

Renal Cell Carcinoma: Sequencing Therapy in 2022

Nancy B. Davis, MD
Associate Professor of Medicine & Urology
Kathleen Jackson Johnstone Director
Vanderbilt-Ingram Cancer Center



Disclosures

- Research Funding to Institution:
 - AstraZeneca, Roche, Pfizer, Merck, Incyte, Mirati Therapeutics, Seattle Genetics, Gilead, Exelixis, Bristol-Myers Squibb, Immunomedics, Calithera Biosciences
- Consulting:
 - Janssen

Outline

- Background
- Adjuvant Setting
- Metastatic Setting
- Future Study
- Conclusions

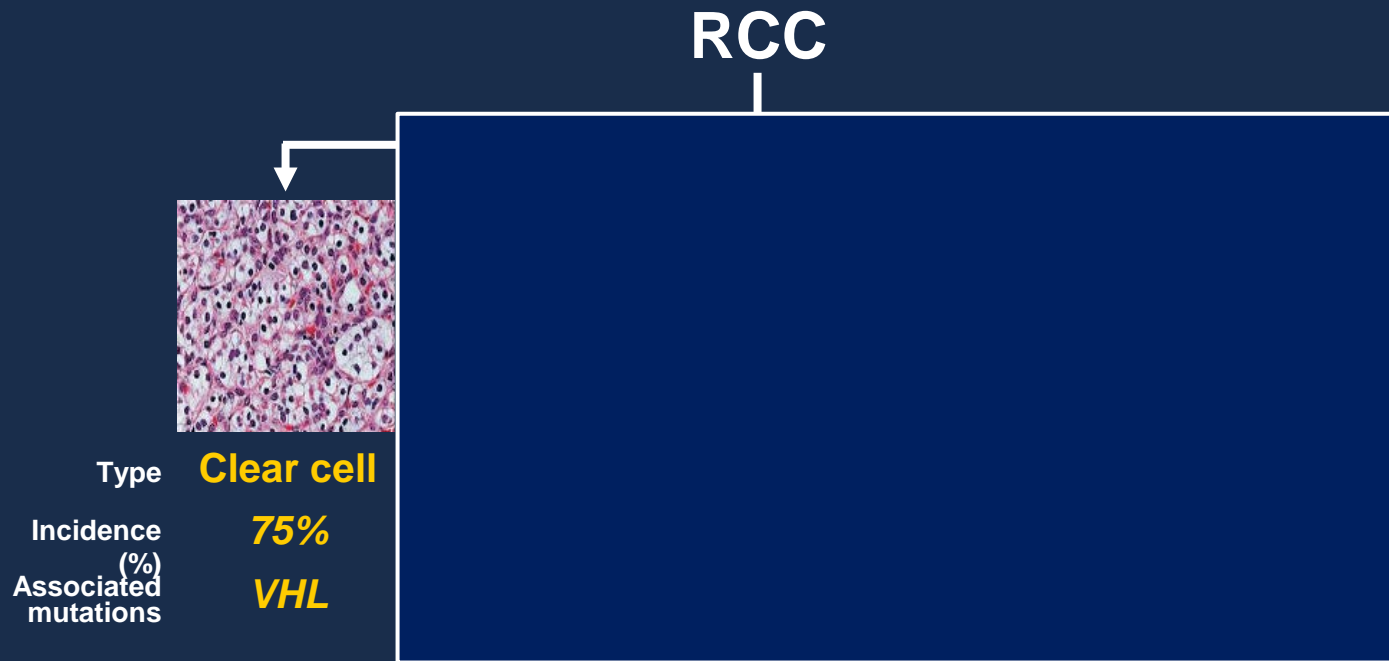
Background: Renal Cell Cancer

- ~ 3% of all malignant tumors
- 5th-7th decades of life
- Incidence is rising
 - 79k estimated new cases 2022¹
 - 39k estimated new cases 2006²
- 25-50% are metastatic at diagnosis

¹Siegel, et. al., Cancer Statistics, 2022

²ACS, Cancer Facts & Figures 2006.

Histological Classification of Human Renal Epithelial Neoplasms

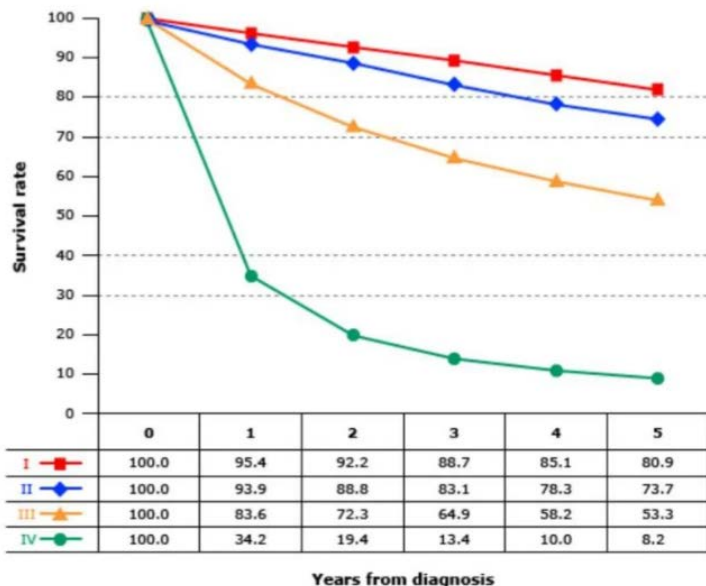


Adjuvant Setting

Adjuvant Therapy: Ideal Setting

- Why?

- High recurrence rates



- Who?

- High risk features

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	
5yr Risk of Recurrence				
31%	47%	54%	63%	?70%

Adjuvant Therapy for RCC

How/What?

Appropriate drug

- active on micrometastases
- low toxicity
- Clinically meaningful outcomes

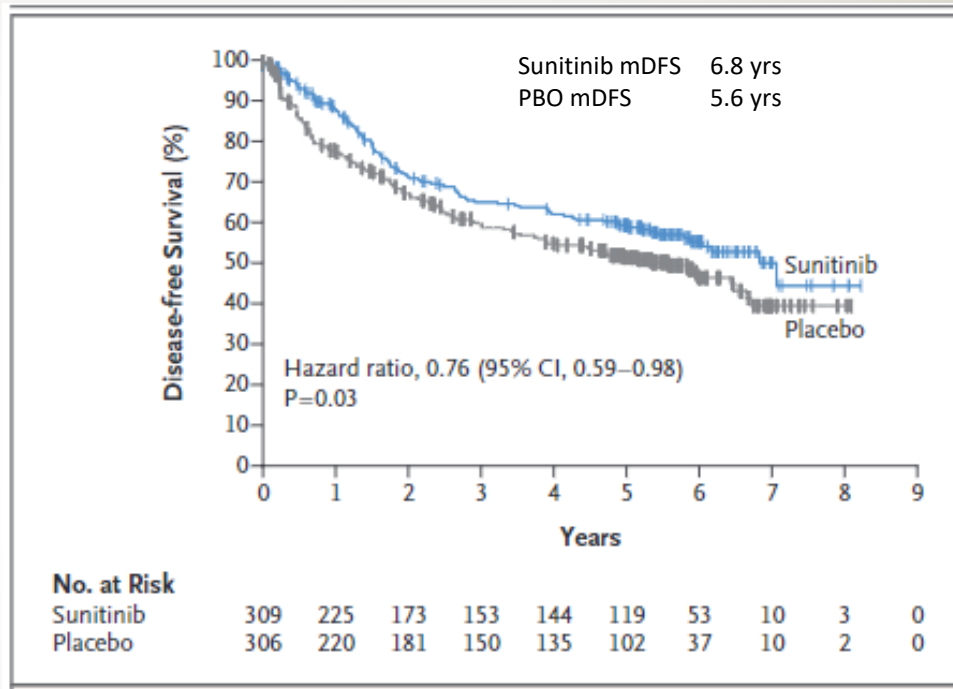
So is that

- “old immunotherapy”?
- VEGF-TKI or mTOR??
- “modern” immunotherapy?

Study	N	Arms	1° Endpoint
Clark, et.al.	69	IL-2 vs obs	DFS
Pizzocaro, et. al.	247	IFN- α 2b vs obs	OS, EFS
ASSURE	1943	1 yr sorafenib vs sunitinib vs PBO	DFS
PROTECT	1538	1 yr pazopanib vs PBO	DFS
ATLAS	724	3 yr axitinib vs PBO	DFS
SORCE	1711	3 rs sorafenib vs PBO	DFS
EVEREST	1218	54 weeks of everolimus vs PBO	DFS
S-TRAC	615	1 yr sunitinib vs PBO	DFS
PROSPER	805	Neo- & Adj nivolumab	RFS
IMmotion010	778	1 yr atezolizumab vs PBO	DFS
CheckMate914	1600	24 wks ipi/nivo vs PBO	DFS
KEYNOTE-564	950	51 wks pembrolizumab vs PBO	DFS

S-TRAC: Adjuvant Sunitinib

- Phase 3 RCT, double-blind
 - 1yr of sunitinib vs PBO
- N=615 (309 vs 305)
- 1^o endpoint: DFS (central)
 - 2^o endpoints: DFS (invest), OS, AE
- High-risk:
 - pT3, N0/x, M0 [91%]
 - Low risk 1/3
 - pT4, N0/x, M0 [1%]
 - pTany, N+, N0 [8%]

