RCC YIR 2020

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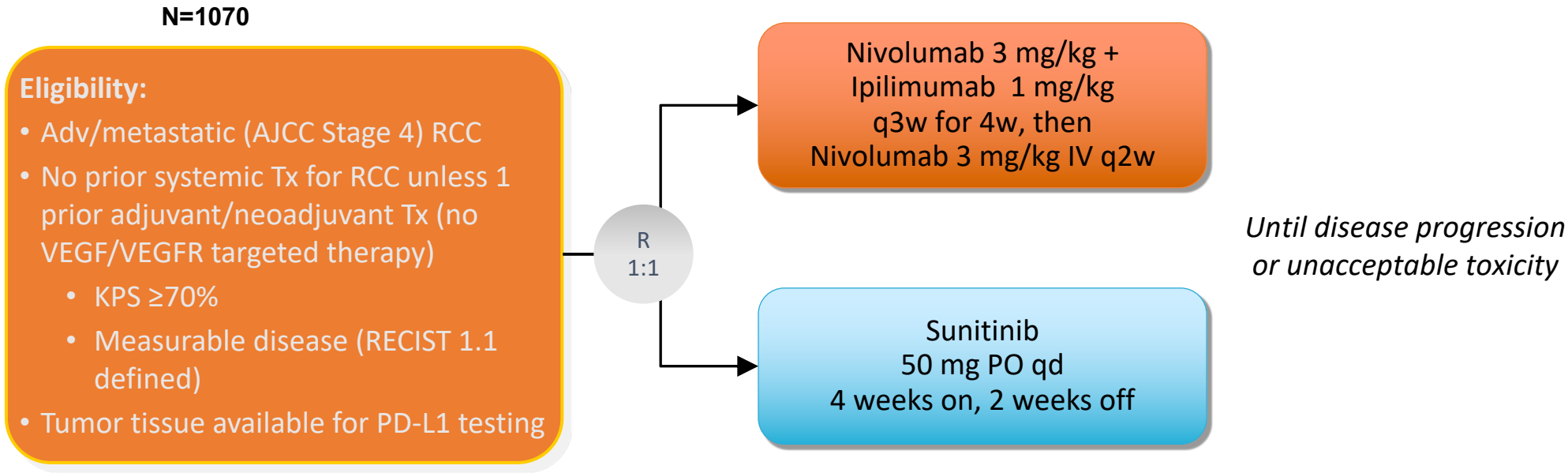
Nivolumab/Ipilimumab as First-line Therapy (CheckMate 214, BIONIKK)

Courtesy of David I Quinn, MBBS, PhD

CheckMate 214: Phase 3 Study of Nivolumab + Ipilimumab vs Sunitinib in 1L Advanced/Metastatic RCC[1,2]



Primary Outcome Measures: PFS, OS, ORR
Secondary Outcome Measure: Safety
Key Exploratory Measures: antitumor activity (ORR, PFS, OS) in favorable risk patients, outcomes by tumor PD-L1 expression level, health-related QoL based on FKSI-19

1. Escudier B et al. Oral Presentation at ESMO 2017. LBA5. 2. Clinicaltrials.gov. NCT02231749. Accessed on October 23, 2017.

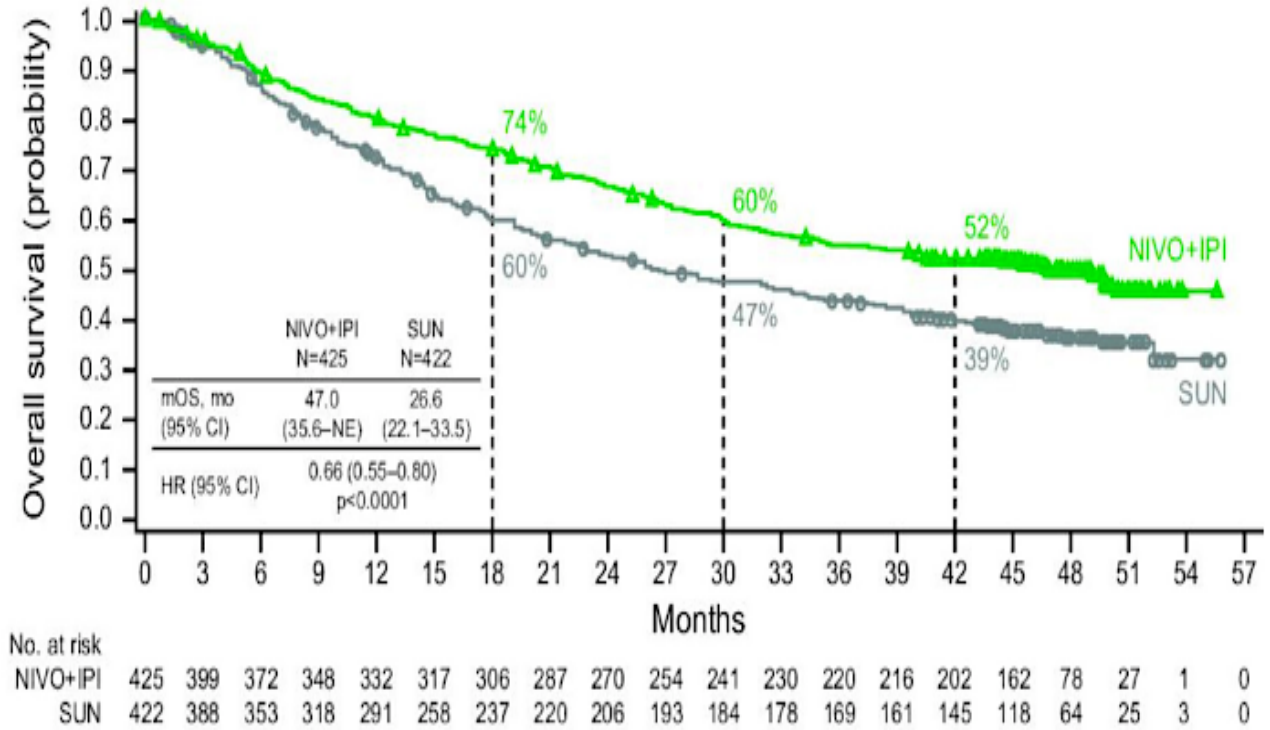
Courtesy of David I Quinn, MBBS, PhD

CM 214: Overall Survival 42 Month Min Follow Up: by IMDC Risk

Intermediate/poor risk

Median OS, months (95% CI)	
NIVO+IPI	47.0 (35.6–NE)
SUN	26.6 (22.1–33.5)

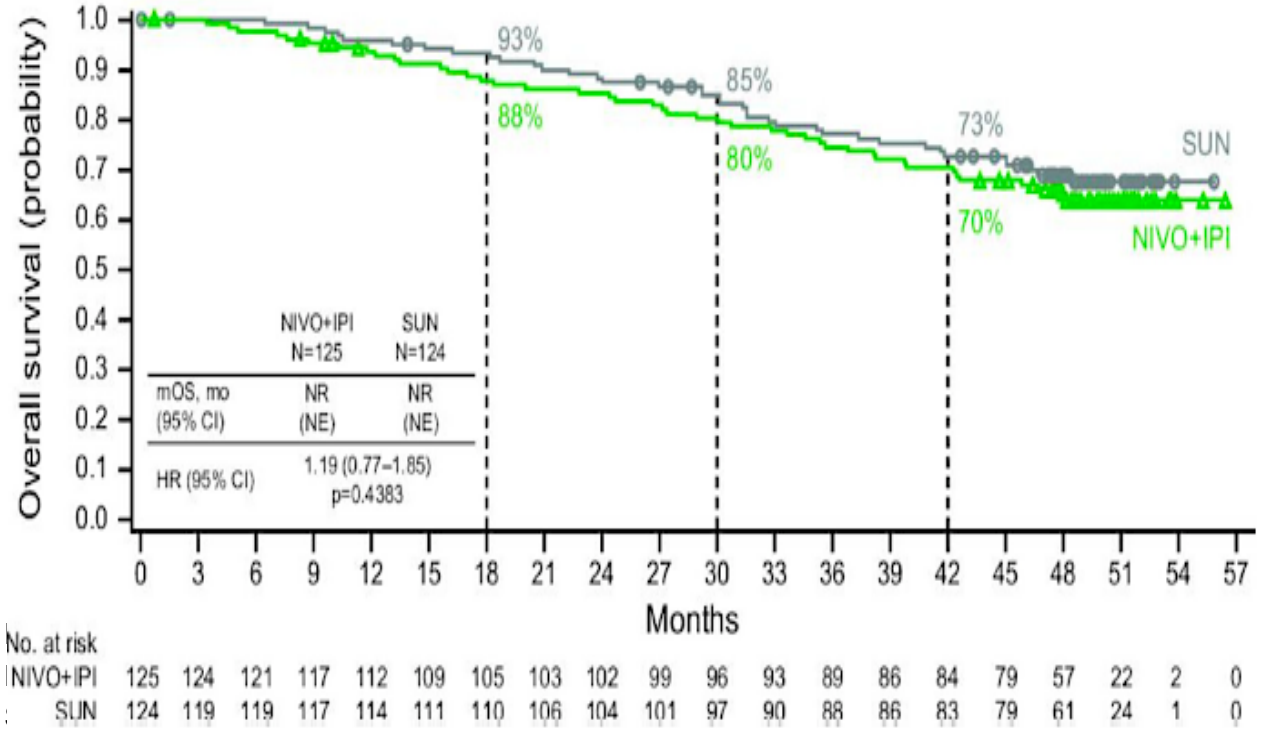
HR (95% CI), 0.66 (0.55–0.80)
P < 0.0001



