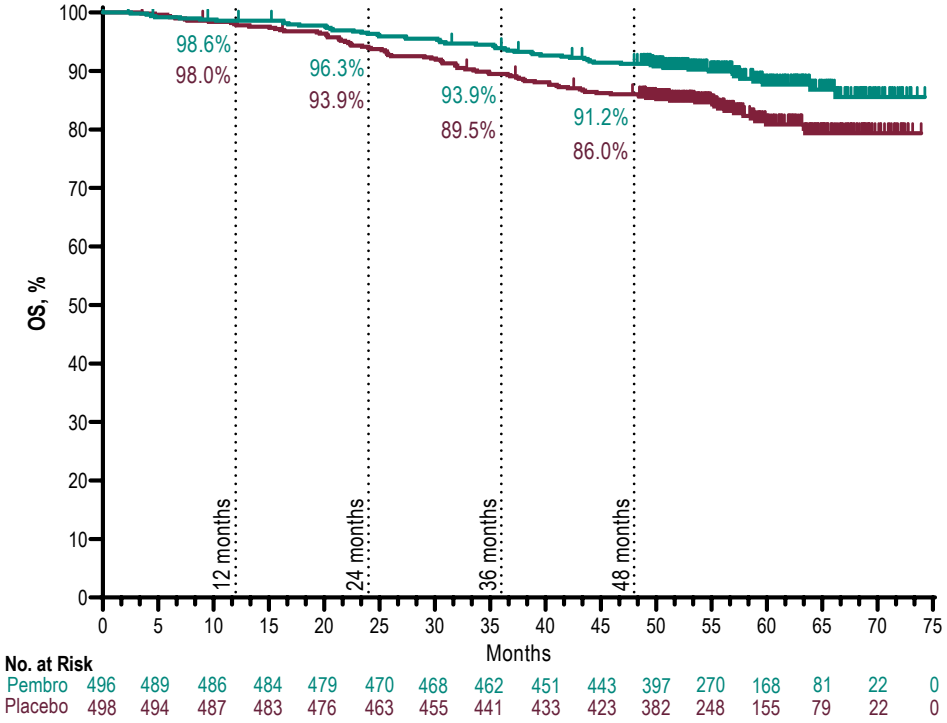
Choueiri NEJM 2023.

Overall Survival by Subgroups



Data cutoff date: September 15, 2023.

Adjuvant pembrolizumab reduces the risk of death. But what do we do at relapse. Rechallange with IO doesn't work.



Tom Powles @tompowles1 · 1d

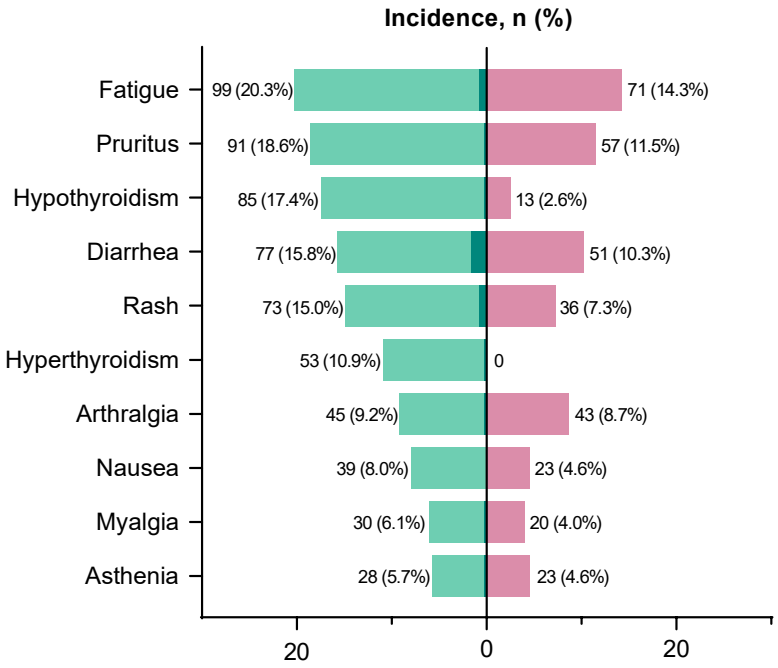
When should immune therapy rechallange at release after adjuvant pembro in clear cell renal cancer occur. @DrChoueiri @montypal @HHammersMD

Never rechallenge	6%
Always rechallenge	10%
Only if >6 mnth since IO	40%
Only if >12 mnth since IO ✓	44%

202 votes · Final results

4 12 19 3.3K

Treatment-Related AEs with Incidence ≥5% for adjuvant pembrolizumab



But what about the rare but significant life changing toxicity

Endocrine, cardiac, respiratory, neurological.

Patients want to know about serious, life changing or long term toxicity, not a couple of days of diarrhoea or a transient grade 2 transaminitis.

As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: June 14, 2021.

Summary of Updated Safety Findings from adjuvant pembrolizumab

	IA3 (57.2 mo follow-up)[a]	
	Pembrolizumab (N = 488)	**Placebo (N = 496)**
Duration of therapy, median (range), months	11.1 (0.03−14.3)	11.1 (0.03−15.4)
Any-cause AEs	470 (96.3%)	453 (91.3%)
Grade 3 to 5	156 (32.0%)	88 (17.7%)
Led to discontinuation	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)
Serious AEs	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)
Treatment-related AEs	386 (79.1%)	263 (53.0%)
Grade 3 to 4	91 (18.6%)	6 (1.2%)
Led to discontinuation	89 (18.2%)	4 (0.8%)
Led to death	0	0
Immune-mediated AEs and infusion reactions[b]	178 (36.5%)	36 (7.3%)
Grade 3 to 4	46 (9.4%)	3 (0.6%)
Led to death	0	0
Required high-dose (≥40 mg/day) systemic corticosteroids	37 (7.6%)	3 (0.6%)