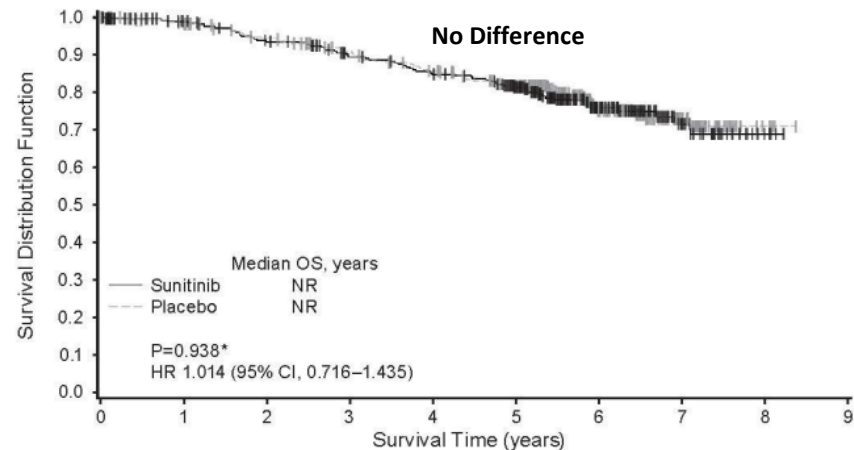


S-TRAC: Adjuvant Sunitinib

- Phase 3 RCT
 - 1yr of sunitinib vs PBO
- N=615 (309 vs 305)
- 1^o endpoint: DFS (central)
 - 2^o endpoints: DFS (invest), OS, AE
- High-risk:
 - pT3, N0/x, M0 [91%]
 - Low risk ~40%
 - pT4, N0/x, M0 [1%]
 - pTany, N+, N0 [8%]

SUPPLEMENTARY FIGURES

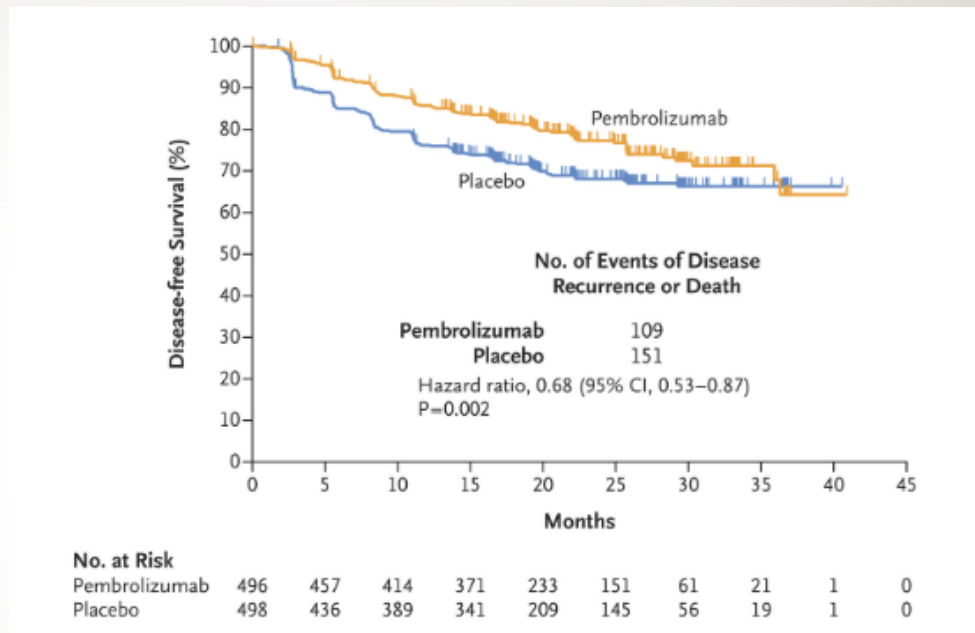
Figure S1. Overall survival



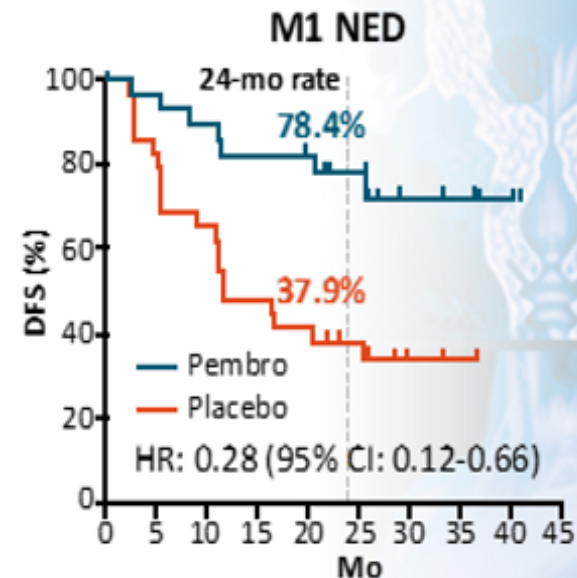
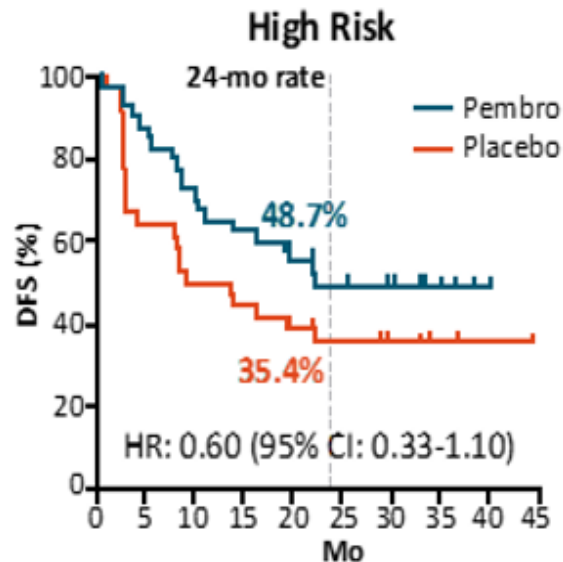
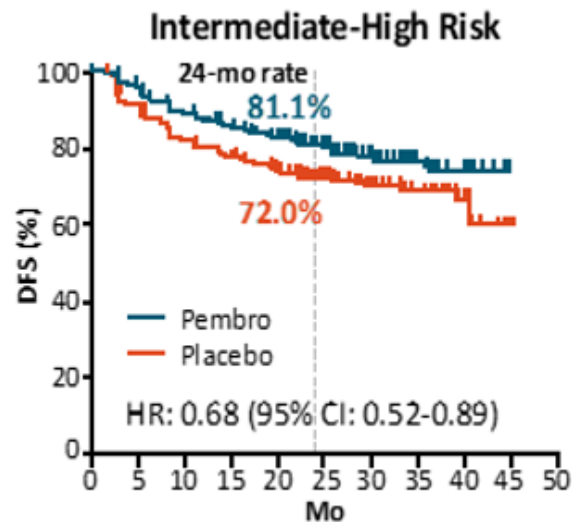
No. at risk										
Sunitinib	309	278	258	236	222	196	98	31	4	0
Placebo	306	289	269	250	231	197	96	40	4	0

Keynote-564: Adjuvant Pembrolizumab

- Phase 3 RCT, double-blind
 - 51 wks pembro vs PBO
- N= 994 (496 vs 498)
- 1^o endpoint: DFS (invest)
 - 2^o endpoints: OS, AE
- High-risk:
 - pT3, N0/x, M0 [86%]
 - Low risk 1/3
 - pT4, N0/x, M0 [8%]
 - pTany, N+, N0 [6%]



Keynote-564: By Risk Group

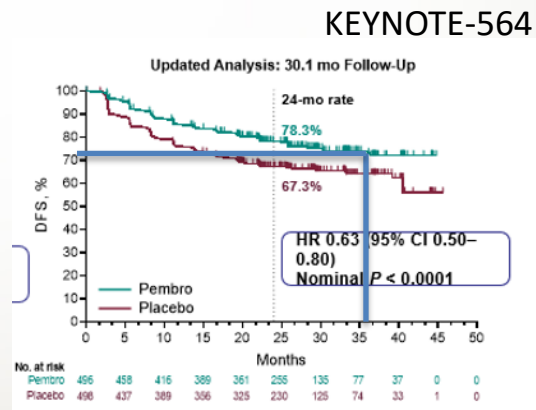
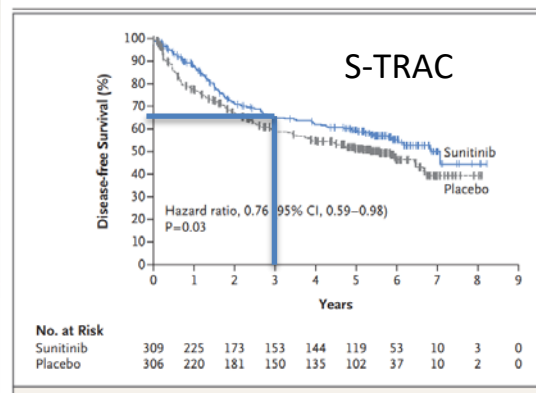


Adjuvant Therapy: TKI or ICI?