Favorable risk

Median OS, months (95% CI)	
NIVO+IPI	NR (NE)
SUN	NR (NE)

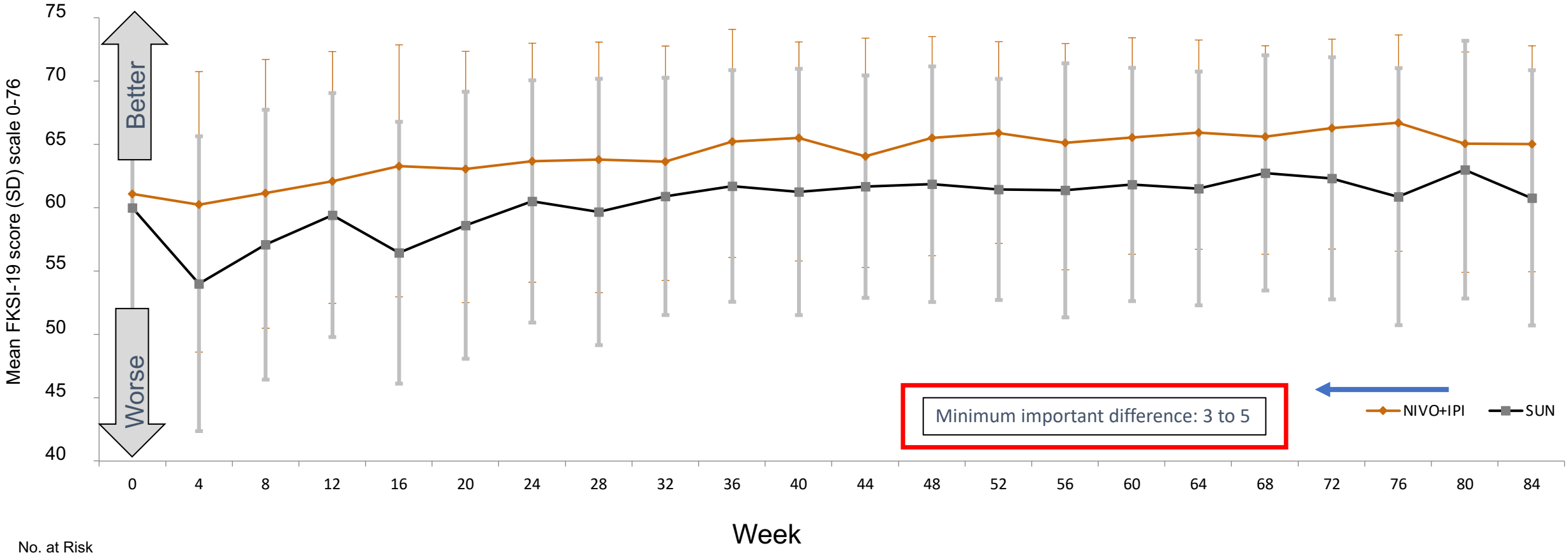
HR (95% CI), 1.19 (0.73–2.04)
P = 0.4383



Motzer RJ et al. J Immunother Cancer 2020

Courtesy of David I Quinn, MBBS, PhD

CM 214: Exploratory endpoint
Health-related quality of life: Intention to treat



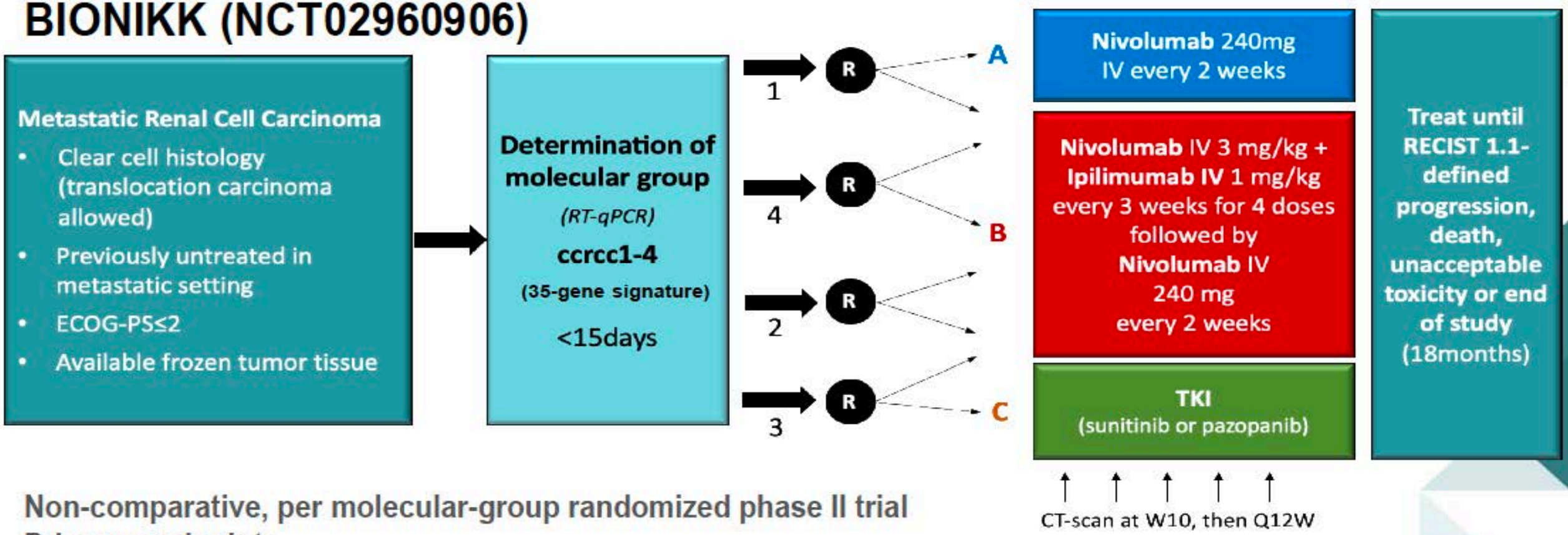
No. at Risk

NIVO+IPI	532	502	399	350	323	298	288	188	142	190	126	118	154	118	103	114	108	104	119	89	90	103
SUN	515	502	460	402	383	294	311	169	111	215	134	98	173	103	92	156	91	71	132	82	64	106

Courtesy of David I Quinn, MBBS, PhD

METHODS: study design

BIONIKK (NCT02960906)



Non-comparative, per molecular-group randomized phase II trial

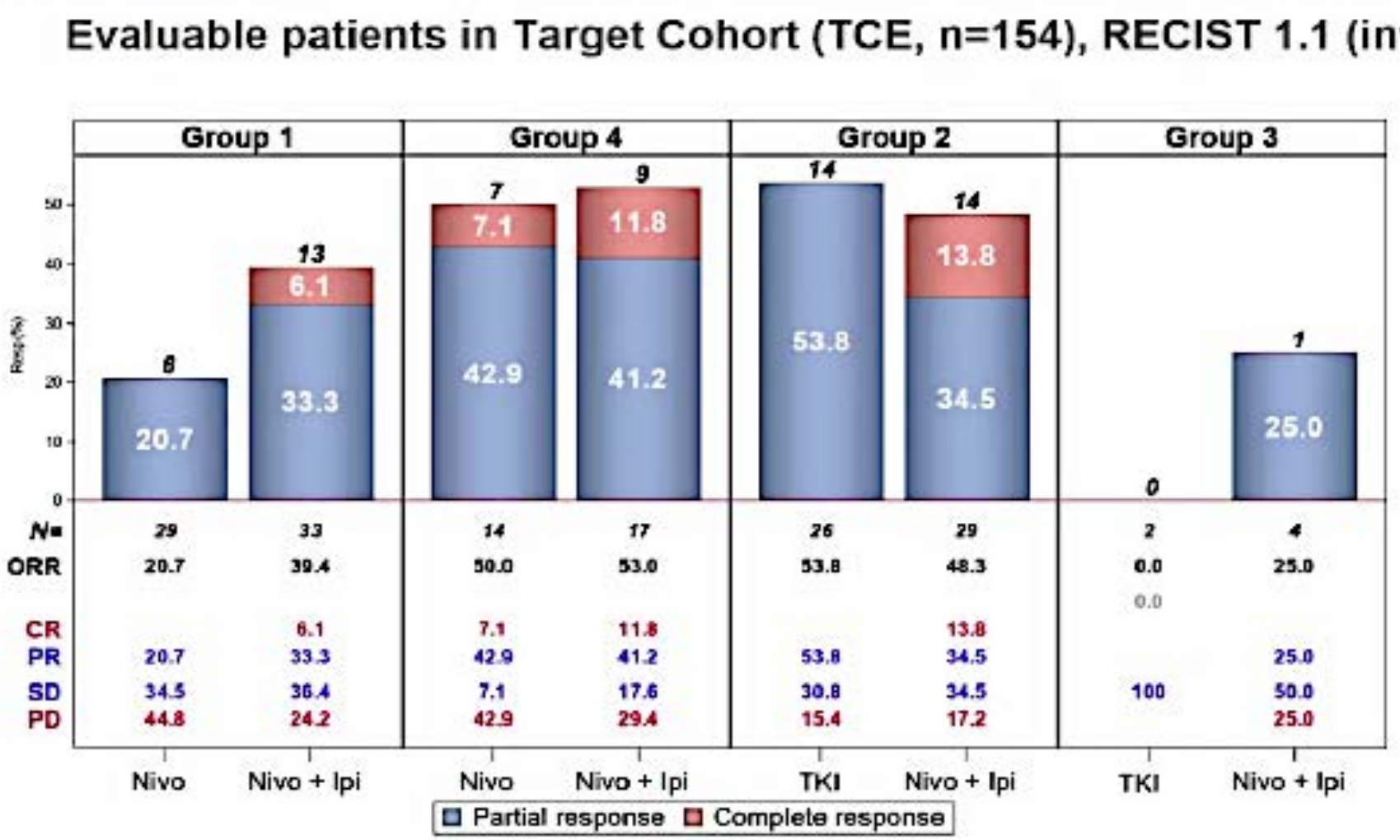
Primary endpoint:

Overall response rate (ORR: CR+PR) using RECIST 1.1 per investigator

Vano Y et al. ESMO 2020;Abstract LBA25.