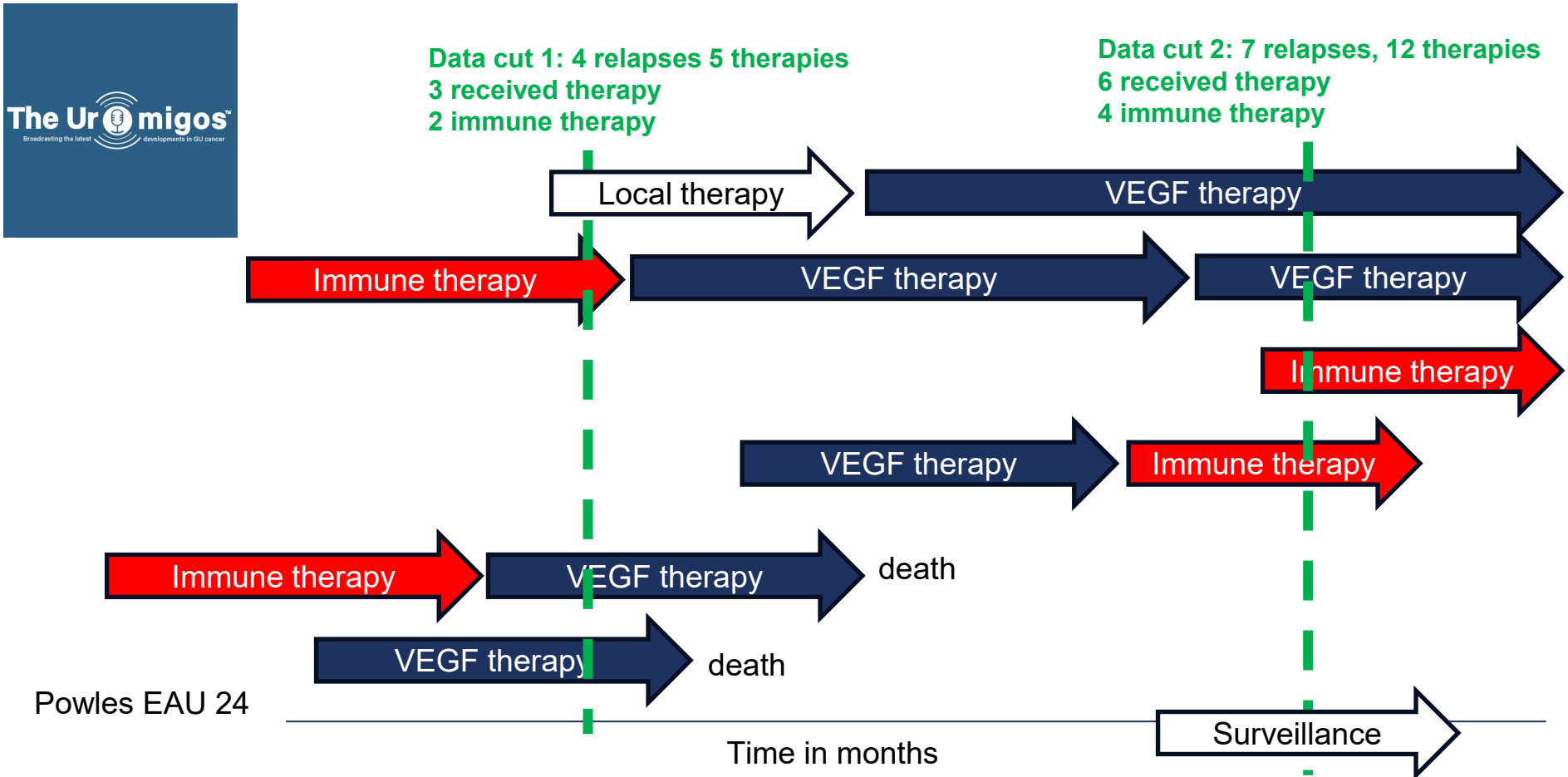
[a]AEs were graded per the NCI CTCAE v4.0 and reported from randomization to 30 days (90 days for serious AEs) after study therapy discontinuation. [b]Based on a list of preferred terms intended to capture known risks of pembro and were considered regardless of attribution to study treatment by the investigator.
Data cutoff date: September 15, 2023.

Subsequent Therapies, Intention-to-Treat Population

	Participants with Documented Recurrence	
	Pembrolizumab (N = 161)	**Placebo (N = 210)**
Received any subsequent therapy[a,b]	128/161 (79.5%)	171/210 (81.4%)
Received systemic anticancer drug therapy Anti–PD-(L)1 therapy[c] VEGF/VEGFR inhibitor[d] Other[e]	102/128 (79.7%) 42/102 (41.2%) 94/102 (92.2%) 32/102 (31.4%)	145/171 (84.8%) 101/145 (69.7%) 123/145 (84.8%) 60/145 (41.4%)
Received radiation therapy	31/128 (24.2%)	33/171 (19.3%)
Received surgery	35/128 (27.3%)	50/171 (29.2%)
No subsequent therapy	28/161 (17.4%)	28/210 (13.3%)
No subsequent therapy data available	5/161 (3.1%)	11/210 (5.2%)

[a]An additional 4 and 1 pts respectively in the pembro and placebo arms who are not included in the figure received subsequent therapy without documented recurrence. [b]Pts could have multiple subsequent anticancer therapies for RCC; each pt is counted once in each applicable category. [c]Atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab. [d]Axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, tivozanib. [e]Included but was not limited to belzutifan, everolimus, and ipilimumab.
Data cutoff date: September 15, 2023.

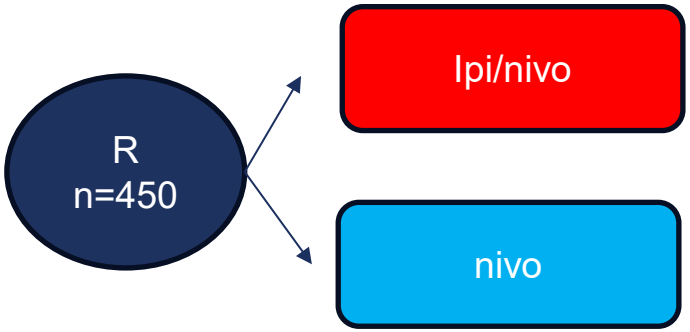
Analysis of subsequent therapy from adjuvant trials is time dependant
Time dependant multiple options in RCC data makes presentation is complex.



Powles EAU 24

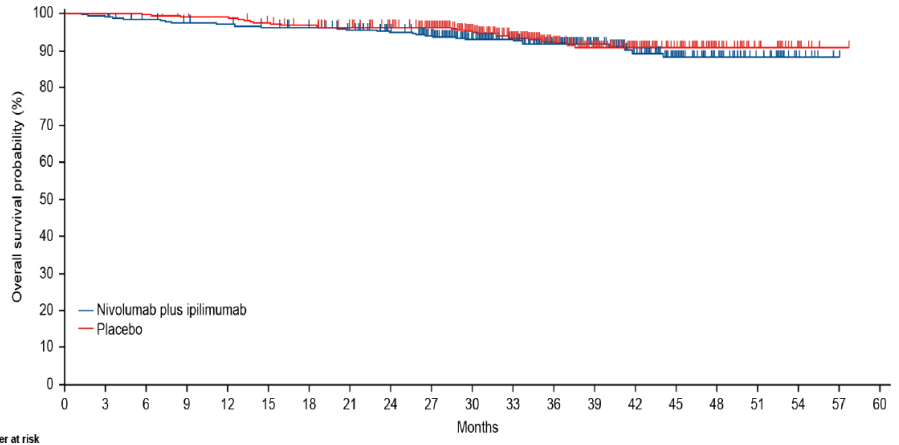
Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial

The 8Y8 study: RR and PFS as primary endpoint



NCT 03873402

Overall survival



Number at risk (number censored)																						
Nivolumab plus ipilimumab	405 (0)	399 (3)	391 (8)	386 (10)	383 (11)	378 (13)	374 (17)	363 (25)	348 (38)	330 (52)	278 (101)	230 (149)	184 (192)	137 (239)	96 (277)	68 (304)	40 (332)	23 (349)	8 (364)	1 (371)	0 (372)
Placebo	411 (0)	403 (8)	400 (10)	396 (12)	395 (13)	386 (15)	381 (18)	372 (25)	361 (36)	343 (53)	292 (101)	237 (151)	184 (201)	138 (245)	98 (285)	66 (317)	36 (347)	22 (361)	10 (373)	1 (382)	0 (383)

Motzer lancet 2023

In the UK only 60% of patients receive PD-1 therapy despite universal access: so give best treatment first. VEGF/PD-1 frist line for all?