Outcome	S-Trac	Keynote-564
mDFS	6.8 yrs	NR
2 yr DFS	~71%	78%
3 yr DFS	65%	71%
mOS	NR	NR
Gr3/4 tox	63.4%	32%

S-TRAC: Ravaud, et. al., NEJM 2016

Keynote-564: Choueiri, et. al. NEJM 2021

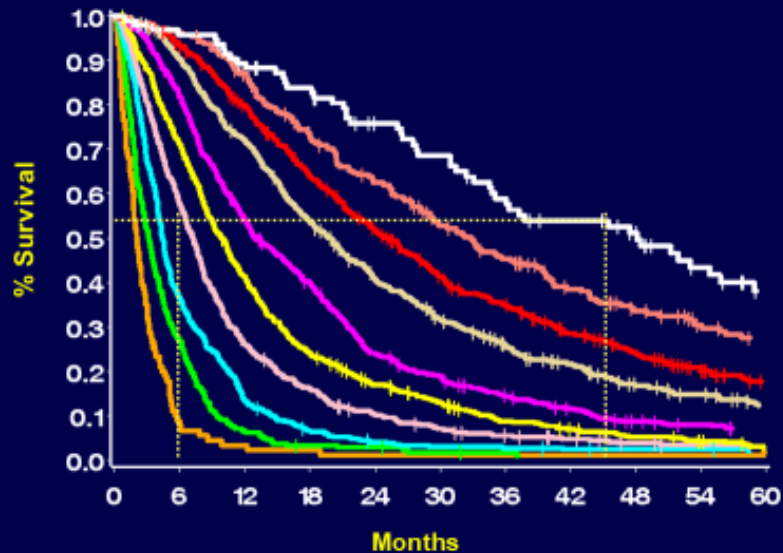


Metastatic Setting



Natural Hx mRCC

RCC is an inherently diverse disease



Reference	No.	1 Year	2 Years	5 Years
Riches et al, ³³ 1951*	409	33	3	0.5
Middleton, ³⁴ 1967	141	10	—	0
Bottiger, ⁸ 1970	40	42	17	4
Skinner et al, ⁶ 1971	77	—	—	8
Johnson et al, ³⁵ 1975	93	26	—	—
Thompson et al, ³⁶ 1975	65	22	9	0
Klugo et al, ²⁶ 1977	64	12	—	3
Montie et al, ³⁷ 1977	78	18	—	—
deKernion et al, ⁹ 1978	86	43	21	10
Patel and Lavengood, ³⁸ 1978	42	17	—	2
Lieber et al, ¹⁴ 1981	15	< 50	—	8
McNichols et al, ¹⁸ 1981	56	—	—	14
Siminovitch et al, ³⁹ 1983	71	—	—	< 5
Selli et al, ²⁰ 1983	20	—	20	13
Bassil et al, ⁷ 1985	53	—	—	18
Golimbu et al, ¹² 1986	88	—	—	2
Maldazys and deKernion, ¹⁷ 1986	32	21	3	—
Neves et al, ¹⁹ 1988	158	—	15	—
Giuliani et al, ¹¹ 1990	50	—	—	7

High-dose
IL-2

IFN α

1992



Cytokine era

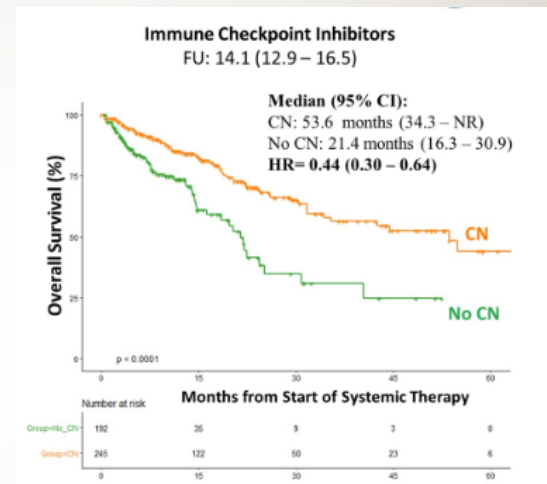
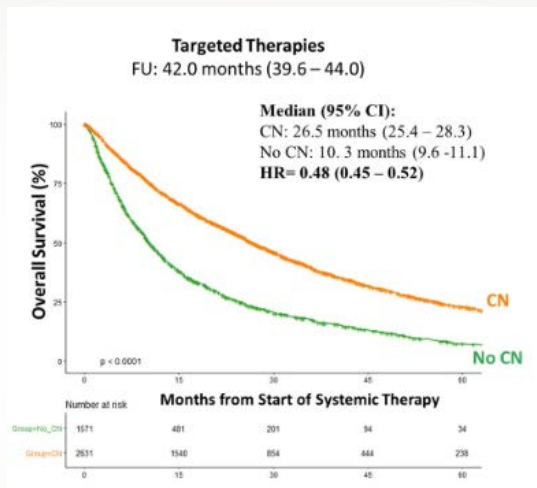
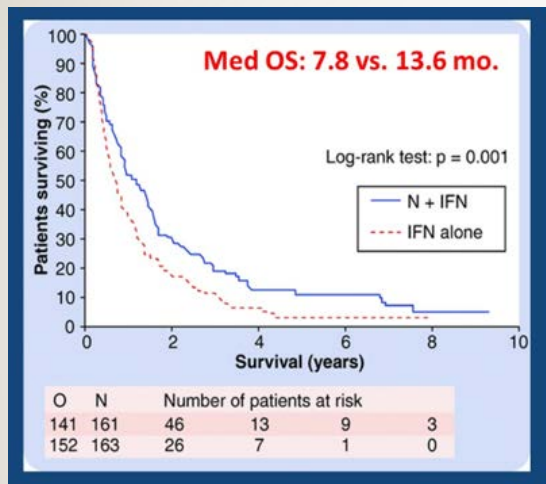
mRCC Treatment Options

- Cytoreductive Nephrectomy?
- Metastectomy?
- TKI?
- IO/IO?
- IO/TKI?
- Other?

Cytoreductive Nephrectomy

- Is it Required?
 - Controversial with conflicting data
 - Original study with IFN showed benefit
 - CARMENA was an OS (-) trial
 - SURTIME was a PFS (-) trial
 - OS (+) only if NAC TKI
 - NCDB meta-analysis OS (+) trial
 - Does the drug class matter?
 - TKI vs ICI?

Overall Survival for CN by Drug Class



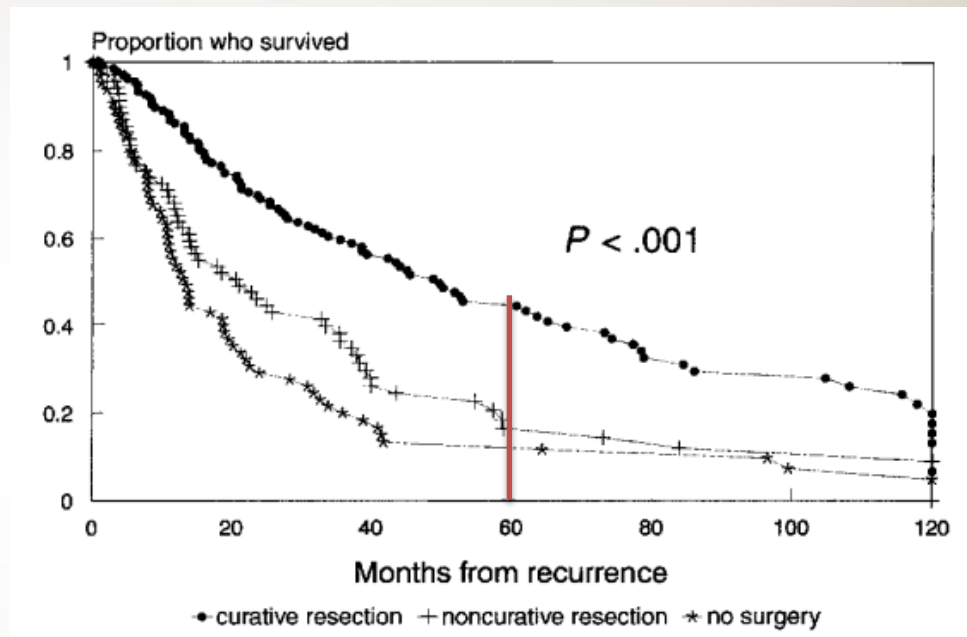
Treatment	2yr CN+	2 yr CN -	HR (95% CI)
TT	54.1%	25.8%	0.56 (0.51-0.62)
ICI	69.1%	41.4%	0.39 (0.19-0.83)

CN: When to consider

- (When) Should it be done?
 - Conflicting data
- “Best” guesses
 - **Upfront:**
 - For absolute indications
 - (minimal) lung mets only
 - (Consider if) asymptomatic from mets
 - **Delayed:**
 - Bone mets
 - Symptomatic from mets
 - IDMC int/poor

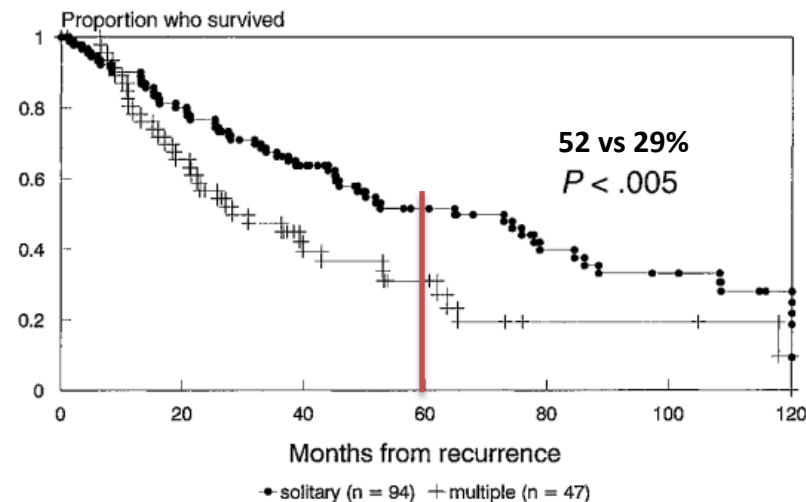
What About Metastasectomy?

- Not a “new” concept
 - 1st case 1939*
- 5 yr OS following mRCC metastasectomy is 35-50%
- Retrospective review n=278, 1st relapse (MSKCC)
 - 141 “curative metastasectomy”
 - 70 “non-curative surgery”
 - 67 “non-surgical therapy”



What About Metastasectomy?

- Prognostic Variables for OS
 - DFS > 12 months
 - Solitary metastatic site*
 - Curative metastasectomy
 - Age < 60yrs
- Other 5-yr OS observations:
 - Lung > brain (54 vs 18%)



Treatment: TKI?