Courtesy of David I Quinn, MBBS, PhD

BIONIKK RESULTS: Primary Endpoint: Objective Response Rate (2)



[1]TCE: evaluable pts in target cohort
[2]ACE: evaluable pts in additional cohort

Vano Y et al. ESMO 2020;Abstract LBA25.

Courtesy of David I Quinn, MBBS, PhD

BIONIKK RESULTS: Safety

All randomized patients (n=202)

No new safety signals compared to published data

	Arm A Nivolumab n=61	Arm B Nivolumab-ipilimumab n=101	Arm C TKI n=40[1]
All grades G3-4, n (%)	26 (42)	65 (64)	28 (70)
All grades TRAE, n (%)	54 (88)	99 (98)	37 (92)
Grades 3-4 TRAE, n (%)	11 (18)	45 (44)	22 (55)
Treatment-related deaths, n (%)	0	1 (1)	2 (5)

TRAE: treatment-related adverse event

[1]sunitinib 33 ; pazopanib 7

Vano Y et al. ESMO 2020;Abstract LBA25.

Courtesy of David I Quinn, MBBS, PhD

Nivolumab/Ipilimumab as First-line Therapy (CheckMate 214, BIONIKK)

- **Impact on Patient Care and Treatment Algorithm**
  - CM 214 shows ongoing OS advantage for NI over SU with 42 months minimal FU.
  - The OS advantage is seen in Intermediate and Poor Risk patients but not Favorable risk at this time.
  - QoL is better with NI than SU
  - NI remains a Standard First line Option for Intermediate and Poor Risk.
  - What is the SOC for favorable risk?

  - BIONIKK suggests that we may be able to prospectively select whether a patient needs CTLA-4 in addition to PD-1 based on tumor tissue signature.
  - PD-1 seems to be as efficacious and less toxic in selected patients

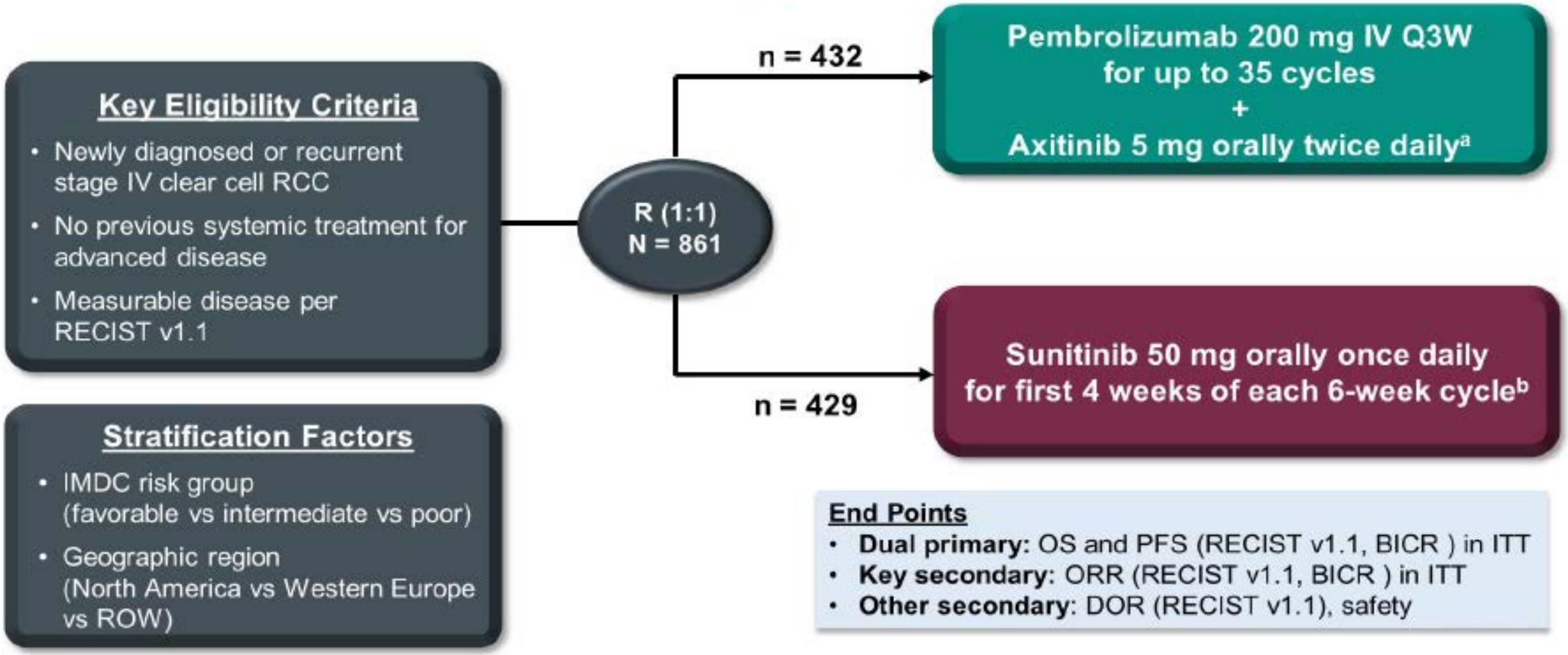
- **Implications for Future Research**
  - Further FU on CM 214?
  - Prospective biomarker driven RCC trial?

Courtesy of David I Quinn, MBBS, PhD

KEYNOTE-426: Pembrolizumab/Axitinib as First-line Therapy

Courtesy of David I Quinn, MBBS, PhD

KEYNOTE-426 Study Design

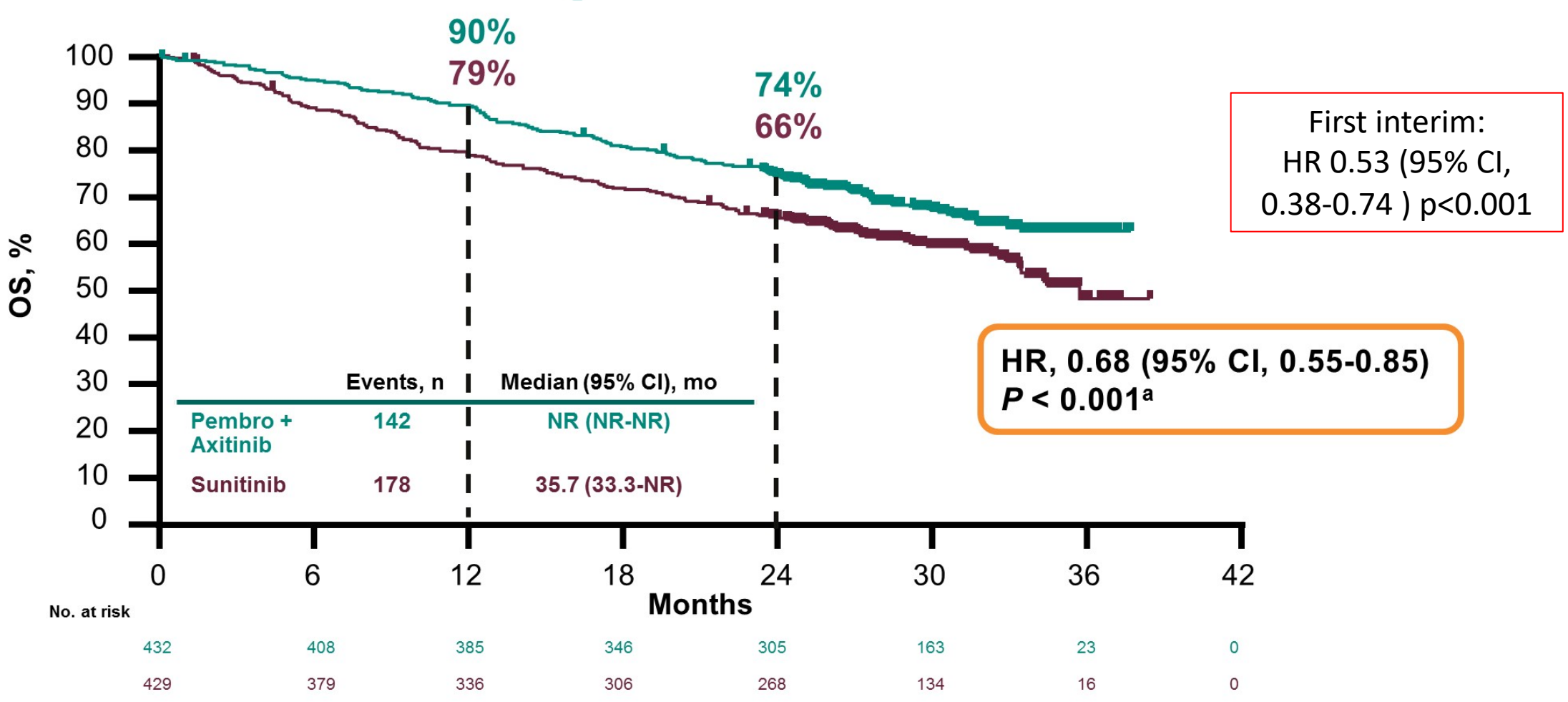


[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 6, 2020.