Patterns of prescribing

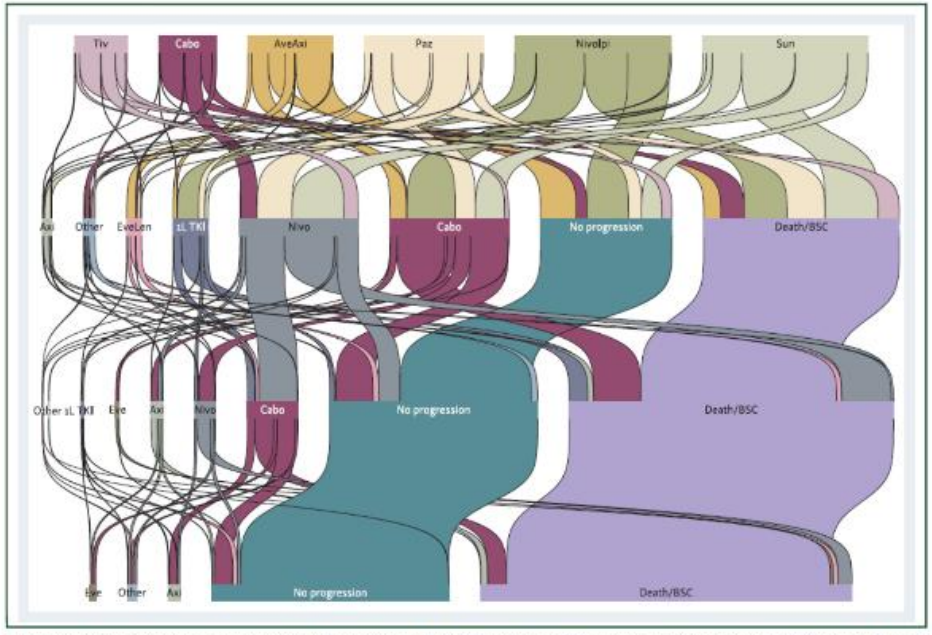


Figure 1. Sankey diagram showing the percentage of patients who received which treatment per line of therapy and how treatment in the previous line influenced the choice in the subsequent line.
AveAxi, avelumab plus axitinib; Axi, axitinib; BSC, best supportive care; Cabo, cabozantinib; Eve, everolimus; EveLen, everolimus plus lenvatinib; 1L, first line; Nivo, nivolumab; Nivolpi, nivolumab plus ipilimumab; Paz, pazopanib; Sun, sunitinib; Tiv, tivozanib; TKI, tyrosine kinase inhibitor.

% of patients who did not receive immune therapy at any stage

Good risk 44%
Intermediate risk 33%
Poor risk 40%

John McGrane Cancer Medicine 2023

Adjuvant therapy

Discuss it with your patients

- The risks and benefits of adjuvant therapy should be discussed
- They should know there is an OS advantage.
- Don’t go beyond the inclusion criteria.
- Discuss there have been other trials with diffferent drugs that have not been positive.

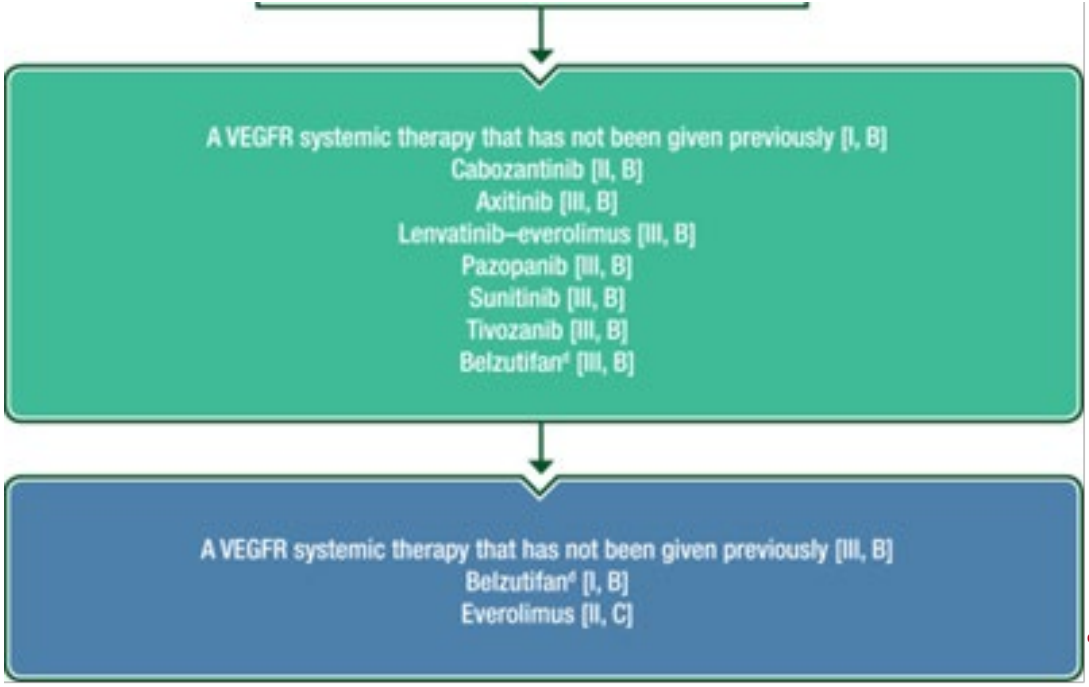
1st line metastatic disease

Pick one
Use it well

- Focus on delivery
- The data does not support rechallenge with immune therapy
- Encourage VEGF TKI treatment breaks if especially after 2 years
- Don’t pick therapy based on IMDC

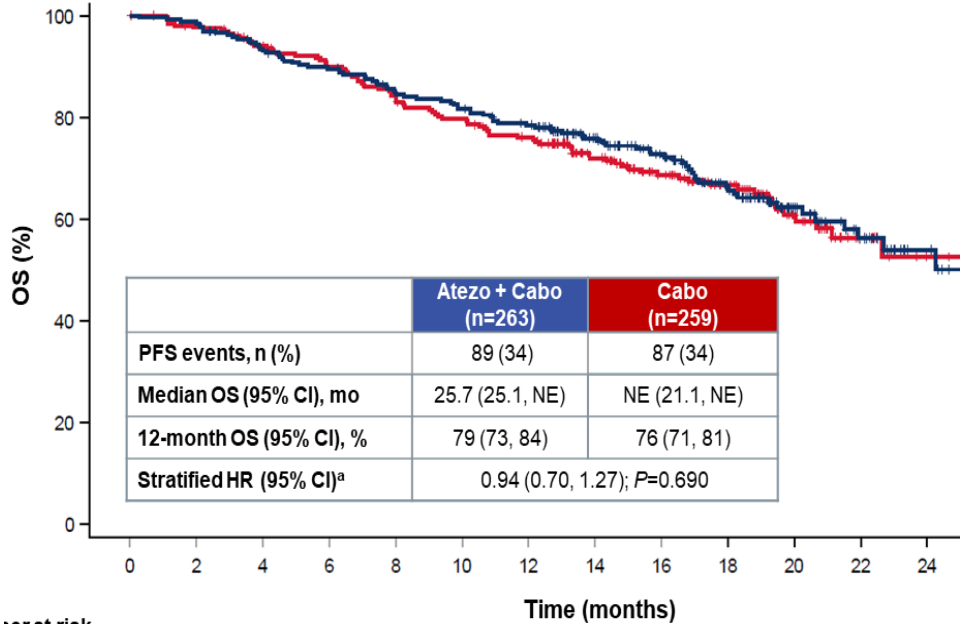
Second and third line therapy for advanced disease.

POST 1st line PD-1 bases therapy



Re-challange with PD-(L)1 therapy does not improve efficacy.