- Between 2005 and 2016, 8 TKIs approved
- Monotherapy was most common

Single Agent Immunotherapy

IL-2
IFN- α 2b
Nivolumab

Single Agent Angiogenesis Inhibitors

Sorafenib
Sunitinib
Pazopanib
Axitinib
Bevacizumab
Cabozantinib

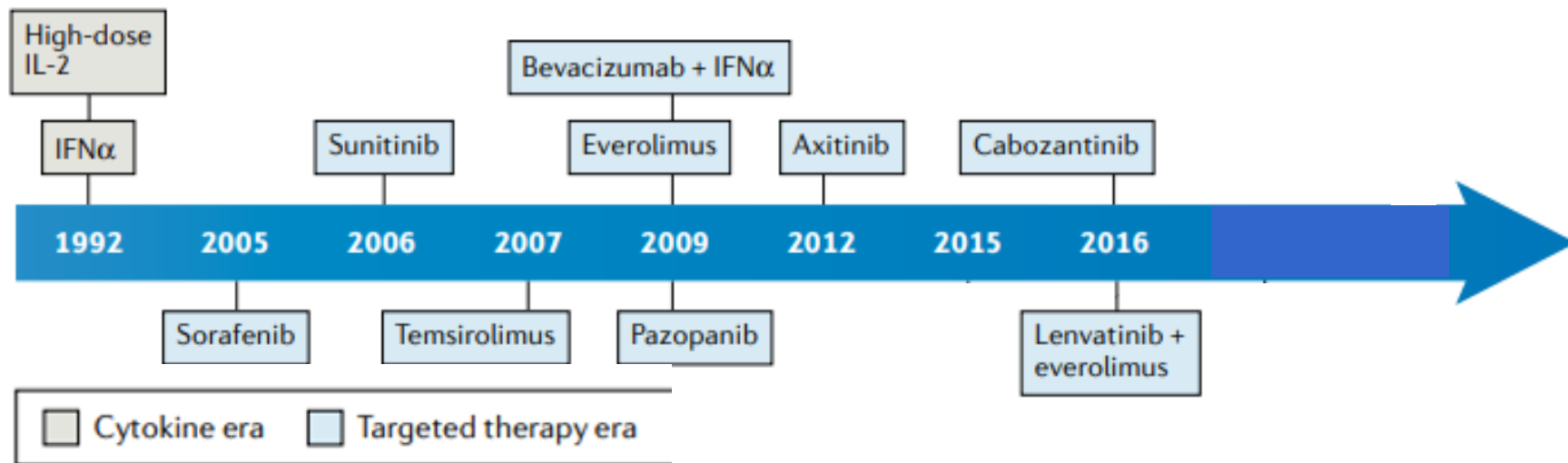
Single agent mTOR Inhibitors

Temsirolimus
Everolimus

Combination Therapies

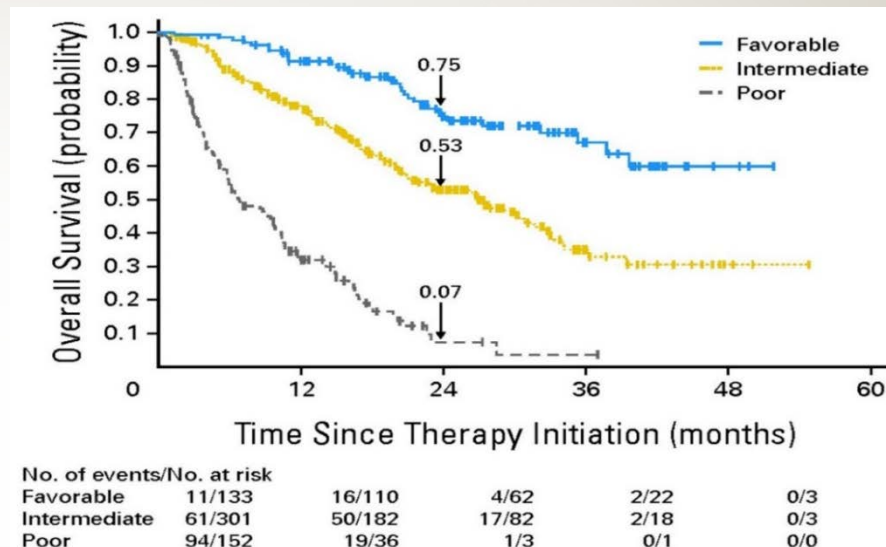
Bevacizumab + IFN

Treatment: TKI?



IMDC Prognostic Criteria

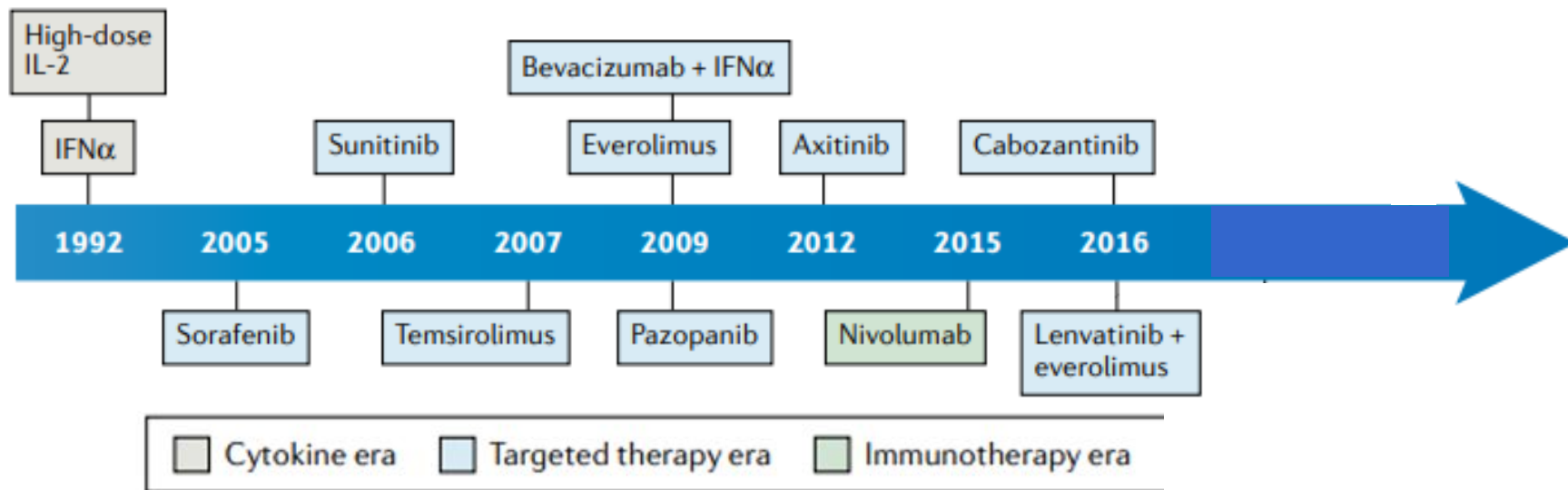
- **Clinical**
 - KPS < 80%
 - Time from diagnosis to treatment < 1 year
- **Laboratory**
 - Hemoglobin < LLN
 - Calcium > ULN
 - Neutrophil count > ULN
 - Platelet count > ULN



IDMC Risk Group	Overall Survival (TKI Era)
Favorable (0 Risk Factors)	3-4 yrs
Intermediate (1-2 Risk Factors)	27 months
Poor (≥ 3 Risk Factors)	8.8 months

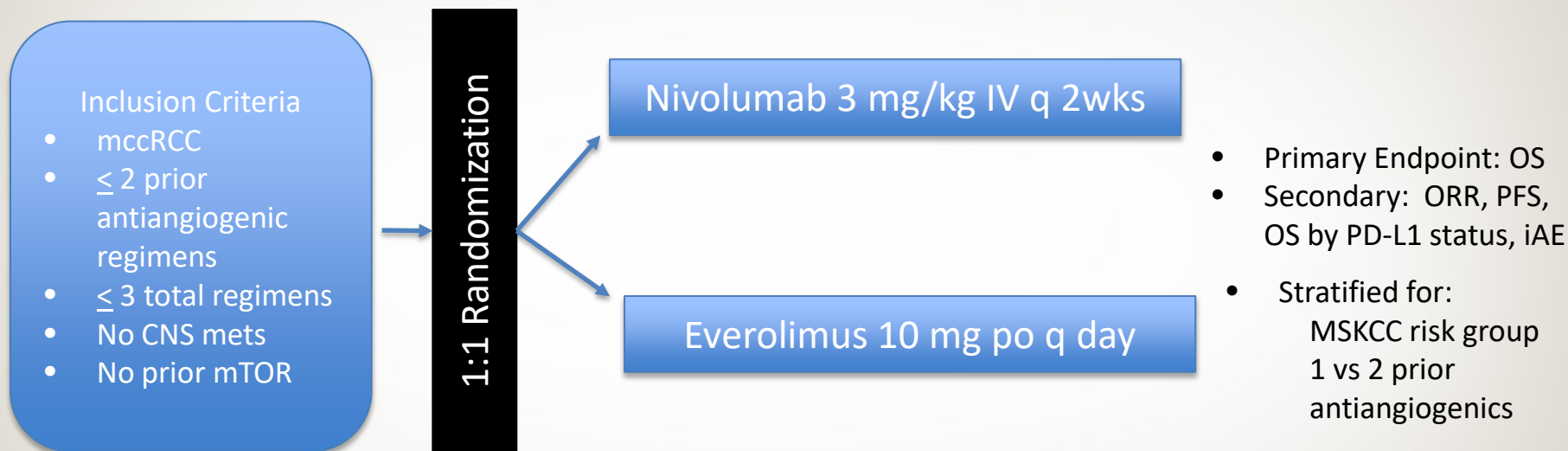
- Heng DY, et al. J Clin Oncol. 2009;27:5794-5799.

Treatment: IO?