Plimack E et al. ASCO 2020;Abstract 5001.

Courtesy of David I Quinn, MBBS, PhD

KEYNOTE-426: OS in the ITT Population



First interim:
HR 0.53 (95% CI, 0.38-0.74) p<0.001

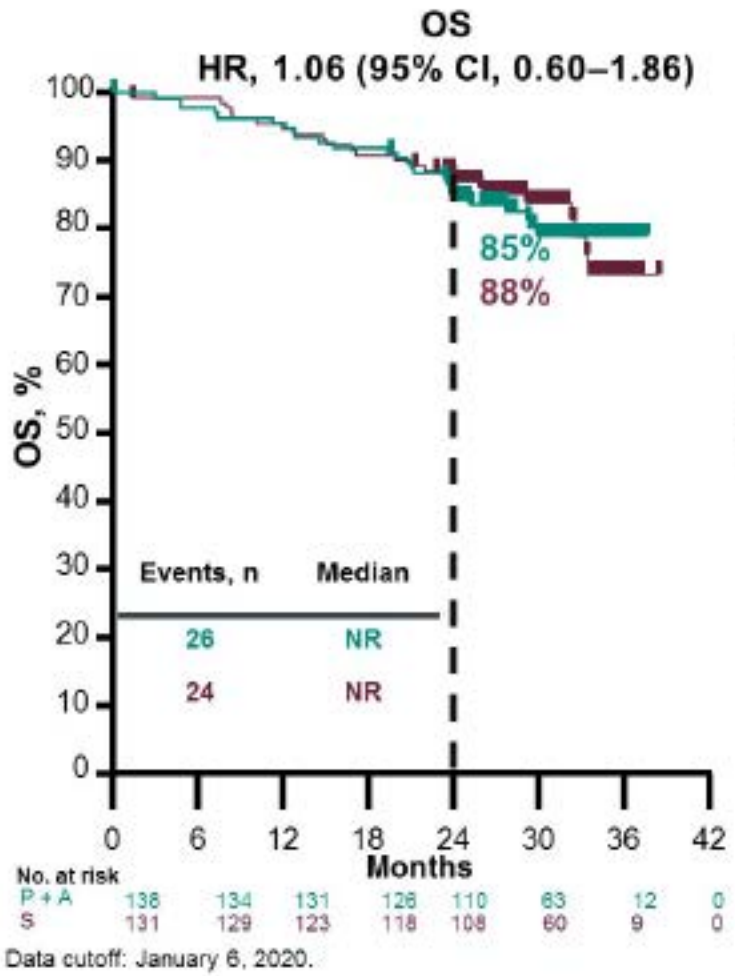
HR, 0.68 (95% CI, 0.55-0.85)
***P* < 0.001[a]**

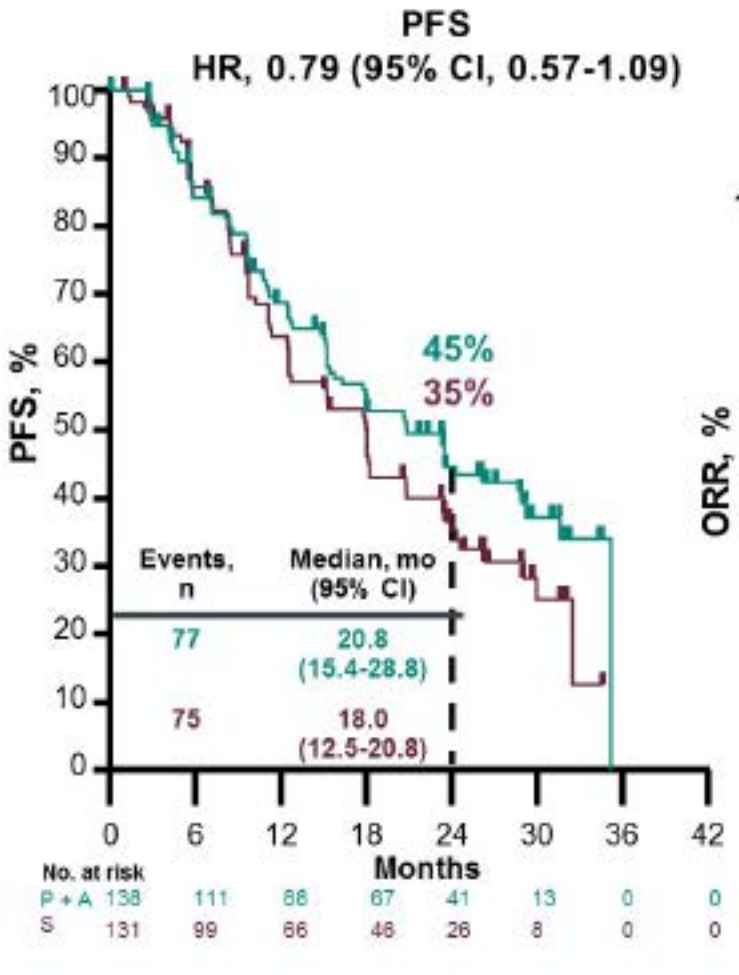
[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

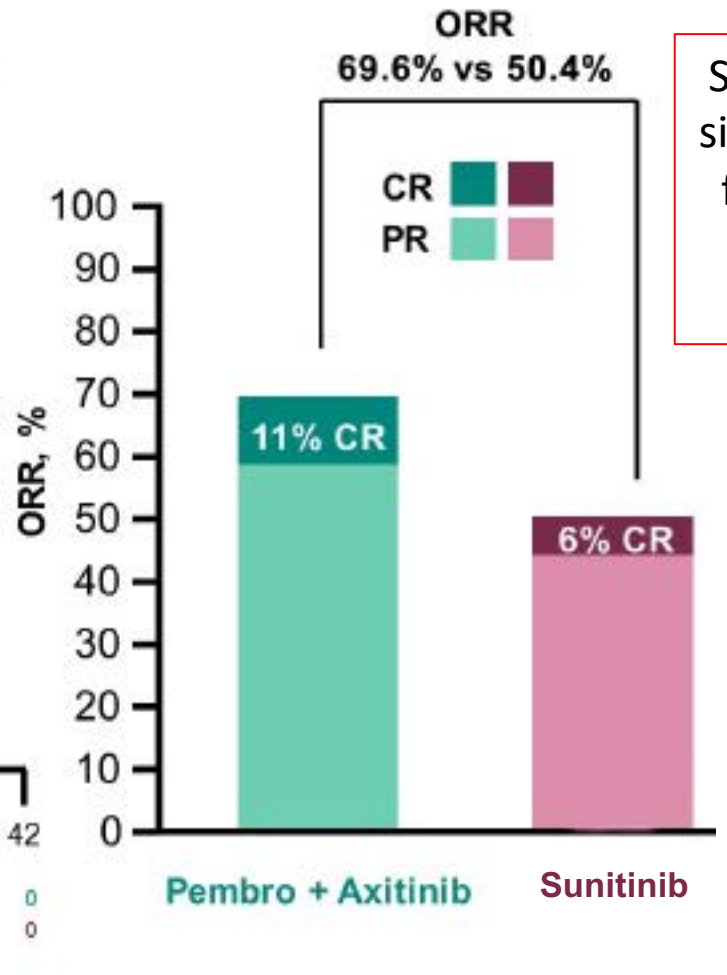
Plimack E et al. ASCO 2020;Abstract 5001; Powles T et al. *Lancet Oncol* 2020.