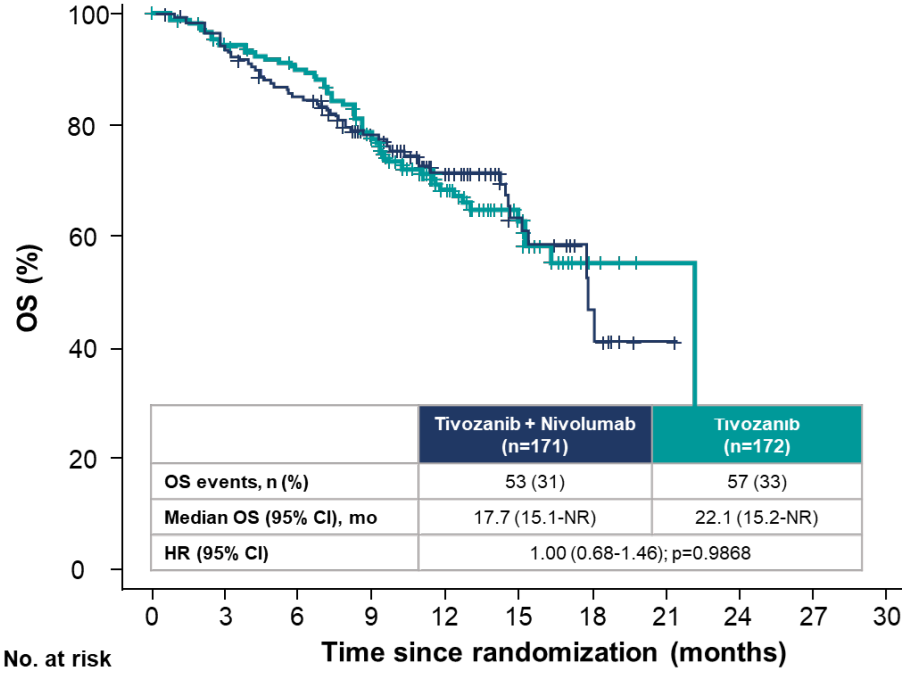
OS for Cabozantinib +/- atezolizumab



	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	

No. at risk

OS for tivozanib +/- nivolumab



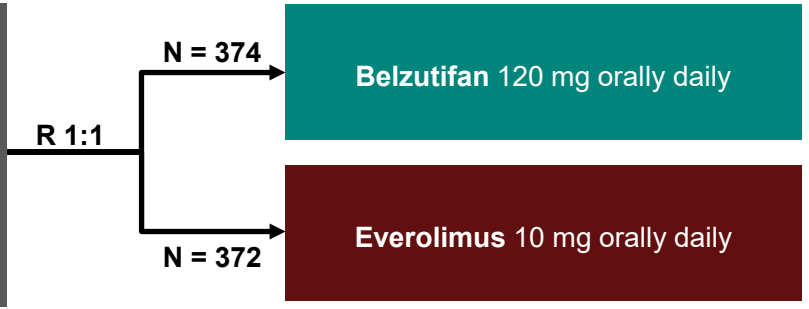
	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
OS events, n (%)	53 (31)	57 (33)
Median OS (95% CI), mo	17.7 (15.1-NR)	22.1 (15.2-NR)
HR (95% CI)	1.00 (0.68-1.46); p=0.9868	

No. at risk

LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti−PD-(L)1 mAb and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%



Stratification Factors

- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS
- The study was considered positive if either of the dual primary endpoints was met

Key Secondary Endpoint:

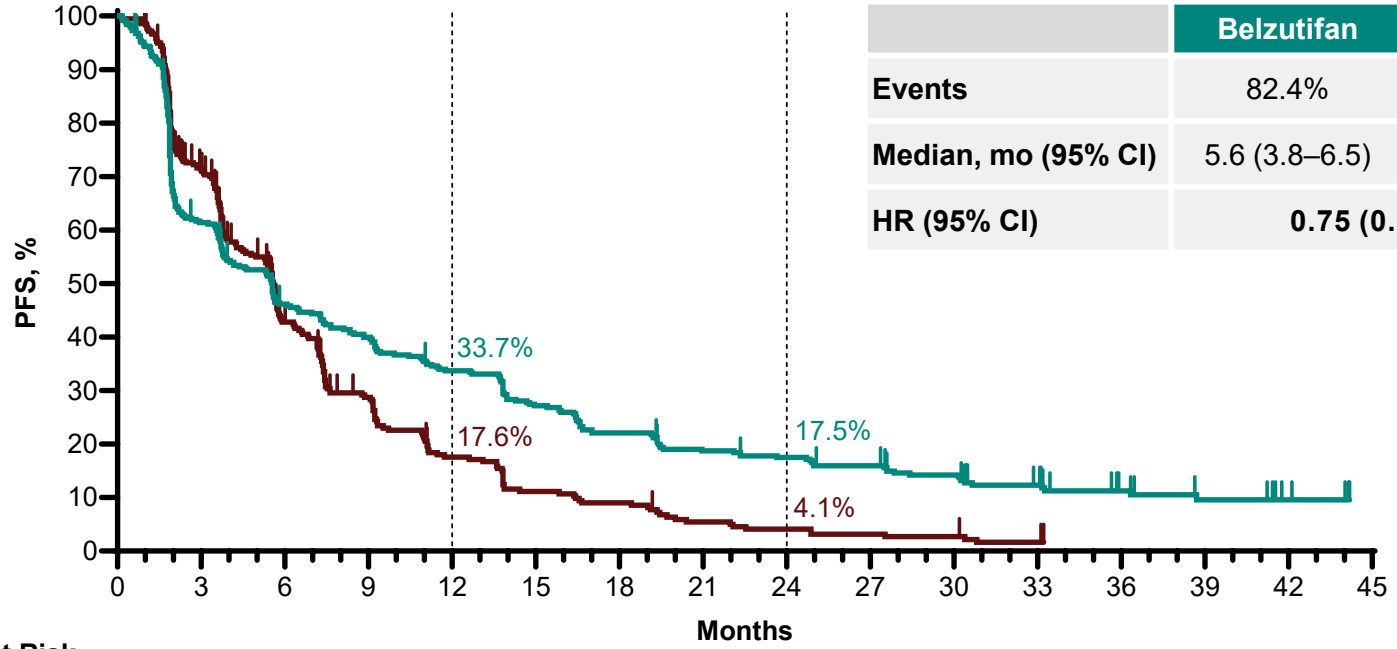
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety

[a]Based on the number of present risk factors according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). BICR, blinded independent central review.