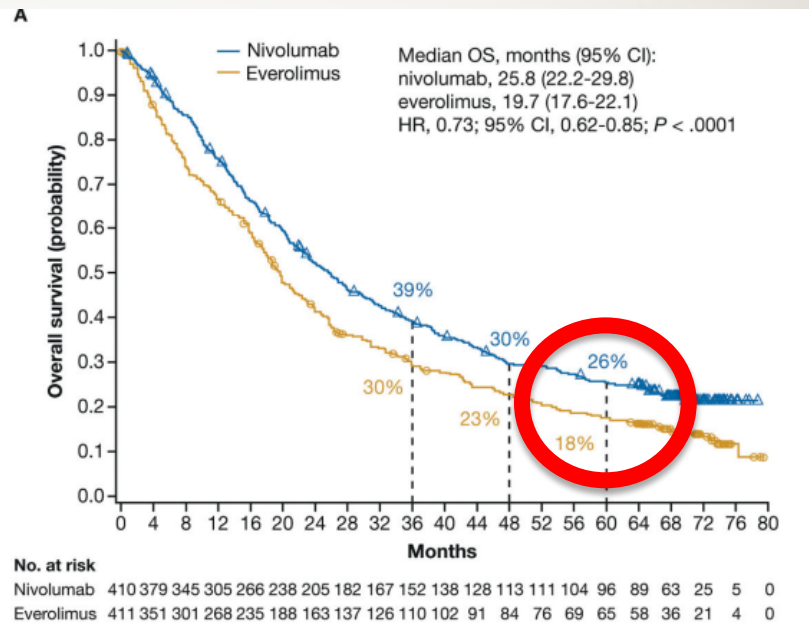
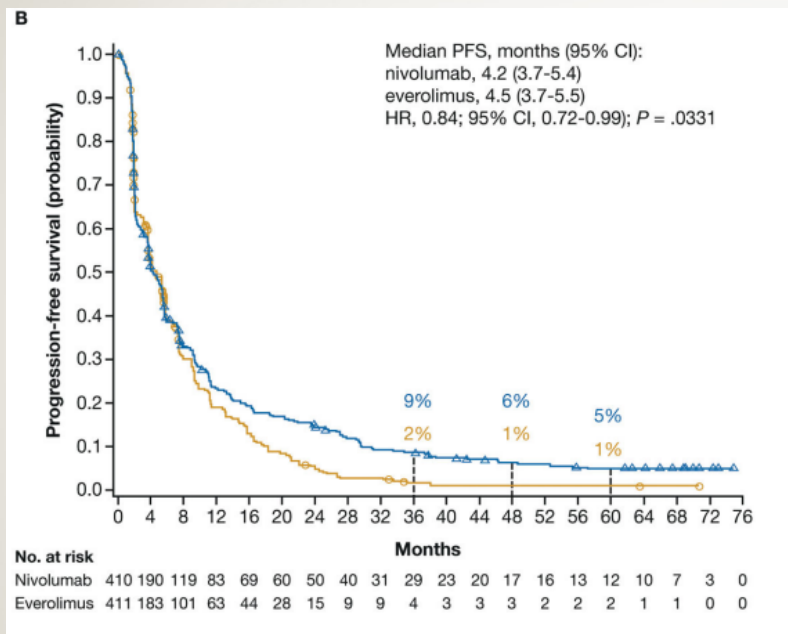




2nd Line Nivolumab Monotherapy: Checkmate 025



Checkmate 025: Nivolumab vs. Everolimus monotherapy



Combination Therapy now SOC in mRCC

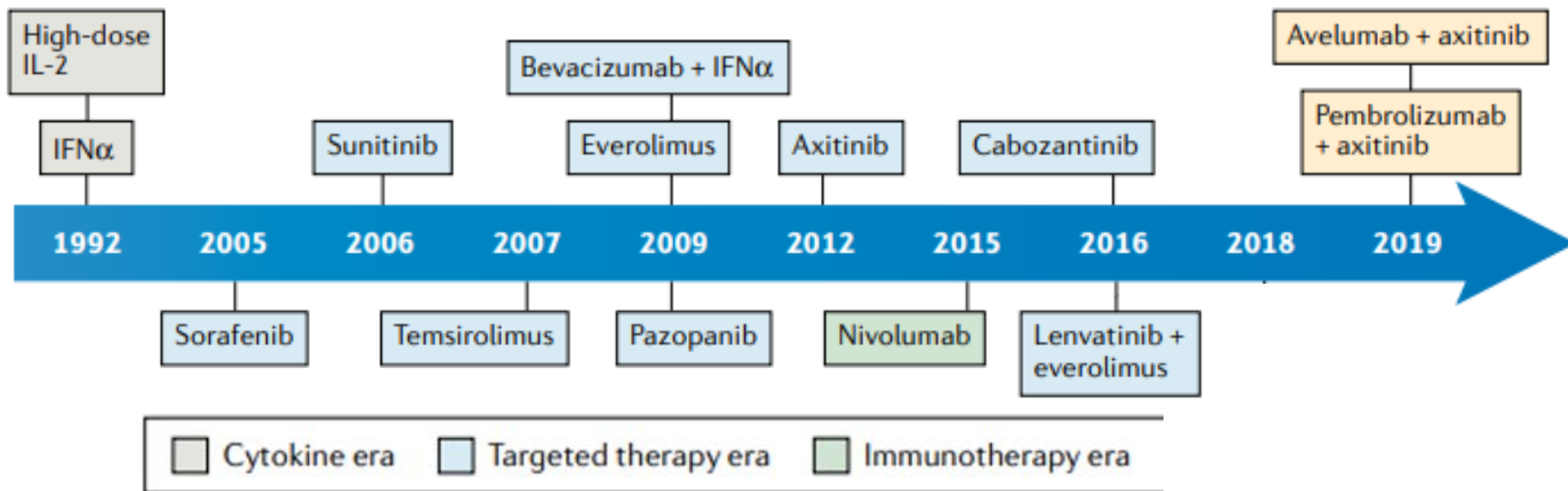
Single Agent Immunotherapy
IL-2
IFN- α 2b
Nivolumab

Single Agent Angiogenesis Inhibitors
Sorafenib
Sunitinib
Pazopanib
Axitinib
Bevacizumab
Cabozantinib

Single agent mTOR Inhibitors
Temsirolimus
Everolimus

Combination Therapies
Bevacizumab + IFN
Lenvatinib + Everolimus
Nivolumab + Ipililumab
Pembrolizumab + Axitinib
Avelumab + Axitinib
Pembolizumab + Lenvatinib
Nivolumab + Cabozantinib

Treatment: IO/IO & IO/TKI?



Treatment: IO/IO & IO/TKI

- Multiple studies show benefit in 1st line therapy over sunitinib
 - CheckMate 214: Ipilimumab/Nivolumab
 - KEYNOTE 426: Pembrolizumab/Axitinib
 - Javelin Renal 101: Avelumab/Axitinib
 - CheckMate 9ER: Cabozantinib/Nivolumab
 - CLEAR: Pembrolizumab/Lenvatinib (cohort 1)

Treatment: IO/IO & IO/TKI

	CheckMate 214 (Ipi/Nivo) ¹ (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro) ² (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo) ³ (n=323 vs n=328)	CLEAR (Len/Pembro) ⁴ (n=355 vs n=357)
HR	0.72	0.73	0.70	0.72
mOS, months	55.7 vs 38.4	45.7 vs 40.1	37.7 vs 34.3	NR vs NR
Landmark OS 12m	83% vs 78%	90% vs 79%	86% vs 76%	90% vs 79% (est.)
Landmark OS 24m	71% vs 61%	74% vs 66%	70% vs 60%	79% vs 70%
HR	0.86	0.68	0.56	0.39
mPFS, months	12.3 vs 12.3	15.7 vs 11.1	16.6 vs 8.3	23.9 vs 9.2
ORR %	39 vs 32	60 vs 40	56 vs 28	71 vs 36
CR %	12 vs 3	10 vs 4	12 vs 5	16 vs 4
Primary PD %	18	11	6	5
IDMC population	Intermediate/Poor	All risk groups	All risk groups	All risk groups
Prior Nephrectomy %	82	83	69	74
Median f/u, months	67.7	42.8	32.9	33.7
Landmark PFS	30% (5 yrs)	29% (3 yrs)	39% (2 yrs)	

Treatment: IO/IO & IO/TKI

	CheckMate 214 (Ipi/Nivo) ¹ (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro) ² (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo) ³ (n=323 vs n=328)	CLEAR (Len/Pembro) ⁴ (n=355 vs n=357)
HR mOS, months	Consistent OS benefit compared to VEGF TKI			0.72 NR vs NR
Landmark OS 12m	83% vs 78%	90% vs 79%	86% vs 76%	90% vs 79% (est.)
Landmark OS 24m	71% vs 61%	74% vs 66%	70% vs 60%	79% vs 70%
HR mPFS, months	0.86 12.3 vs 12.3	0.68 15.7 vs 11.1	0.56 16.6 vs 8.3	0.39 23.9 vs 9.2
ORR %	33	33	33	33
CR %	12 vs 5	10 vs 4	12 vs 5	16 vs 4
Primary PD %	18	Less early PD with TKI containing regimens		5
IDMC population	Intermediate/Poor	All risk groups	All risk groups	All risk groups
Prior Nephrectomy %	82	83	69	74
Median f/u, months	67.7	42.8	32.9	33.7
Landmark PFS	30% (5 y)	CTLA-4 regimen might have higher tail of curve		

2. Rini et al. ASCO 2021
4. Motzer et al. ASCO GU 2021.

1. Motzer et al. ESMO 2021
3. Motzer et al. ASCO GU 2022

IO/TKI vs. IO/IO

	Pros	Cons
IO/TKI	<ul style="list-style-type: none">• Consistent effects on OS, PFS and ORR across IMDC risk groups• Significant tumor burden reduction reflected in high ORR and long PFS• Manageable toxicity• QoL maintained vs TKI alone	<ul style="list-style-type: none">• Long-term durability of response yet to be demonstrated• Potential for acute and chronic TKI toxicity
IO/IO	<ul style="list-style-type: none">• OS and ORR advantages over TKI monotherapy• Durability of response / disease-control• Treatment-free interval possible• QoL improved vs TKI	<ul style="list-style-type: none">• Potential for significant initial toxicity• Lower ORR and shorter PFS compared with IO/TKI regimens• Less effective in favorable risk patients

