# Evolving Front-Line Therapy in Metastatic Renal Cell Carcinoma

Christopher J Kane

Professor and Chair of Urology

Dean of Clinical Affairs, CEO of Physician Group

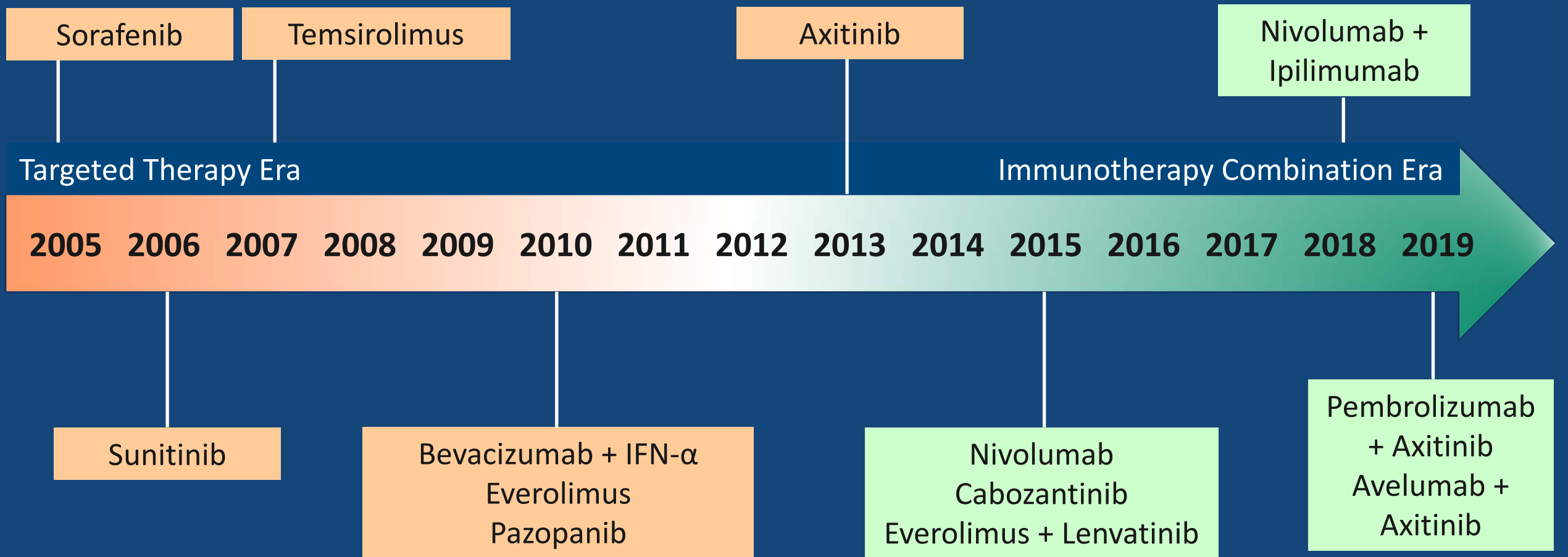
Joseph D. Schmidt Presidential Chair of Urology

University of California San Diego

# Outline

- **Abstract 4500**: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for metastatic renal cell carcinoma: Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study
- **Abstract 4501**: A pilot randomized study evaluating nivolumab or nivolumab + bevacizumab or nivolumab + ipilimumab in patients with metastatic renal cell carcinoma eligible for cytoreductive nephrectomy, metastasectomy or post-treatment biopsy
- **Abstract 4502**: Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: A trial of the ECOG-ACRIN cancer research group (E2810)

# Treatment Landscape for Metastatic RCC




RCC=Renal cell carcinoma; IFN-α=Interferon alpha.