Primary Endpoint: PFS per RECIST 1.1 by BICR



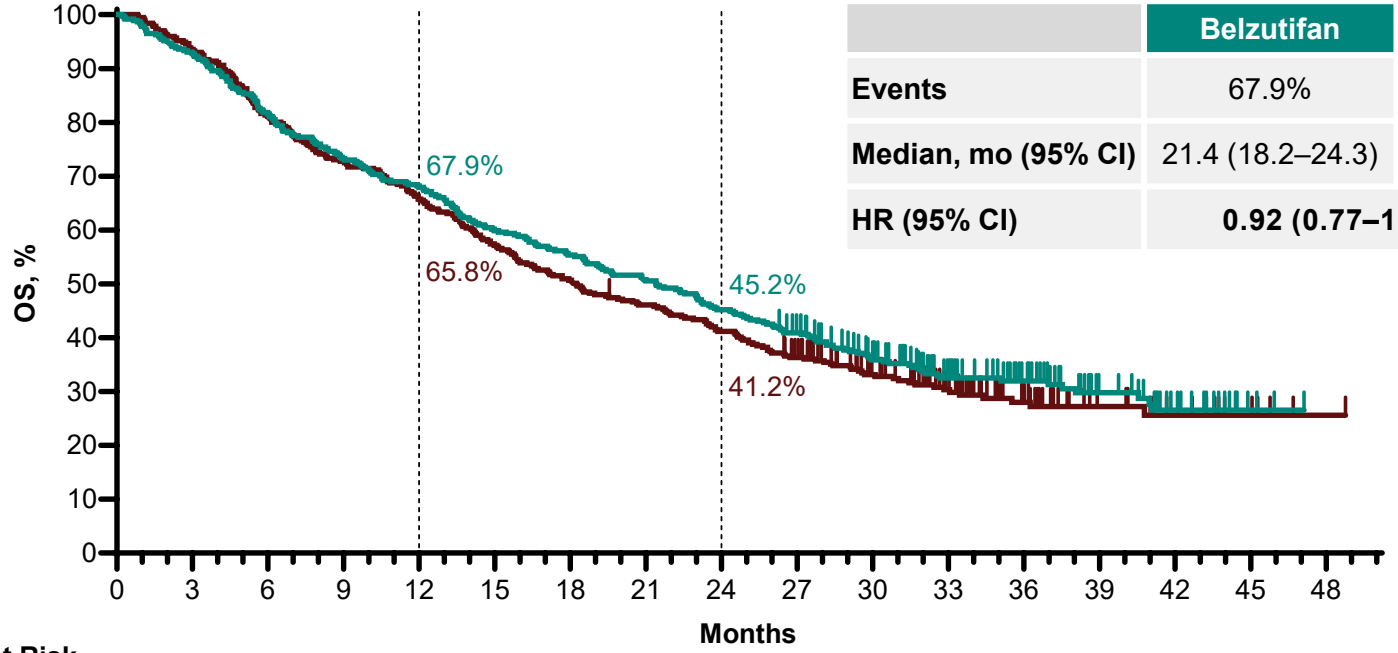
	Belzutifan	Everolimus
Events	82.4%	75.0%
Median, mo (95% CI)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	**0.75 (0.63–0.88)**	

No. at Risk

Belzutifan	374	218	156	135	113	91	74	61	56	50	39	27	16	10	5	0
Everolimus	372	226	113	70	41	26	21	12	9	7	6	3	0	0	0	0

Data cutoff date: April 15, 2024.

Primary Endpoint: OS



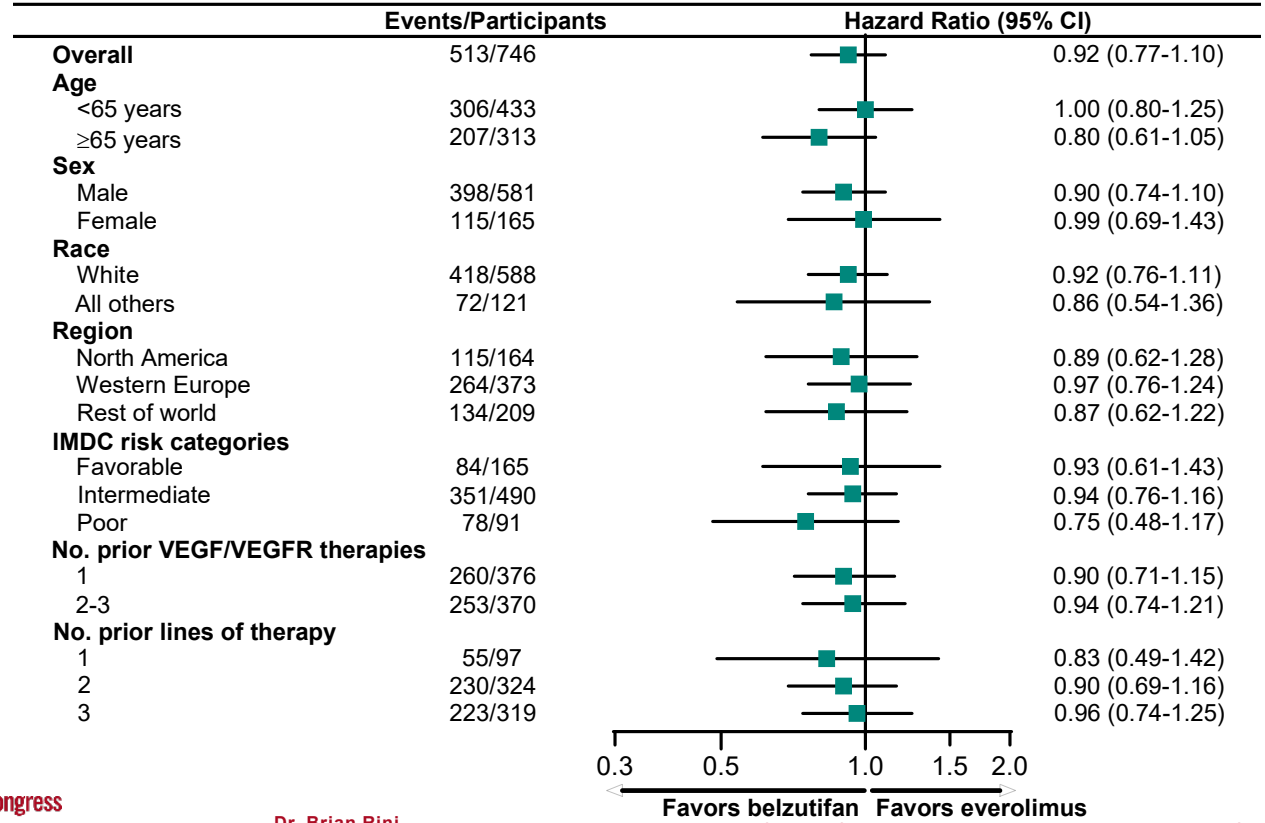
	Belzutifan	Everolimus
Events	67.9%	69.6%
Median, mo (95% CI)	21.4 (18.2–24.3)	18.2 (15.8–21.8)
HR (95% CI)	**0.92 (0.77–1.10); *P*=0.18**	

No. at Risk

Belzutifan	374	347	305	274	254	224	207	189	169	148	111	75	54	31	18	4	0
Everolimus	372	347	301	270	244	212	188	170	152	128	92	64	38	20	12	5	1

Data cutoff date: April 15, 2024.

OS in Subgroups



Data cutoff date: April 15, 2024.

Summary of Adverse Events[a]