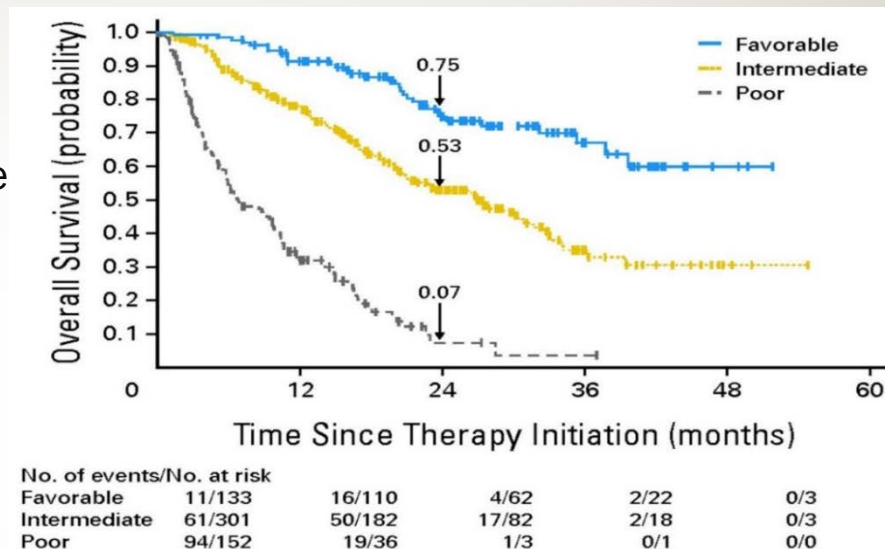
IMDC Prognostic Criteria

- **Clinical**

- KPS < 80%
- Time from diagnosis to treatment < 1 ye

- **Laboratory**

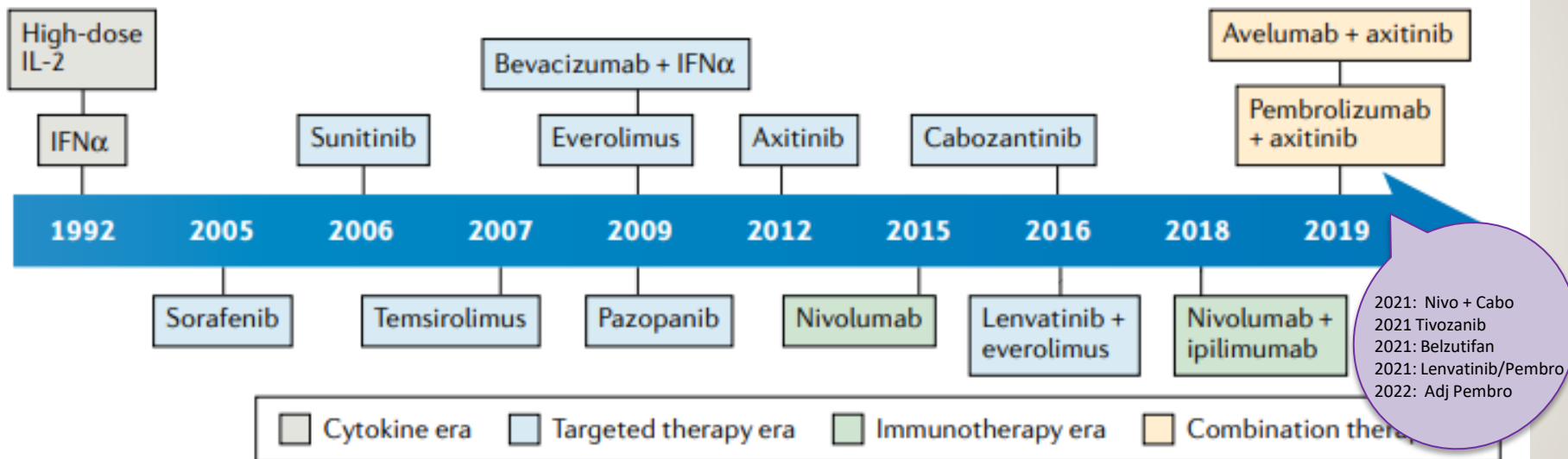
- Hemoglobin < LLN
- Calcium > ULN
- Neutrophil count > ULN
- Platelet count > ULN



- Favorable: 0 risk factors → means slow-growing and/or VEGF-responsive
- Intermediate: 1-2 risk factors → medium growth rate and somewhat VEGF-responsive
- Poor: 3-6 risk factors → fast-growing and VEGF-unresponsive

- Heng DY, et al. J Clin Oncol. 2009;27:5794-5799.

Evolution of Treatment Paradigm in mRCC



Treatment: Other?

Prospective phase 2 trial of Active Surveillance in mRCC

- Clinically-evident metastatic RCC of any histologic subtype
- First documentation (radiographic or histologic) of metastatic RCC up to 12 months prior to registration on study
- No prior systemic therapy for RCC in the metastatic or neo/adjuvant setting.
- Prior XRT (including for CNS metastases) and prior nephrectomy/metastasectomy permitted but not required
- No disease-related symptoms
- Measurable / evaluable disease per RECIST v 1.0

CTs q 3 months year 1; q4m year 2,
then q 6 months

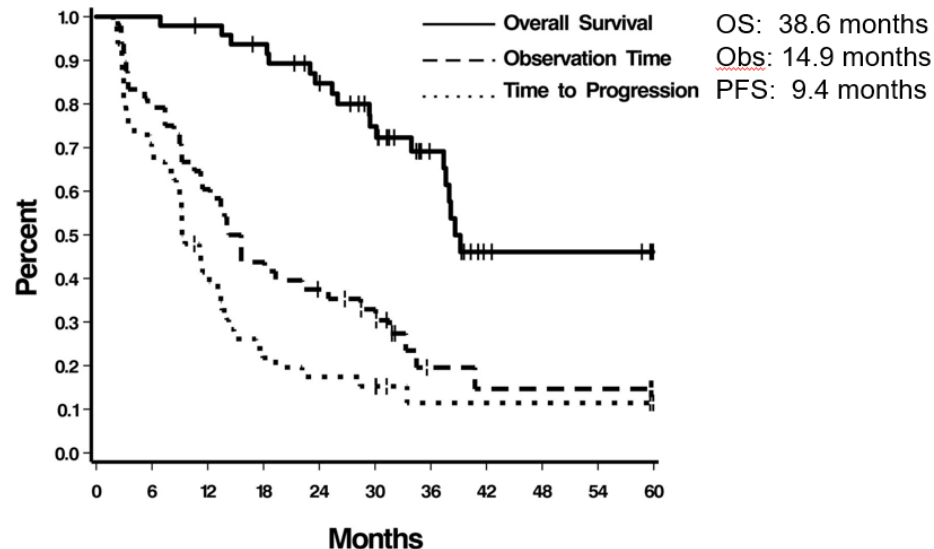
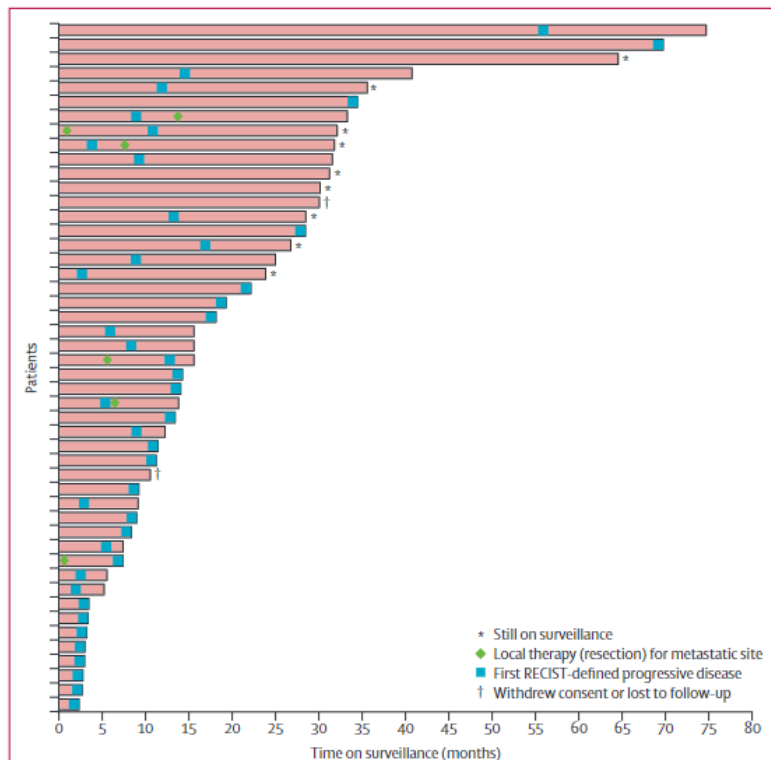
Initiation of
systemic
treatment
per MD / pt
discretion

- FKSI-DRS (QOL) and HADS (anxiety/depression) administered at baseline and every CT scan timepoint.
- Peripheral blood for immune cell quantification drawn at baseline and every CT scan timepoint.