Courtesy of David I Quinn, MBBS, PhD

KEYNOTE-426: IMDC Favorable Risk: OS, PFS, and ORR





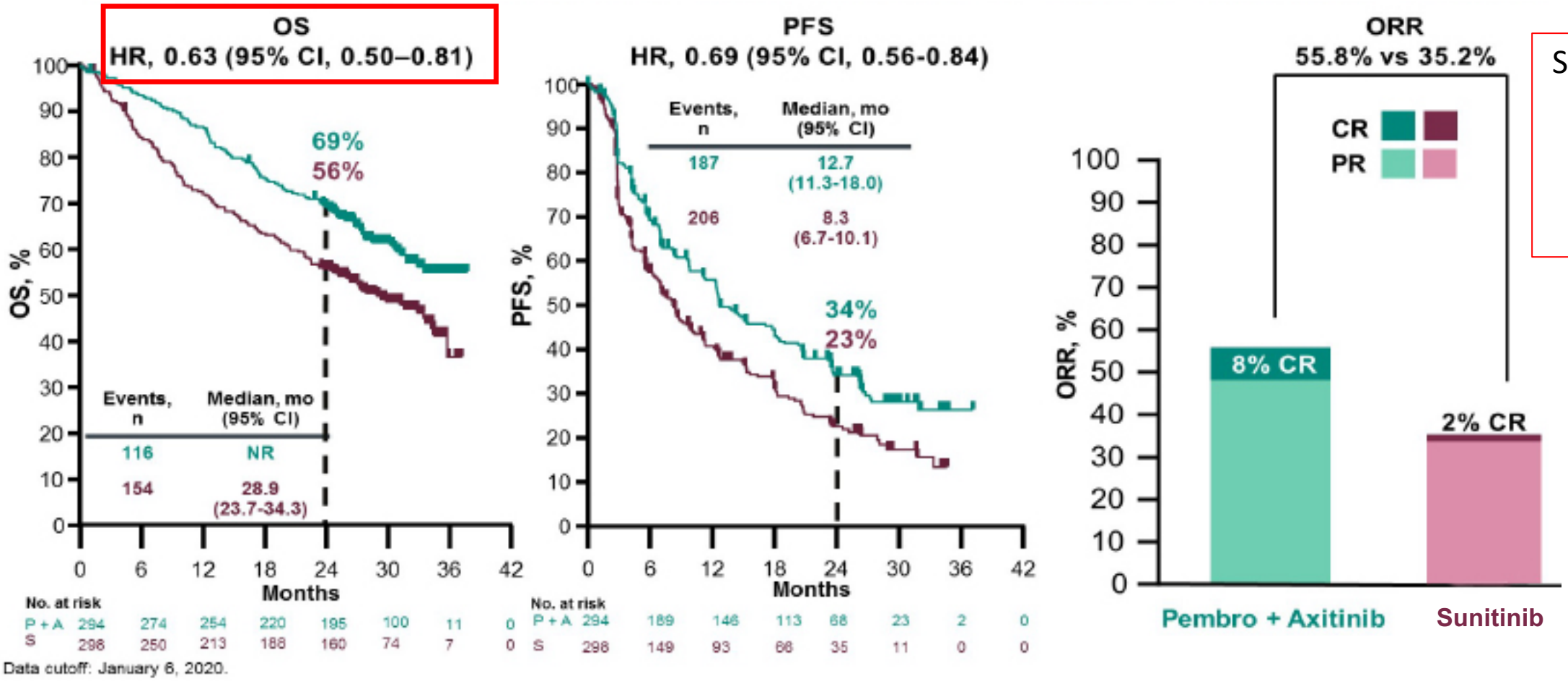


Superior ORR but similar OS and PFS for Ax + Pembro compared to Sunitinib

Plimack E et al. ASCO 2020;Abstract 5001; Powles T et al. *Lancet Oncol* 2020.

Courtesy of David I Quinn, MBBS, PhD

KEYNOTE-426: IMDC Intermediate/Poor Risk: OS, PFS, and ORR



Data cutoff: January 6, 2020.

Superior OS, PFS, ORR for Ax + Pembro compared to Sunitinib

Plimack E et al. ASCO 2020;Abstract 5001; Powles T et al. *Lancet Oncol* 2020.

Courtesy of David I Quinn, MBBS, PhD

KEYNOTE-426: Summary and Conclusions

- With extended follow-up, pembrolizumab + axitinib continued to demonstrate clinically significant improved efficacy compared with sunitinib for previously untreated, advanced RCC
  - OS: HR, 0.68; $P < 0.001$[a]; 24-month rate, 74% vs 66%
  - PFS: HR, 0.71; $P < 0.0001$[a]; 24-month rate, 38% vs 27%
  - ORR: 60% vs 40%; $P < 0.0001$[a]
  - CR rate: 9% vs 3%
- Exploratory landmark analysis demonstrated that greater depth of tumor shrinkage was associated with increased OS in the pembrolizumab + axitinib arm
  - Patients with ≥80% tumor reduction had similar survival rates as patients who achieved confirmed CR by RECIST v1.1 within 6 months after randomization
- These results continue to support pembrolizumab + axitinib as a standard of care for patients with previously untreated advanced RCC

Limited benefit differential in favorable risk patients

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated; only nominal *P* values are reported.

Plimack E et al. ASCO 2020;Abstract 5001.

Courtesy of David I Quinn, MBBS, PhD

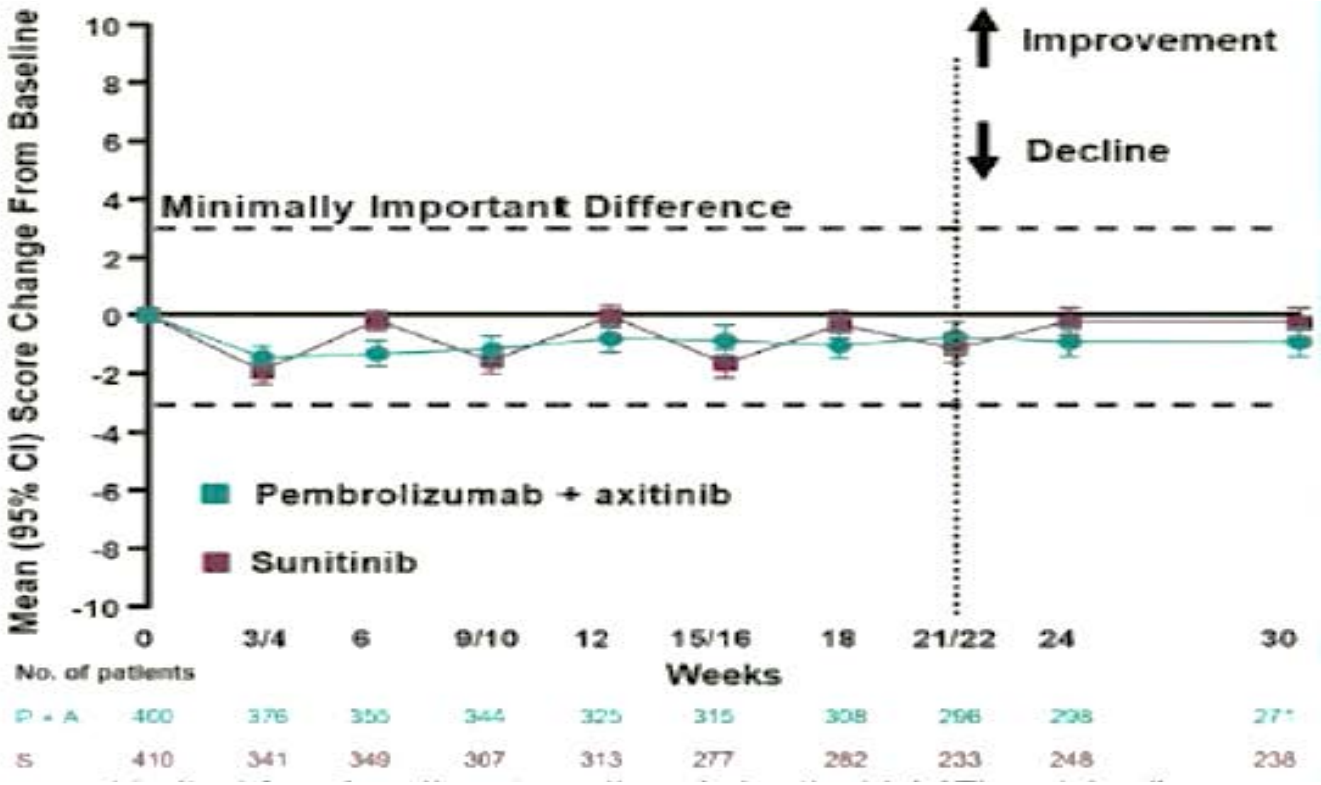
KEYNOTE-426: Pembrolizumab/Axitinib as First-line Therapy

- **Impact on Patient Care and Treatment Algorithm**
  - KN-426 shows ongoing OS advantage for PA over SU with 24 months minimal FU.
  - The OS advantage is seen in Intermediate and Poor Risk patients but not Favorable risk at this time.
  - QoL is not better with PA than SU (see below)
  - PA remains a Standard First line Option for Intermediate and Poor Risk mRCC.
  - What is the SOC for favorable risk?

- **Implications for Future Research**
  - Further FU on KN 426? Biomarkers?
  - Compare with CM 9ER and the CLEAR trial

Courtesy of David I Quinn, MBBS, PhD

KEYNOTE-426: FKSI-Disease-Related Symptom Subscale Health-Related Quality of Life



There were also no differences between the treatment groups in time to deterioration in the confirmed analysis (HR 1.12; 95% CI 0.91-1.38), as well as in the unconfirmed analysis (HR 1.02; 95% CI 0.86-1.20).

- FKSI-DRS subscale measures nine RCC related symptoms: lack of energy, fatigue, weight loss, pain, bone pain, shortness of breath, cough, fever, and hematuria
- Minimally important differences for KEYNOTE-426 were defined as ≥3 point change

FKSI-DRS=Functional Assessment of Cancer Therapy Kidney Symptoms Index – Disease Related Symptoms; LS=least square.

Bedke J, et al. EAU20 Virtual Congress, 17-26 July 2020,. Game-changing Session 4.

Courtesy of David I Quinn, MBBS, PhD

JAVELIN Renal 101: Avelumab/Axitinib as First-line Therapy

With further follow up, the PFS advantage for AA over SU is very consistent but OS remains elusive.

The lack of OS advantage, relegates the use of AA to a place behind behind NI, PA and CN regimens and possibly LenPem.

Choueiri TK et al. *Ann Oncol* 2020.