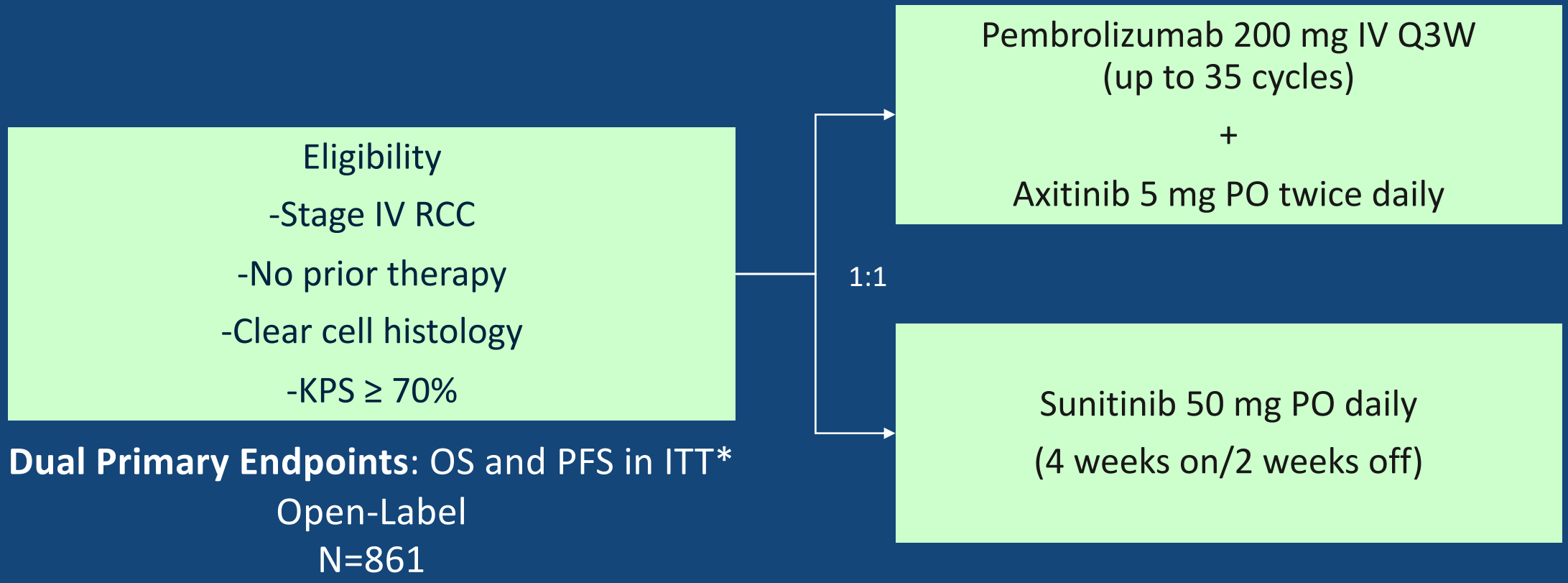
# 1L Combination Therapy Trials – ITT

| Variable | | Nivolumab + Ipilimumab CheckMate 214 n=1096 | Pembrolizumab + Axitinib Keynote 426 n=861 | Avelumab + Axitinib Javelin 101 n=886 |
|---|---|---|---|---|
| Median Follow-Up (months) | | 25.2 | 12.8 | 12.0 |
| ORR | | 39.0% | 59.3% | 51.4% |
| CR | | 10.2% | 5.8% | 3.4% |
| PFS (months) | Combination Arm | 12.4 | 15.1 | 13.8 |
| | Sunitinib | 12.3 | 11.1 | 8.4 |
| | HR (CI) | 0.98 (99.1% CI 0.79-1.23) | 0.69 (95% CI 0.57-0.84) | 0.69 (95% CI 0.56-0.84) |
| OS | HR (CI) | 0.68 (99.8% CI 0.49-0.95) | 0.53 (95% CI 0.38-0.74) | 0.78 (95% CI 0.55-1.08) |

OS=Overall survival; ITT=Intent-to-treat; HR=Hazard ratio; CI=Confidence interval; PFS=Progression-free survival; ORR=Objective response rate; CR=Complete response rate.