Treatment: Active Surveillance

- Some RCC is indolent
- Avoidance of toxicity of therapy for as long as reasonable in select group
- Primary endpoint: TT systemic therapy
- N = 52, 48 in analysis
- Median f/u was 38.1 months

Treatment: Active Surveillance



Frontline Treatment for mRCC

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable ^a	<ul style="list-style-type: none"> • Axitinib + pembrolizumab^b (category 1) • Cabozantinib + nivolumab^b (category 1) • Lenvatinib + pembrolizumab^b (category 1) 	<ul style="list-style-type: none"> • Axitinib + avelumab^b • Cabozantinib (category 2B) • Ipilimumab + nivolumab^b • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Active surveillance^c • Axitinib (category 2B) • High-dose IL-2^d (category 2B)
Poor/ intermediate ^a	<ul style="list-style-type: none"> • Axitinib + pembrolizumab^b (category 1) • Cabozantinib + nivolumab^b (category 1) • Ipilimumab + nivolumab^b (category 1) • Lenvatinib + pembrolizumab^b (category 1) • Cabozantinib 	<ul style="list-style-type: none"> • Axitinib + avelumab^b • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Axitinib (category 2B) • High-dose IL-2^d (category 3) • Temsirolimus^e (category 3)

2ND Line Treatments in 2022

- 1st line -- IO based combinations
- Ongoing prospective RCTs to determine best 2nd line outcomes
 - Post IO/IO – patient progressed to 1 MOA
 - Post IO/TKI – patient progressed to 2 MOA
- Current guidelines suggest TKI not previously used

2nd & Later Line Treatment for mRCC

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred Regimens

- Cabozantinib (category 1)
- Lenvatinib + everolimus
- Nivolumab^b (category 1)

Other Recommended Regimens

- Axitinib (category 1)
- Axitinib + pembrolizumab^b
- Cabozantinib + nivolumab^b
- Ipilimumab + nivolumab^b
- Lenvatinib + pembrolizumab^b
- Pazopanib
- Sunitinib
- Tivozanib^g (category 1)
- Axitinib + avelumab^b (category 3)

Useful in Certain Circumstances

- Everolimus
- Bevacizumab^f (category 2B)
- High-dose IL-2 for selected patients^d (category 2B)
- Sorafenib (category 3)
- Temsirolimus^e (category 2B)
- Belzutifan (category 2B)

Treatment: Other?

- **Unanswered Questions:**
 - Would a 1st line triplet improve outcomes vs doublet?
 - Can we utilize gene expression data to choose best 1st line treatment?
 - Can ipilimumab salvage response?

Triplet vs Doublet? COSMIC-313

Ongoing First-line Phase 3 Study in Renal Cell Carcinoma Comparing Nivolumab vs Cabomimet

COSMIC-313 Study Schematic

Advanced or metastatic RCC

- Clear cell component
- Intermediate/poor risk
- Measurable disease
- Previously untreated

Stratification factors

- IMDC risk score (1-2 vs 3-6 factors)
- Region ([US or Canada or Europe or Australia or New Zealand] vs [Latin America or Asia])

Randomization 1:1

Cabozantinib 40 mg PO QD
Nivolumab 3 mg/kg IV Q3W (4 doses)
Ipilimumab 1 mg/kg IV Q3W (4 doses)
Followed by
Cabozantinib 40 mg PO QD
Nivolumab 480 mg flat dose IV Q4W (2 yrs)

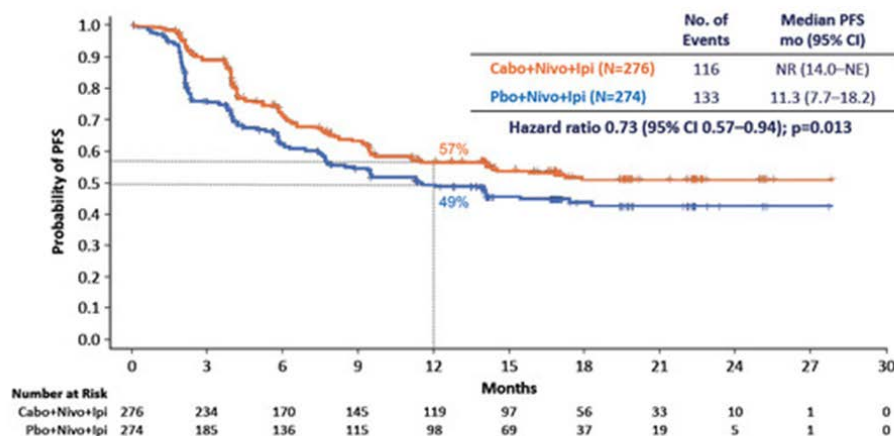
Cabo-matched Placebo PO QD
Nivolumab 3 mg/kg IV Q3W (4 doses)
Ipilimumab 1 mg/kg IV Q3W (4 doses)
Followed by
Cabo-matched Placebo PO QD
Nivolumab 480 mg flat dose IV Q4W (2 yrs)

Primary endpoint: PFS per RECIST 1.1 by BIRC
Secondary endpoint: Overall survival

NCT03937219

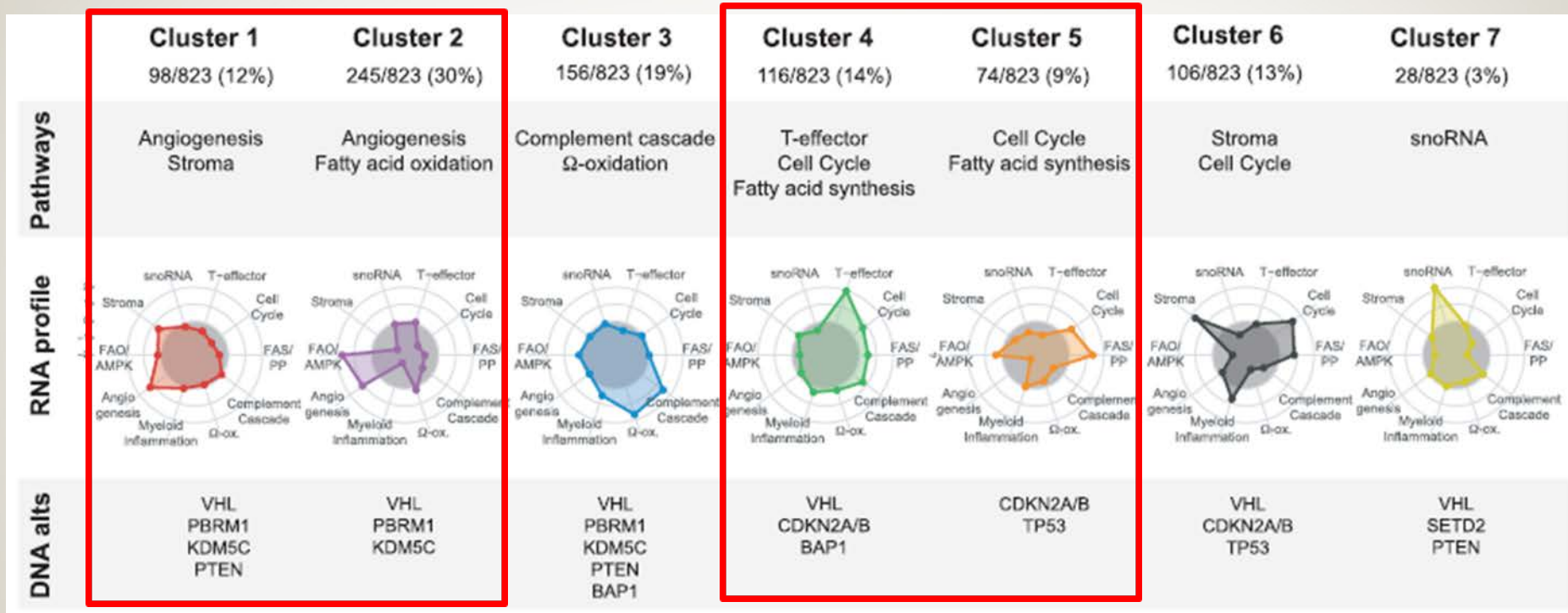
Choueiri, et al. ESMO 2022

Final Analysis (PITT Population)

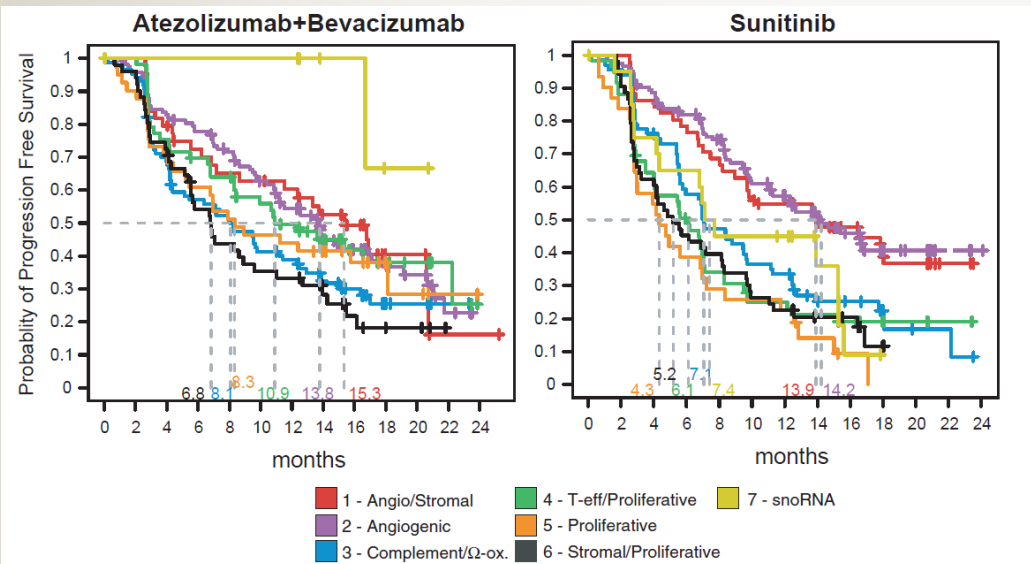


PFS per RECIST v1.1 by BIRC.
Data cut-off: Aug 23, 2021

Harness Gene Expression to Choose 1st Line?