Courtesy of David I Quinn, MBBS, PhD

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CheckMate 9ER: Nivolumab/Cabozantinib as First-line Therapy

Courtesy of David I Quinn, MBBS, PhD

CheckMate 9ER: Study design

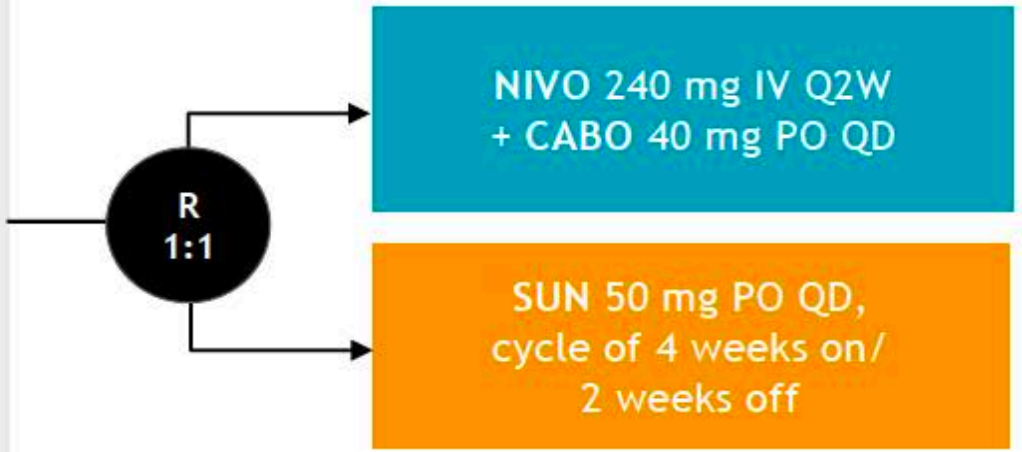
N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region



Treat until RECIST v1.1-defined progression or unacceptable toxicity[b]

Median study follow-up, 18.1 months (range, 10.6-30.6 months)

Primary endpoint: PFS

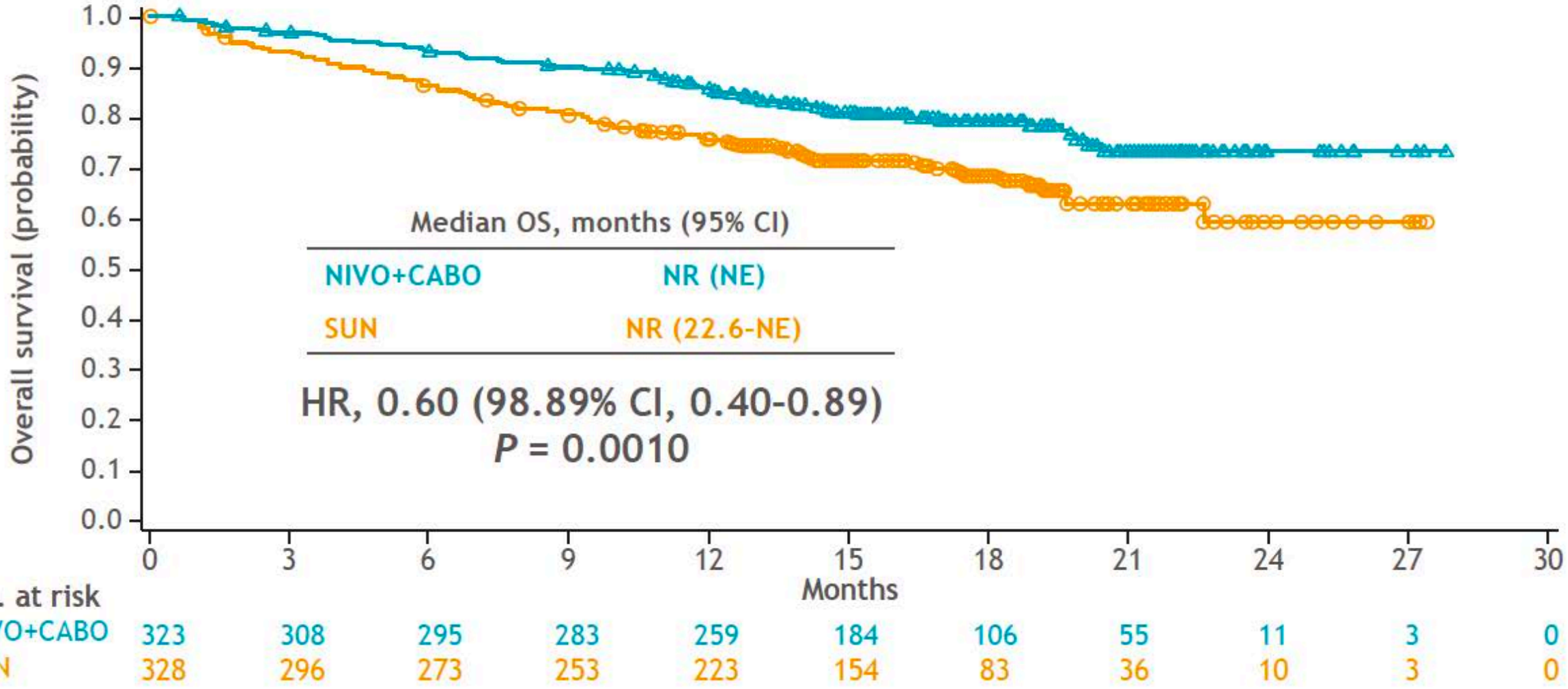
Secondary endpoints: OS, ORR, and safety

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

Courtesy of David I Quinn, MBBS, PhD

CheckMate 9ER: Overall survival



Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

Choueiri T et al. ESMO 2020;Abstract 696O.

Courtesy of David I Quinn, MBBS, PhD

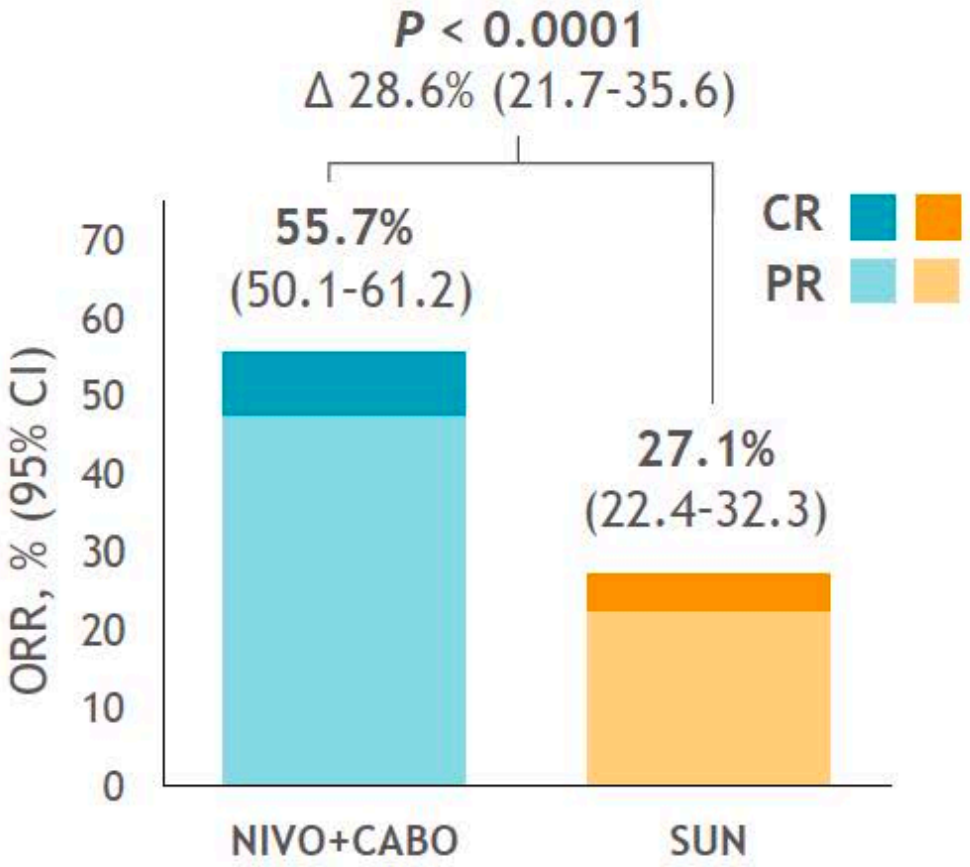
CheckMate 9ER: Overall survival in subgroups

Subgroup	NIVO+CABO Events/no. of patients	SUN Events/no. of patients	HR for death (95% CI)
Overall	67/323	99/328	0.60 (0.44-0.82)
Region			
US/Europe	26/158	45/161	0.48 (0.30-0.79)
Rest of world	41/165	54/167	0.71 (0.48-1.07)
IMDC prognostic risk			
Favorable	10/74	11/72	0.84 (0.35-1.97)
Intermediate	40/188	51/188	0.70 (0.46-1.07)
Poor	17/61	37/68	0.37 (0.21-0.66)
PD-L1 expression			
≥ 1%	28/83	30/83	0.80 (0.48-1.34)
< 1% or indeterminate	39/240	69/245	0.51 (0.34-0.75)
Age			
< 65 years	31/191	66/210	0.44 (0.29-0.67)
≥ 65 years	36/132	33/118	0.90 (0.56-1.44)
Sex			
Male	47/249	66/232	0.59 (0.40-0.85)
Female	20/74	33/96	0.68 (0.39-1.18)
Karnofsky performance status			
90-100	45/257	56/241	0.69 (0.47-1.03)
≤ 80	22/66	43/85	0.52 (0.31-0.86)
Bone metastases			
Yes	24/78	33/72	0.54 (0.32-0.92)
No	43/245	66/256	0.61 (0.41-0.89)
Previous nephrectomy			
Yes	36/222	66/233	0.49 (0.33-0.74)
No	31/101	33/95	0.79 (0.48-1.29)

Choueiri T et al. ESMO 2020;Abstract 696O.