Motzer et al, NEJM, 2018
Rini et al, NEJM, 2019
Motzer et al, NEJM, 2019

# Phase III Keynote-426 Trial




**Dual Primary Endpoints**: OS and PFS in ITT*

Open-Label

N=861

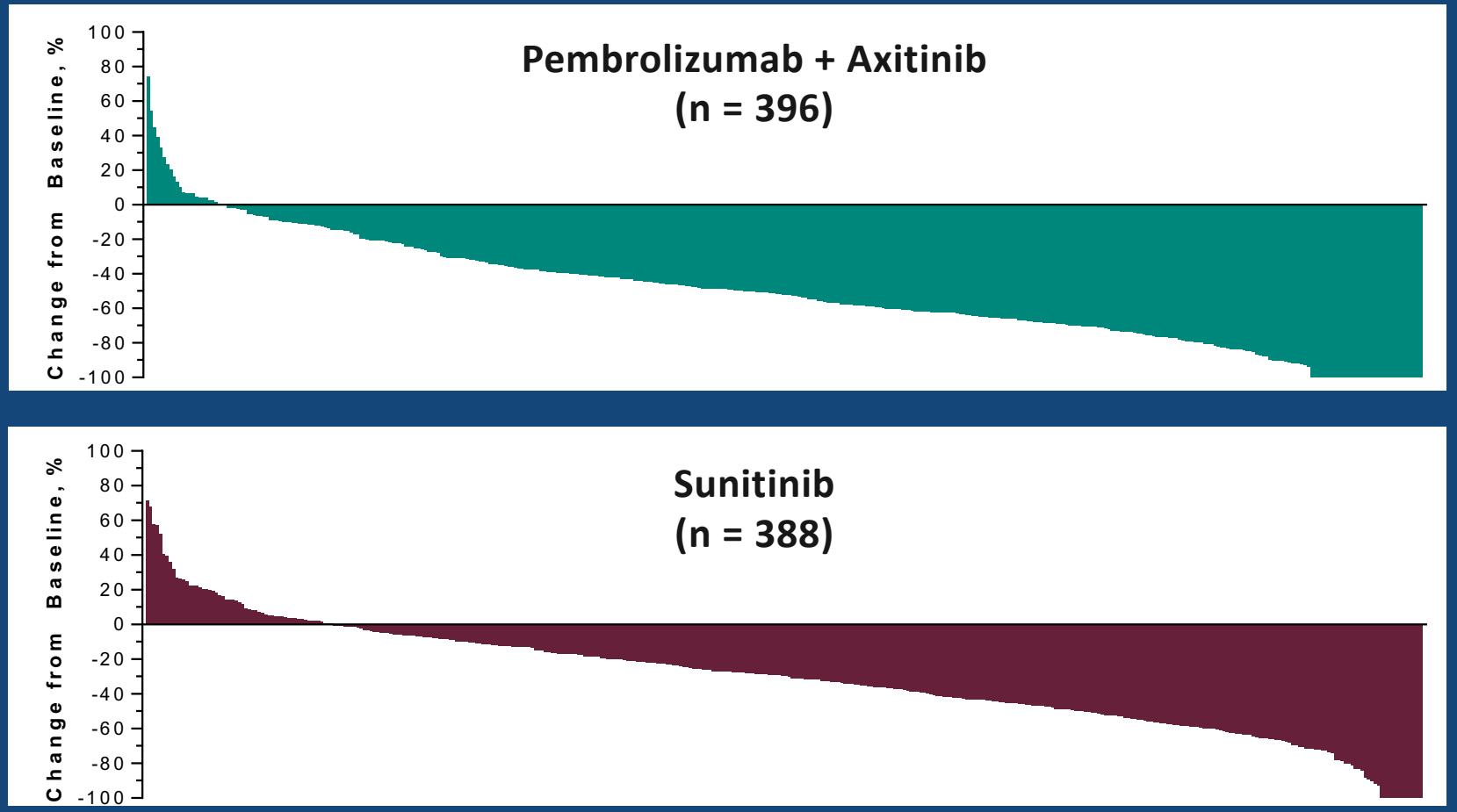
Stratified by IMDC risk group (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus Rest of World).

*Per RECIST version 1.1 by blinded independent central radiology review committee.

RCC=Renal cell carcinoma; KPS=Karnofsky performance status; IV=Intravenously; IV=Intravenous; PO=Orally; PFS=Progression-free survival; OS=Overall survival; ITT=Intent to Treat.

Rini et al, NEJM, 2019

# Phase III Keynote 426 – Percent Change in Baseline Target Lesion Size




- Highlight the shortcomings of using RECIST version 1.1 for measurement of tumor response to immunotherapy
- CR is defined as:
  - Disappearance of all target lesions
  - Disappearance of all non-target lesions
  - Lymph nodes < 1.0 cm
- Is there a threshold of response that correlates with durability and survival?

RECIST=Response Evaluation Criteria In Solid Tumors; CR=Complete response rate.

Eisenhauer et al, Eur J Cancer, 2009

# Phase III Keynote 426

| | Overall | | Favorable Risk | | Intermediate/Poor Risk | |
|---|---|---|---|---|---|---|
| | Pembro+Axi (n=432) | Sunitinib (n=429) | Pembro+Axi (n=138) | Sunitinib (n=131) | Pembro+Axi (n=294) | Sunitinib (n=298) |
| ORR* | 59.3% | 35.7% | 66.7% | 49.6% | 55.8% | 29.5% |
| P value | <0.001 | | - | | - | |
| CR | 5.8% | 1.9% | - | - | 4.8% | 0.7% |
| **Benefit observed independent of risk group across all efficacy parameters** | | | | | | |
| 12-month OS | 89.9% | 78.3% | 95% | 94% | 87% | 71% |
| Hazard Ratio (95% CI) | 0.53 (0.38-0.74) | | 0.64 (0.24-1.68) | | 0.52 (0.37-0.74) | |
| P value | <0.0001 | | - | | - | |

*Per blinded independent radiology review committee by RECIST version 1.1.