IMmotion 151 Responses Based on Cluster

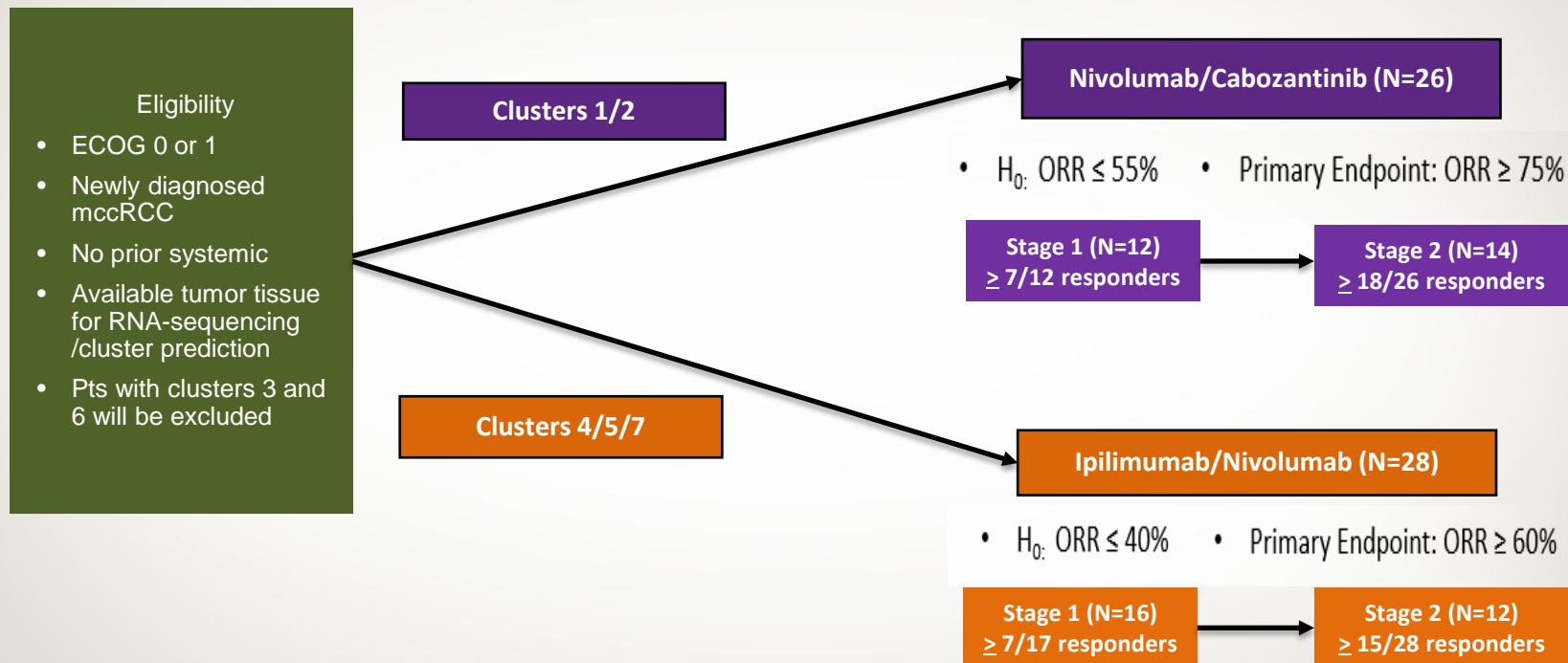


Cluster	PFS HR (95% CI)	p-value	A/B mPFS	Sunitinib mPFS	
1 - Anglo/stromal	1.11 (0.65-1.88)	0.708	15.3	13.9	
2 - Angiogenic	1.16 (0.82-1.63)	0.397	13.8	14.2	
3 - Complement/Ω-ox.	0.92 (0.63-1.34)	0.666	8.1	7.1	
4 - T-eff/Proliferative	0.52 (0.33-0.82)	0.005	10.9	6.1	
5 - Proliferative	0.47 (0.27-0.82)	0.007	8.3	4.3	
6 - Stromal/Proliferative	0.81 (0.52-1.25)	0.331	6.8	5.2	
7 - snoRNA	0.10 (0.01-0.77)	0.028	NR	7.4	

0.088 0.177 0.354 0.707 1.410 4.00

Better in Atezo+Bev **HR PFS** Better in Sunitinib

OPTIC RCC Trial (NCT 05361720)



Ipilimumab as Salvage?

- If you are going to give Ipi, give it early.....
- Not a good salvage agent
- Patients less likely to tolerate

	HCRN ASCO GU 2022	OMNIVORE ASCO 2020	FRACTION ASCO 2020	TITAN RCC ESMO 2019	Salvage Ipi/Nivo (JCO 2020)
N	35	83	46	207	45
Prior TKI	No	Yes	Yes	Yes	Yes
Timing	Nivo→Ipi	Nivo→Ipi	Nivo+Ipi	Nivo→Ipi	Nivo+Ipi after prior IO
Ipi doses	4	2	4	4	4
ORR	11%	4%	15%	12%	20%
CR	3%	0%	0%	3%	0%

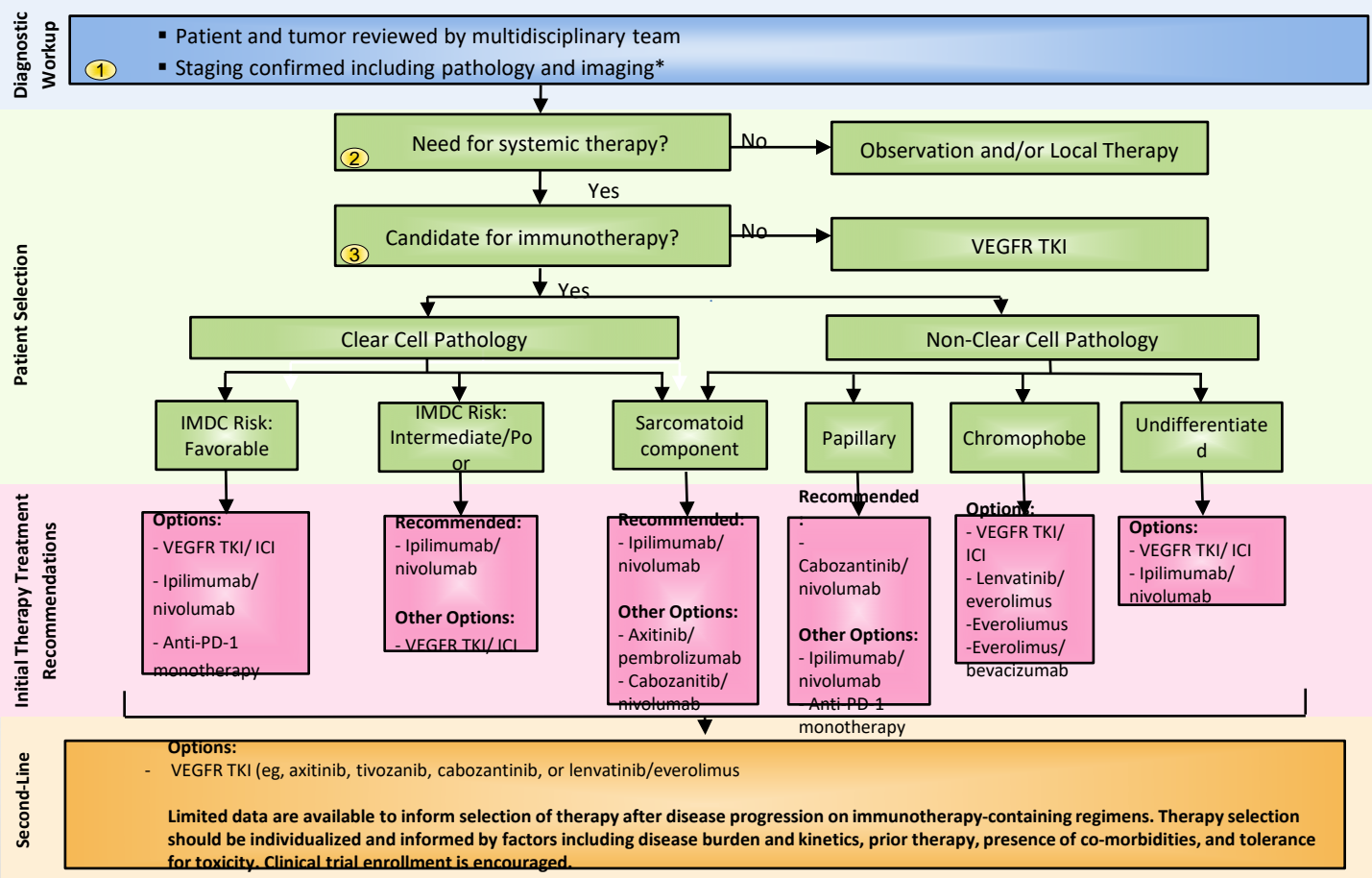
Nivo+ipi combo untreated ccRCC ORR 39%, CR 12% (Checkmate 214)¹

Sequencing Therapy in 2022

- Goal is ***CURE***
- Immunotherapy offers best chance for cure
- Angiogenesis is active throughout ccRCC natural history

Sequencing Therapy in 2022

- RCC is an angiogenic and inflammatory disease responsive to both anti-VEGF and IO therapy
- IO-based doublets with an anti-PD1 backbone have transformed initial management of mRCC
 - IO +VEGF regimens leading to the highest ORR/longest PFS
 - IO/IO regimens are notable for DOR/disease control
 - potential for disease control off therapy
- Single agent TKI is **no longer** the standard of care unless IO absolutely contraindicated
 - *Every* patient deserves a chance at cure with IO-based therapy
- Biomarker-based trials for personalized therapy based on tumor biology



Thank you!