Courtesy of David I Quinn, MBBS, PhD

CheckMate 9ER: Objective response and best overall response per BICR



Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0-19.4)	4.2 (1.7-12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3-NE)	11.5 (8.3-18.4)

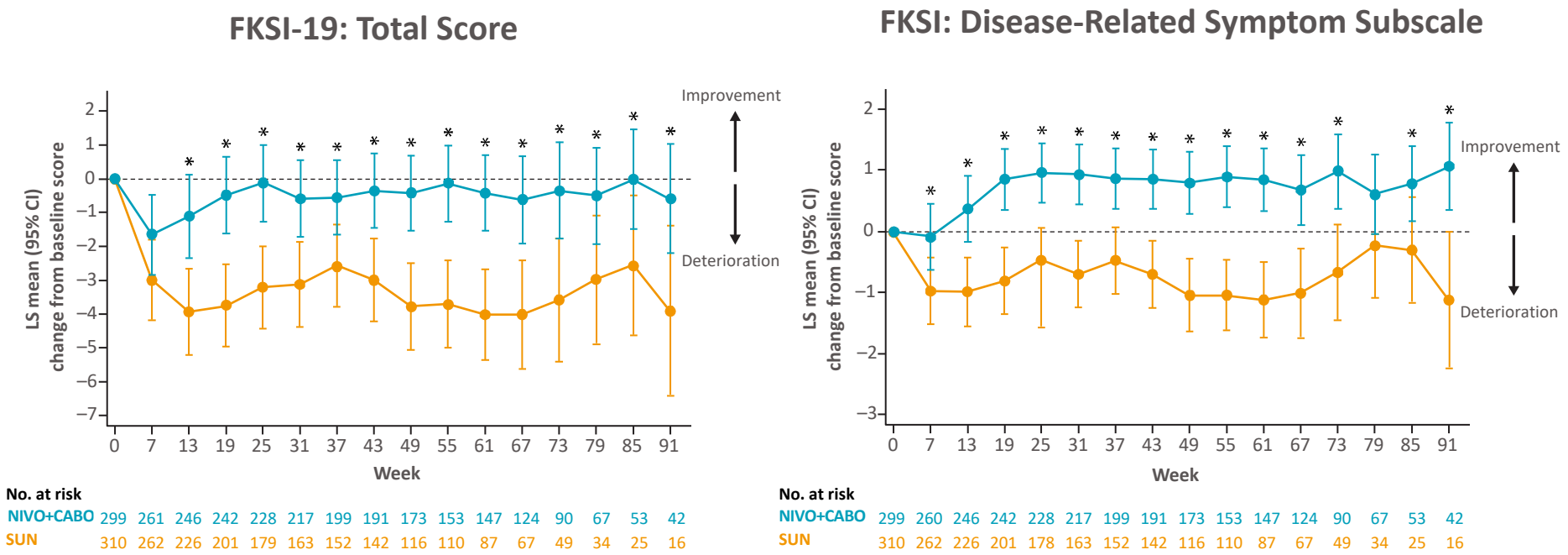
- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; [b]Median time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO+CABO, n = 89 patients with SUN).

Choueiri T et al. ESMO 2020;Abstract 696O.

Courtesy of David I Quinn, MBBS, PhD

CheckMate 9ER: Health-Related Quality of Life



*Between-arm difference was statistically significant at this time point ($P<0.05$). Change from baseline was assessed using descriptive statistics and a mixed-model repeated measures analysis, which controlled for treatment arm, time point, baseline patient-reported outcomes score, IMDC prognostic score, PD-L1 tumor expression, and region. No. at risk denotes intention-to-treat patients with baseline plus at least 1 post-baseline HRQOL assessment with non-missing patient-reported outcome data. Time 0 indicates baseline.

FKSI-19=Functional Assessment of Cancer Therapy Kidney Symptom Index-19; LS=least square.

Choueiri TK, et al. ESMO 2020. Presentation #6960.

Courtesy of David I Quinn, MBBS, PhD

CheckMate 9ER: Nivolumab/Cabozantinib as First-line Therapy

- **Impact on Patient Care and Treatment Algorithm**
  - CM 9ER shows early ORR, PFS and OS advantage for CN over SU
  - The OS advantage is seen in Intermediate and Poor Risk patients but not Favorable risk at this time.
  - QoL is better with CN than SU
  - CN is a Standard First line Option for Intermediate and Poor Risk mRCC.
  - What is the SOC for favorable risk?

- **Implications for Future Research**
  - Triple combination in ccRCC
  - Activity in nccRCC

Courtesy of David I Quinn, MBBS, PhD

COSMIC-021: Atezolizumab/Cabozantinib as First-line Therapy

- **Impact on Patient Care and Treatment Algorithm**

  Atezo + Cabo shows significant activity and acceptable toxicity in first line and small cohort of previously treated (n=10) mRCC patients

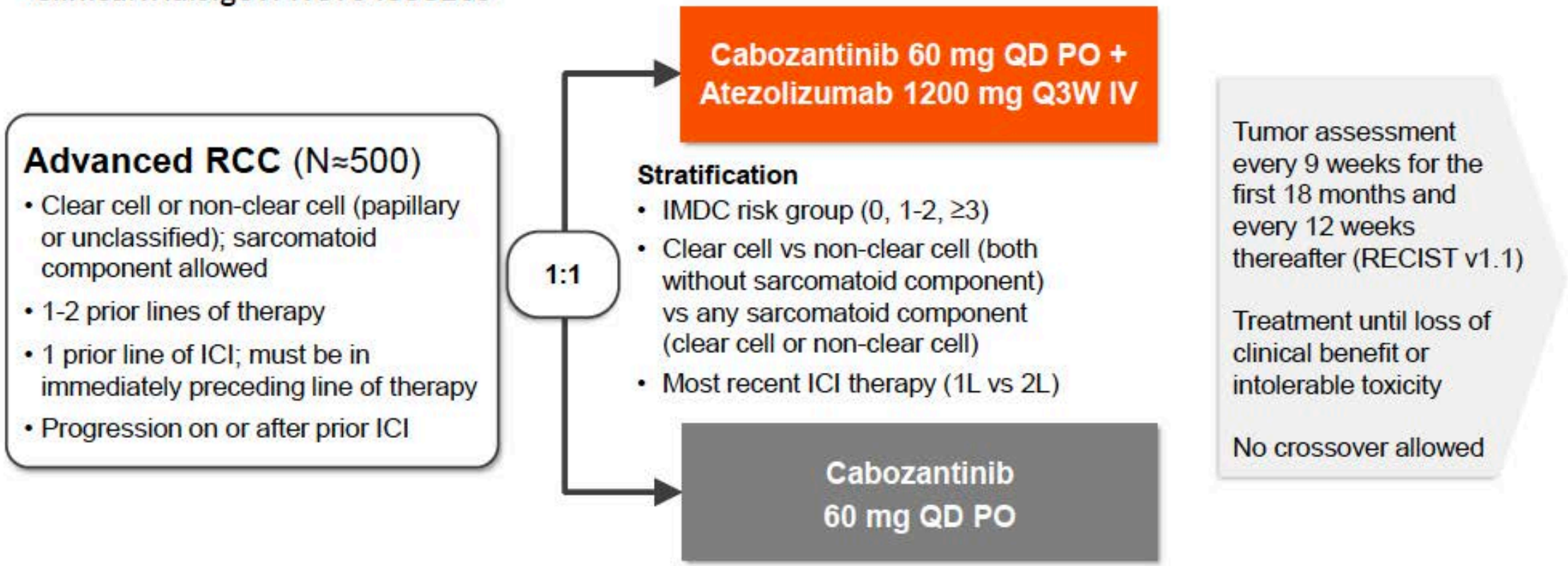
- **Implications for Future Research**
  - CONTACT-03 TRIAL

Pal S et al. ESMO 2020;Abstract 702O.

Courtesy of David I Quinn, MBBS, PhD

CONTACT-03 Study Design

ClinicalTrials.gov: NCT04338269



Primary Endpoints: PFS by Independent Review Facility (IRF), OS

Secondary Endpoints: PFS by Investigator, ORR by Investigator and IRF, DOR by Investigator and IRF

Courtesy of David I Quinn, MBBS, PhD

Nivolumab/Ipilimumab in Previously-treated Advanced RCC

- Generally trying to do an adapative design in mRCC has been challenging.
- OMNIVORE, HCRN GU 16-260 AND TITAN trials suggest:
  - Cross over is difficult to manage in a trial with many dropouts and some adverse effect issues
  - The addition of CTLA-4 inhibition may change disease trajectory in 5-13% of patients.
  - Single agent Nivolumab is active in the first line.
    - We already have data on Pembrolizumab in this setting (KN427)

- **Implications for Future Research**
  - Biomarker driven selection would be optimal either from start of therapy or at progression

McKay RR et al. *J Clin Oncol* 2020; Atkins MB et al. ASCO 2020;Abstract 5006; Gul A et al. *J Clin Oncol* 2020.