Pembro+Axi=Pembrolizumab + axitinib; ORR=Objective response rate; CR=Complete response; PFS=Progression-free survival; CI=Confidence interval; OS=Overall survival.

Rini et al, NEJM, 2019

# Conclusions – Abstract 4500

- Immunotherapy combinations are now the new standard frontline treatment for ALL patients with metastatic RCC without contraindications
- Deep responses can be achieved in a subset of patients
- Presence of sarcomatoid differentiation is associated with improved outcomes with IO combination therapy

RCC=Renal cell carcinoma; IO=Immunotherapy.

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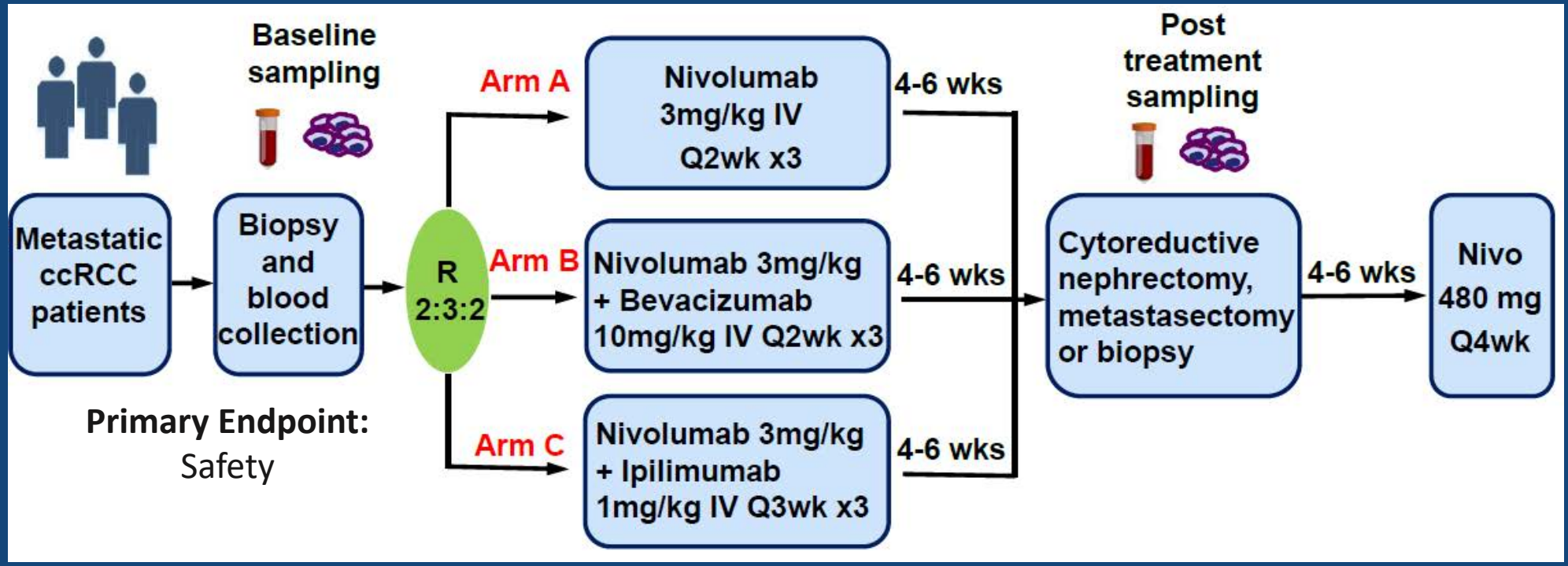
# Study Schema




- Initially designed as a pilot peri-operative study.
- Given slower accrual expanded to include non-operable patients willing to undergo an on-treatment biopsy.
- Not intended to compare outcomes between arms or between surgical and non-surgical patients.