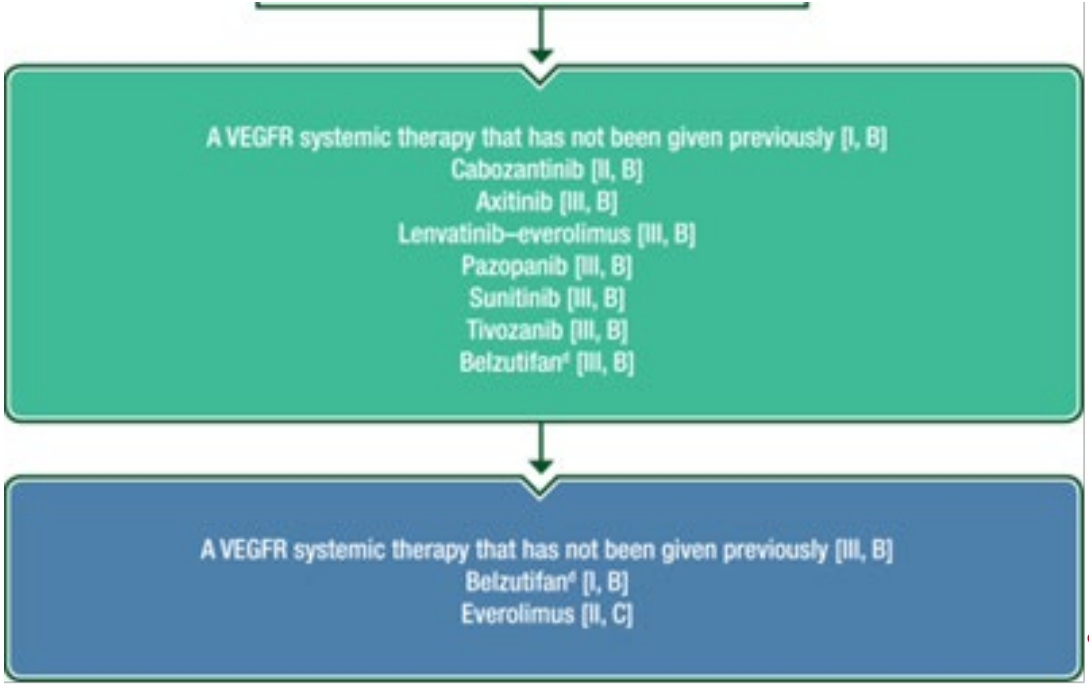
	Belzutifan (N = 372)	Everolimus (N = 360)
Median duration of therapy, mo (range)	7.6 (0.1–45.9)	3.9 (0.03–41.8)
All-cause AEs, n (%)	369 (99.2%)	357 (99.2%)
Grade ≥3	234 (62.9%)	226 (62.8%)
Serious	160 (43.0%)	139 (38.6%)
Led to discontinuation	23 (6.2%)	55 (15.3%)
Led to death	14 (3.8%)	19 (5.3%)
Treatment-related AEs, n (%)	333 (89.5%)	322 (89.4%)
Grade ≥3	147 (39.5%)	144 (40.0%)
Serious	49 (13.2%)	48 (13.3%)
Led to death	1 (0.3%)[b]	2 (0.6%)[c]

[a]Among all participants who received ≥1 dose of study therapy. [b]Multiple organ dysfunction syndrome. [c]Sepsis (n = 1) and acute kidney injury (n = 1).

Data cutoff date: April 15, 2024.

Second and third line therapy for advanced disease.

POST 1st line PD-1 bases therapy



ESMO GUIDELINES:
REAL WORLD CASES

RENAL CELL CANCER

Clinical Practice Perspective

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On behalf of the **ESMO Practising Oncologists Working Group**

ESMO WEBINAR SERIES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

DISCLOSURE INFORMATION

Honorarium (speakership, article review) – Research Review New Zealand

CLINICAL PRACTICE PERSPECTIVE – CASE STUDY

Role for localised therapy in advanced RCC

Considerations when deciding on 1st line therapy

Toxicity management of systemic therapy – ICI, TKI

ROLE FOR LOCALISED THERAPY IN ADVANCED RCC

From case history: Development of several pulmonary lung lesions

Hepatic steatosis work-up

Consultation with Medical Oncology (11 weeks)

Follow up with Medical Oncology (13 months)

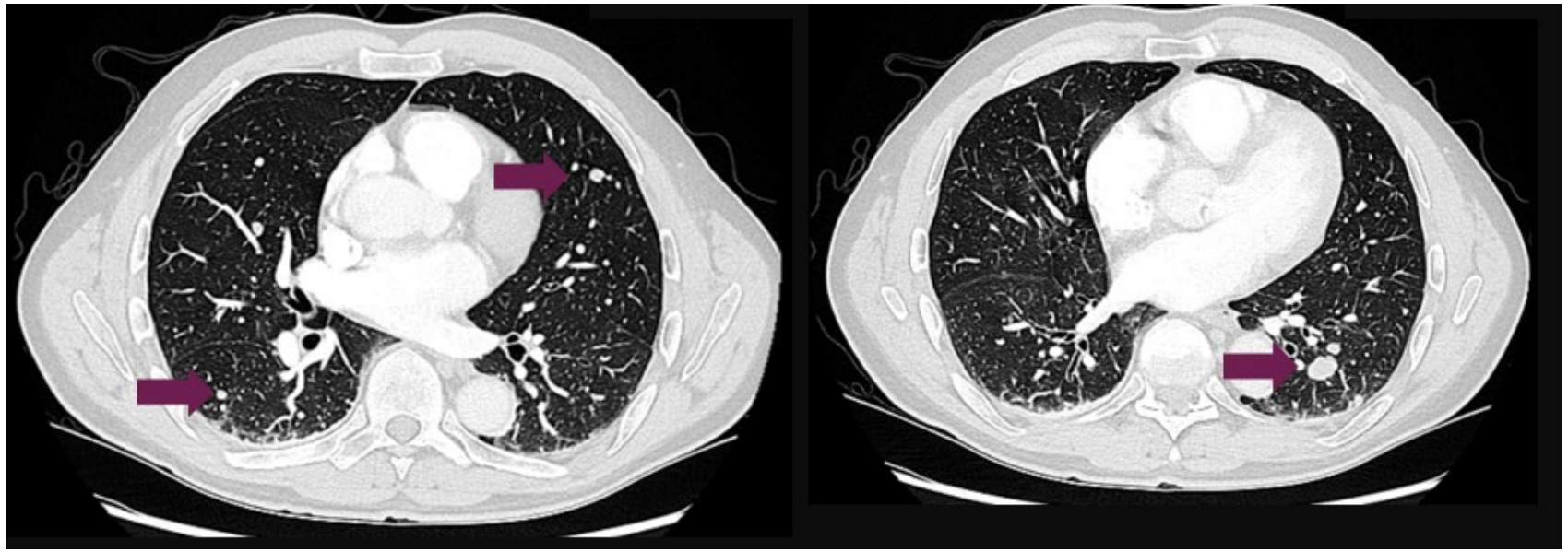
Follow-up CT CAP: Several new lung lesions

Laboratory work-up: Hb 11 g/dL, Platelets 560 k

2020 | 2021 | 2022 | 2023 | 2024

Pembrolizumab

Left hand-assist radical nephrectomy (several surgical complications)



ESMO GUIDELINES: REAL WORLD CASES

ROLE FOR LOCALISED THERAPY IN ADVANCED RCC

Assuming limited number of lung lesions, consideration for resection / ablative therapy.

What is the potential benefit of this approach?

- Delay systemic treatment and associated toxicities of active therapy
- Good local control rates (lung, bones) and symptom control
- Delay switch of an otherwise successful systemic treatment
- Potential survival benefit (retrospective, institutional studies)

ROLE FOR LOCALISED THERAPY IN ADVANCED RCC

Practical Considerations

- Multidisciplinary Team discussion (CTSU, Radiation Oncology, Radiology)
- Comorbidities (Surgical suitability, Respiratory function)
- Location of disease
- Number of sites of disease (how are we defining oligo-metastatic disease)
- Tumour biology / natural history (months, years from diagnosis)

ROLE FOR SBRT IN ADVANCED RCC – DE NOVO OLIGOMETASTASES

Local control rates 85-90% (>90% for intracranial disease)

Grade 3/4 toxicity <10%

Delay systemic treatment for at least 12 months in 70-90% of oligometastatic patients.

Safe/tolerable in combination with ICI and TKI therapy

- Two meta-analyses (54 studies)
- Definition of oligometastases varied, but commonly <5 lesions.