Courtesy of David I Quinn, MBBS, PhD

Lenvatinib/Pembrolizumab in Previously-treated Advanced RCC

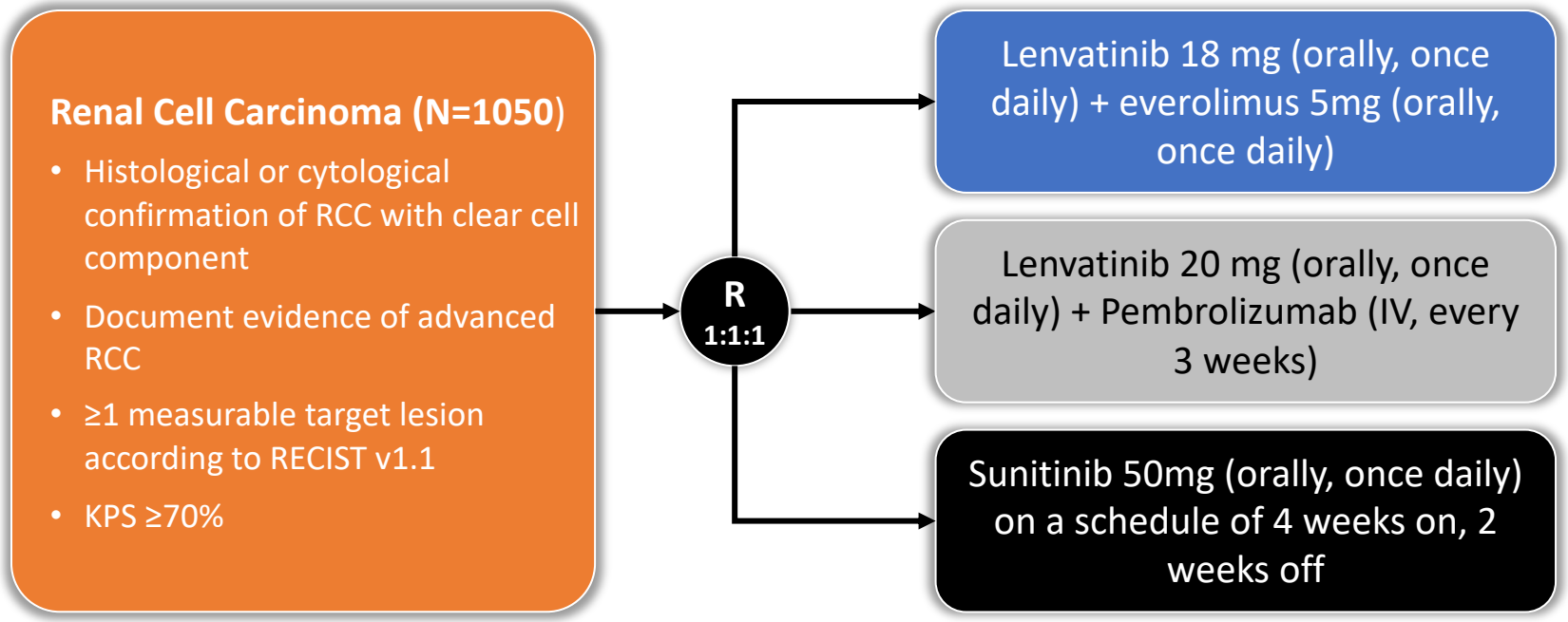
- This combination showed a remarkably high ORR in excess of 50% in patients previously treated with ICI.
- Questions remain
  - About the quality of response assessment coming into the trial, which is difficult to control for.
  - Prior use of which CPI and VEGFrTKi of specific type
    - Likely that Nivolumab and Axitinib predominated
  - Requires validation

- **Implications for Future Research**
  - The first line CLEAR trial awaits ….

Lee C-H et al. ASCO 2020;Abstract 5008.

Courtesy of David I Quinn, MBBS, PhD

CLEAR: A Phase III Study Comparing Lenvatinib + Everolimus vs Lenvatinib + Pembrolizumab vs Sunitinib in Patients With Advanced or Metastatic RCC



Study Endpoints

- Primary: PFS
- Secondary: OS, ORR, safety and tolerability, HRQoL

Stratification

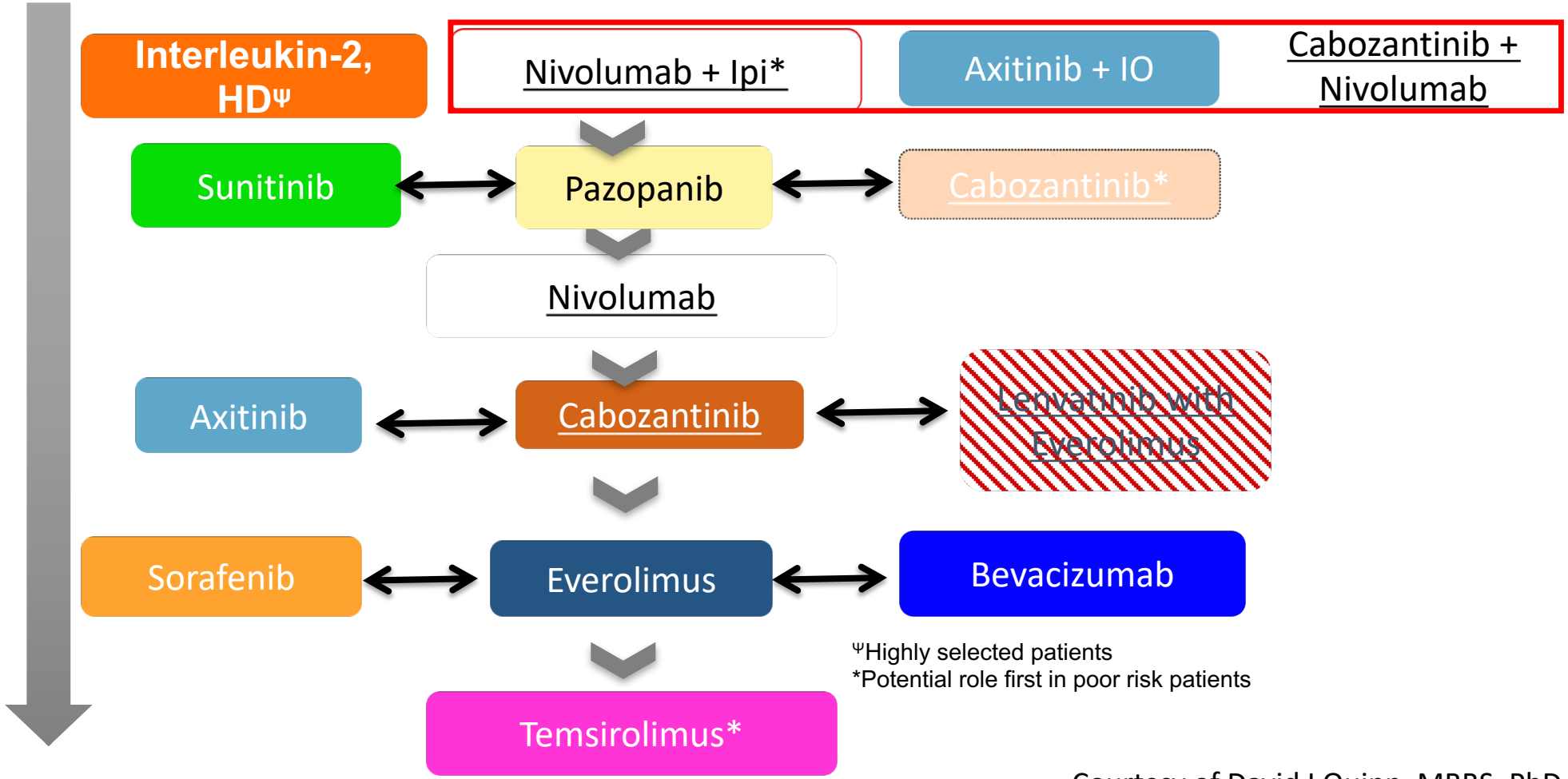
- Geographic region (western Europe and North America vs other)
- MSKCC prognostic groups (favorable, intermediate and poor risk)

https://clinicaltrials.gov/ct2/show/NCT02811861

Courtesy of David I Quinn, MBBS, PhD

David Quinn's Preferred Therapeutic Sequencing and Decision Points for Metastatic RCC 2020

Baseline: ~~Cytoreductive nephrectomy~~; control critical metastases: brain, bone; general health measures: TSH, Vitamin D



ΨHighly selected patients
*Potential role first in poor risk patients

Courtesy of David I Quinn, MBBS, PhD

Renal cell cancer: where to in 2021?

- **We have a wealth of agents with IO, VEGF and mTORi mechanism of action**
- **For first line IO eligible patients who are intermediate to poor risk, Nivo + Ipi, Pembro + Axitinib and Cabo + Nivo provide a robust OS benefit**
- **These are regimens of first choice**
- **Therapy selection may be based on the toxicity of the drug added to the PD-1 agent at the start of treatment**
- **For good risk metastatic patients, IO therapy is an option but first line VEGFrTKI followed by other agents including IO therapy results in a similar OS outcome.**
- **The addition of Ipi to Nivolumab in patients with stable disease or progression produces an incremental response in 10-15% of patients. (GU 16-260, German Urology Group data – TITAN, now OMNIVORE)**
- **Cabozantinib is an excellent alternative or salvage option, relative to IO therapy in intermediate and poor risk cases. Axitinib and other VEGFrTKIs are active if the patient has not had prior exposure.**
- **More data to follow …**

Courtesy of David I Quinn, MBBS, PhD