European Urology 2022. https://doi.org/10.1016/j.eururo.2022.06.017
Lancet Oncology 2021 Dec;22(12):1732-1739. doi: 10.1016/S1470-2045(21)00528-3. Epub 2021 Oct 28

ROLE FOR SBRT IN ADVANCED RCC – OLIGOPROGRESSION

- Phase 2 prospective trial (Cheung et al.) – stable/responsive disease after 3 months of TKI who developed <5 oligo-progressive sites (n=37).
  - 12-month local control rate of 93%
  - 12-month cumulative incidence of changing systemic therapy of 47%
  - Median time to change systemic therapy 12.6 months

- Prospective trial (Hannan et al.) demonstrated that patients (ICI, TKI or combination, n=20), with previous stable/responsive disease who developed up to 3 sites of oligo-progression.
  - 12-month local control rate of 100%
  - Median time to change in systemic treatment of 11.1 months (4.5-19 months).

Eur Urol 2021 Dec;80(6):693-700. doi: 10.1016/j.eururo.2021.07.026. Epub 2021 Aug 13.
Eur Urol Oncol 2022 Apr;5(2):216-224. doi: 10.1016/j.euo.2021.12.001. Epub 2022 Jan 2.

WHAT TO CONSIDER FOR 1ST LINE THERAPY

Practical considerations in this case study

Clear cell histology

Comorbidities – HTN (on losartan)

Post adjuvant pembrolizumab

Low volume lung metastases

Intermediate risk group

REAL WORLD: WHICH COMBINATION (IO/IO VS IO/TKI)

(1) Retrospective analysis (US Oncology Network's iKnowMed database. April 2018-March 2020)

N=193, metastatic ccRCC

1L Nivolumab+Ipilimumab

IMDC Intermediate (56%) / High (44%) risk group

PS 0-1 (60%). PS ≥ 2 (40%)

Median PFS 17.1 months, 12 month PFS rate 58%, 12 month OS 75%, ORR 43%

Comparatively
CM 214 (Nivo/ipi)
12 month OS rate 83%
ORR 42%

TRAEs 47% (fatigue 13%, rash 10%, diarrhoea 7%, nausea 6%, colitis 4%, pruritus 4%)

Treatment-related hospitalisation 5.5%, emergency department review 3%

DOI: 10.1200/JCO.2020.39.28_suppl.305 Journal of Clinical Oncology 39, no. 28_suppl (October 01, 2021) 305-305

REAL WORLD: WHICH COMBINATION (IO/IO VS IO/TKI)

(2) Retrospective database review (Fox Chase CC, Philadelphia. 2018-2022).

N=1506

1L Axitinib/Pembrolizumab (n=547) or Nivolumab/Ipilimumab (n=959)

Primary end-point were OS, real-world PFS, adjusted using propensity score weighting (age, gender, insurance, race, IMDC, practice type and nephrectomy).

Axi/Pembro vs Nivo/Ipi

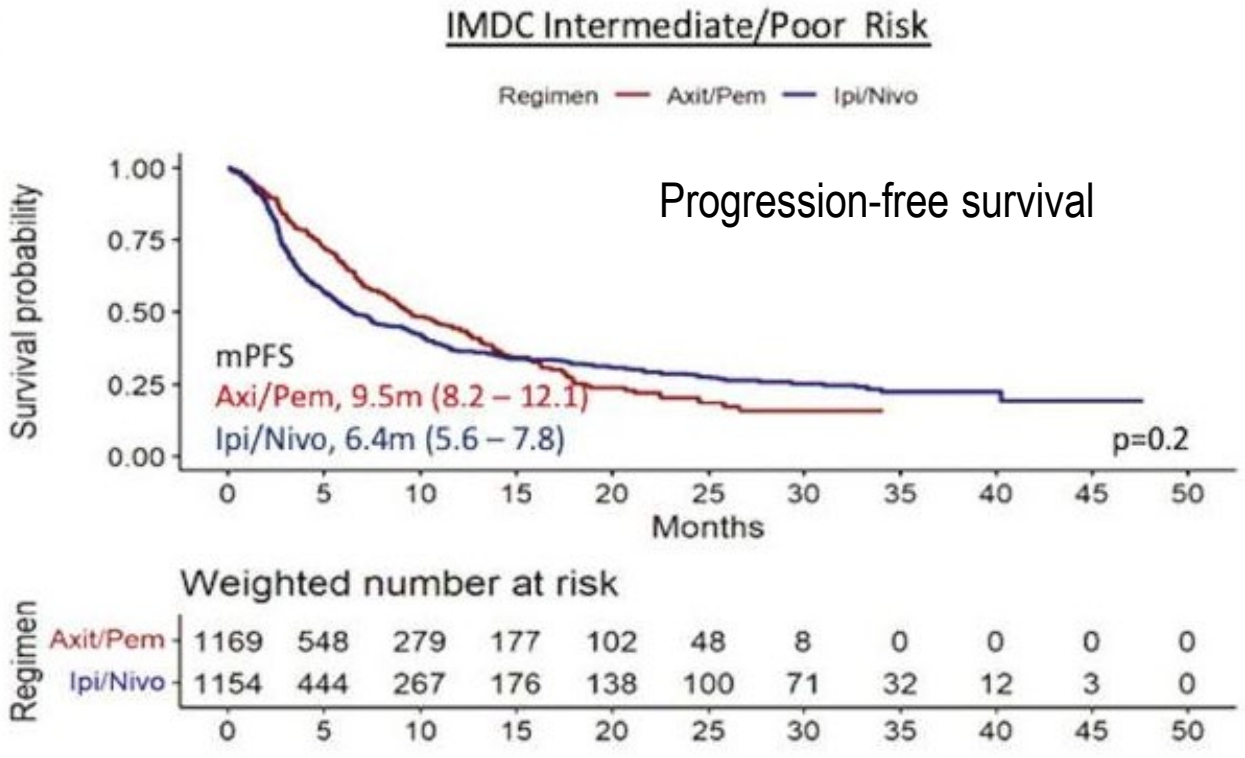
Median age 67 yrs vs 65 years

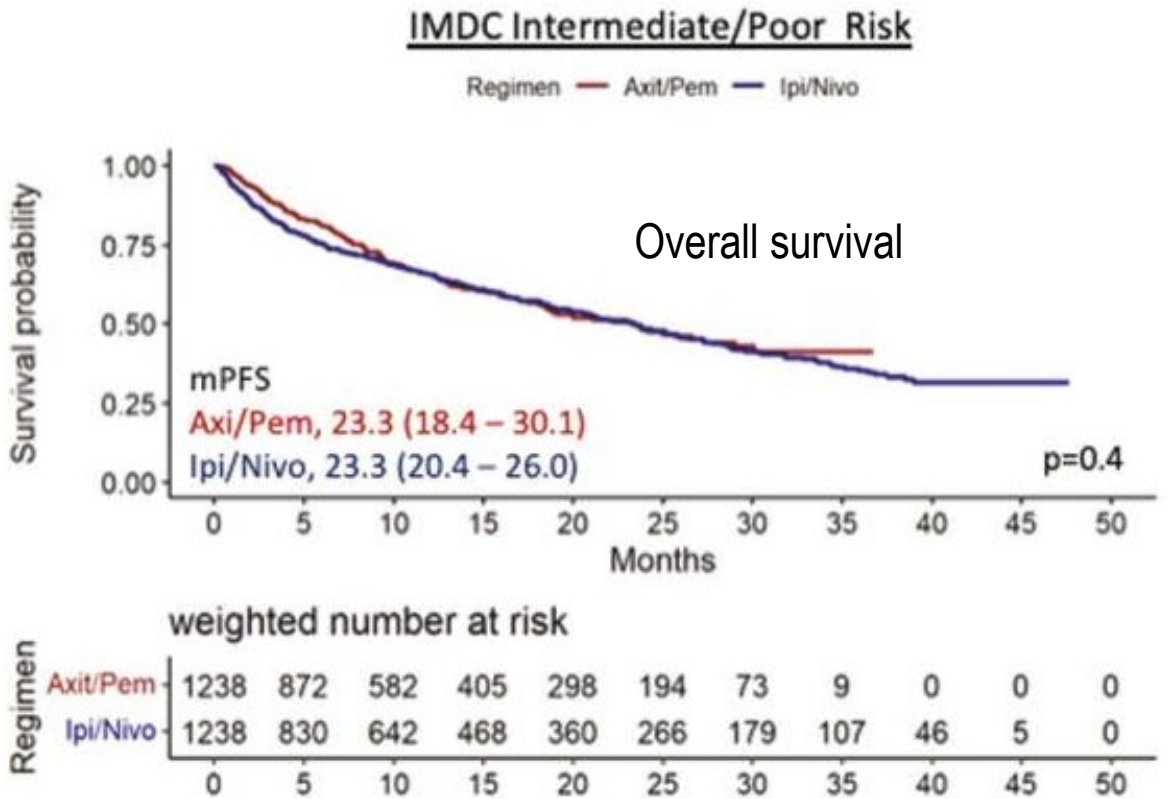
Intermediate/poor 77% vs 85%

Median FU 20 months.

Oncologist. 2022 Oct 6;28(2):157–164. doi: 10.1093/oncolo/oyac195

REAL WORLD: WHICH COMBINATION (IO/IO VS IO/TKI)





Oncologist. 2022 Oct 6;28(2):157–164. doi: 10.1093/oncolo/oyac195

REAL WORLD: WHICH COMBINATION (IO/IO VS IO/TKI)

Real-world and historical survival data with cross-trial comparisons.

	Ipilimumab + nivolumab			Axitinib + pembrolizumab		
IMDC risk category	**Real-world dataset**	**CheckMate-214**	**CheckMate-214 (extended 60 months)**	**Real-world dataset**	**KEYNOTE-426**	**KEYNOTE-426 (extended 30 months)**
ITT/full cohort						
PFS	6.9m	12.4m	12.0m	10.6m	15.1m	15.4m
OS	24.3m	NR	56.0m	28.9m	NR	NR
Favorable risk						
PFS	6.9m	15.3m	12.0m	25.5m	20.8m	—
OS	NR	NR	74.0m	NR	NR	—
Intermediate/poor risk						
PFS	6.4m	11.6m	12.0m	9.5m	12.6m	—
OS	23.3m	NR	47.0m	23.3m	NR	—
ITT/full cohort						
24-month landmark survival	50.2%	78%	—	53.8%	82.3%	74.4%

Oncologist. 2022 Oct 6;28(2):157–164. doi: 10.1093/oncolo/oyac195

WHICH COMBINATION (IO/IO VS IO/TKI)

Things to consider:

IO+ IO (e.g. Nivolumab/Ipilimumab)

- Depth / Durability of response
- Higher iRAE toxicity / need for steroids
- Patients with underlying autoimmune conditions (severity of limitations)
- Opportunity for treatment-free remission

IO + TKI

- Highly symptomatic
- High disease burden (liver, bones), need for rapid treatment response (ORR 57-71%; nivo/cabo – lenva/pembro)

May need to be guided by expected toxicities, histology (eg sarcomatoid – IO/IO), cost/access

TOXICITY MANAGEMENT

Consider IO vs TKI as cause

- Timing of onset of symptoms (early vs late), overlapping symptoms

Which combinations have highest rates of AEs?

Grade 3/4 AEs	Nivolumab/Ipilimumab (CM-214)	Pembrolizumab/Axitinib (KN-426)	Pembrolizumab/Lenvatinib (CLEAR)	Nivolumab/Cabozantinib (CM-9ER)
Any	46%	67%	82%	65%
Diarrhoea	4%	10%	10%	7%
Hypertension	<1	22%	28%	13%
HFS	-	5%	4%	8%
Proteinurea	-	3%	8%	4%

COMMON TOXICITY MANAGEMENT

Hypertension Management

- Identify and treat pre-existing HTN
- Monitor BP on initiation, Q2-4 weekly, titrate dose accordingly
- Ideal goal <140/90 mmHg – lower if existing diabetes or CKD
- Choice of agent
  - Avoid verapamil/diltiazem if using sorafenib/sunitinib (CYP450 inhibition)
  - ARB, ACE-I maybe preferable

- Association between HTN and improved outcomes

COMMON TOXICITY MANAGEMENT

HFS Management

- More common with sorafenib, Axitinib, lenvatinib > sunitinib or pazopanib

- Prevention/management
  - Treatment break followed by dose reduction
  - Emolients upfront
  - Oral/topical Analgesia

- Association between skin toxicity and improved outcomes

COMMON TOXICITY MANAGEMENT

Diarrheoa Management

- Loperamide for Grade 1/2
- Avoidance of foods and supplements (e.g. fibre) that increase GI motility
- Treatment interruption for Grade 3/4 diarrhoea, dose reduction
- Fluid rehydration

-

COMMON TOXICITY MANAGEMENT

Renal function/toxicity

- Proteinurea
  - Asymptomatic – monitor
  - Temporary cessation if protein excretion >2g / 24 hours
- Nephrotic syndrome (>3g/24 hours, oedema, albumin <25)
  - ?Discontinuation – but what if still clinically responding ?Consider use of an ACE-I/ARB.
- Dose adjustments: ICI no dose modifications, TKI data variable

EGFR (ml/min)	Pazopanib	Sunitinib	Lenvatinib	Cabozantinib	Axitinib
15-30	No dose modifications	Use with caution	Suggest 10 mg daily	Use with caution	No dose modifications
<15	No dose modifications	Use with caution	Suggest 10 mg daily	No data	Use with caution
ESRF	No dose modifications	No data	No data	No data	No data

COMMON TOXICITY MANAGEMENT

Immune-related adverse events – early recognition of symptoms, initiation of steroids as indicated, MDT involvement. Raising awareness/education of primary care clinicians who may initially be treating patients on ICI.

(**Ref**: Management of toxicities from Immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up)

Dose adjustment / individualization important to maintain overall dose intensity with VEGF TKIs with associated improved survival outcomes

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Haanen, J. et al. Annals of Oncology, Volume 33, Issue 12, 1217 - 1238

TAKE-AWAY MESSAGES

Role for localized therapy in advanced RCC

- Delay systemic therapy if oligo-metastases
- Delay switch of an otherwise effective systemic treatment in presence of oligo-progression
- Palliation of symptoms.

Choice of first line treatment

- No clear survival difference between combination IO/IO vs IO/TKI in 1L intermediate/poor risk disease
- Important factors such as burden of disease, underlying comorbidities and expected toxicity, cost/access

Toxicity management

- Management of underlying risk factors, comorbidities
- Early recognition and treatment of symptoms, dose adjustments
- Importance of maintaining dose intensity

The ESMO POWG serves to identify the practice needs of oncologists who are hospital and office-based by developing educational services, practice tools and quality indicators that will facilitate the implementation of best practice at the point of care.

The POWG members are relevant stakeholders to the ESMO Guidelines Webinars as experts who are consulting and implementing the guidelines in their daily practices

For more information about the ESMO POWG visit **esmo.org**

ESMO > About ESMO > Organisational Structure > Educational Committee

ESMO PRACTISING ONCOLOGISTS WORKING GROUP

Don't miss:

- The «ESMO Checklists» on OncologyPRO

ESMO GUIDELINES: REAL WORLD CASES

Clinical Practice Perspective

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