# Clinical Outcomes

| | Nivo (n=29) | Nivo+Bev (n=45) | Nivo+Ipi (n=30) |
|---|---|---|---|
| Best Overall Response* | 59% (n=17/29) | 44% (n=20/45) | 43% (n=13/30) |
| Surgical Patients (n=43) | 86% (n=12/14) | 82% (n=14/17) | 69% (n=9/13) |
| Non-Surgical Patients (n=61) | 33% (n=5/15) | 21% (n=6/29) | 24% (n=4/17) |
| 2-year OS | 72% | 60% | 56% |

- While this is a small pilot study with inherent bias in the surgical and non-surgical patients, the combination of multi-modality treatment with nivolumab-based systemic therapy and surgery was safe and results in dramatic responses.
- There were 4 complete responses (3.8%).
- Limited data presented regarding surgical decision making.

*Best overall response = Defined as patients with a complete response + partial response + surgery effect.
Nivo=Nivolumab; Nivo+Bev=Nivolumab + bevacizumab; Nivo+Ipi=Nivolumab + ipilimumab; OS=Overall survival.

# Predictive Biomarkers of Response

Abstract 101

# Biomarker analyses from JAVELIN Renal 101: avelumab + axitinib vs sunitinib in advanced renal cell carcinoma

Toni K. Choueiri,[1] Laurence Albiges,[2] John Haanen,[3] James Larkin,[4] Motohide Uemura,[5] Sumanta Pal,[6] Gwenaelle Gravis,[7] Matthew T. Campbell,[8] Konstantin Penkov,[9] Jae Lyun Lee,[10] Keith A. Ching,[11] Xinmeng Jasmine Mu,[11] Xiao Wang,[11] Weidong Zhang,[12] Jing Wang,[12] Aleksander Chudnovsky,[12] Alessandra di Pietro,[13] Paul B. Robbins,[11] Robert J. Motzer[14]

IFN=Interferon; TMB=Tumor mutation burden.

# Conclusions – Abstract 4501

- Cytoreductive nephrectomy and metastatectomy are safe in the context of nivolumab-based systemic therapy
- Cytoreductive nephrectomy and metastatectomy continue to have a role in select patients with metastatic RCC
- There is a need to identify and validate predictive biomarkers to guide therapy selection

# Outline

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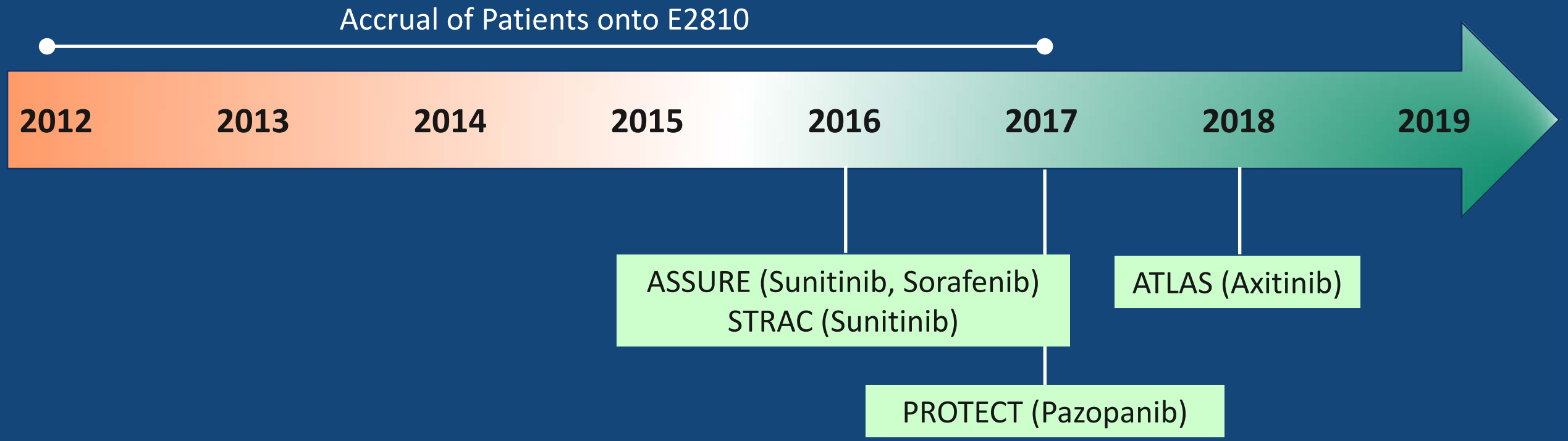
# Timeline of Reporting of Adjuvant Studies



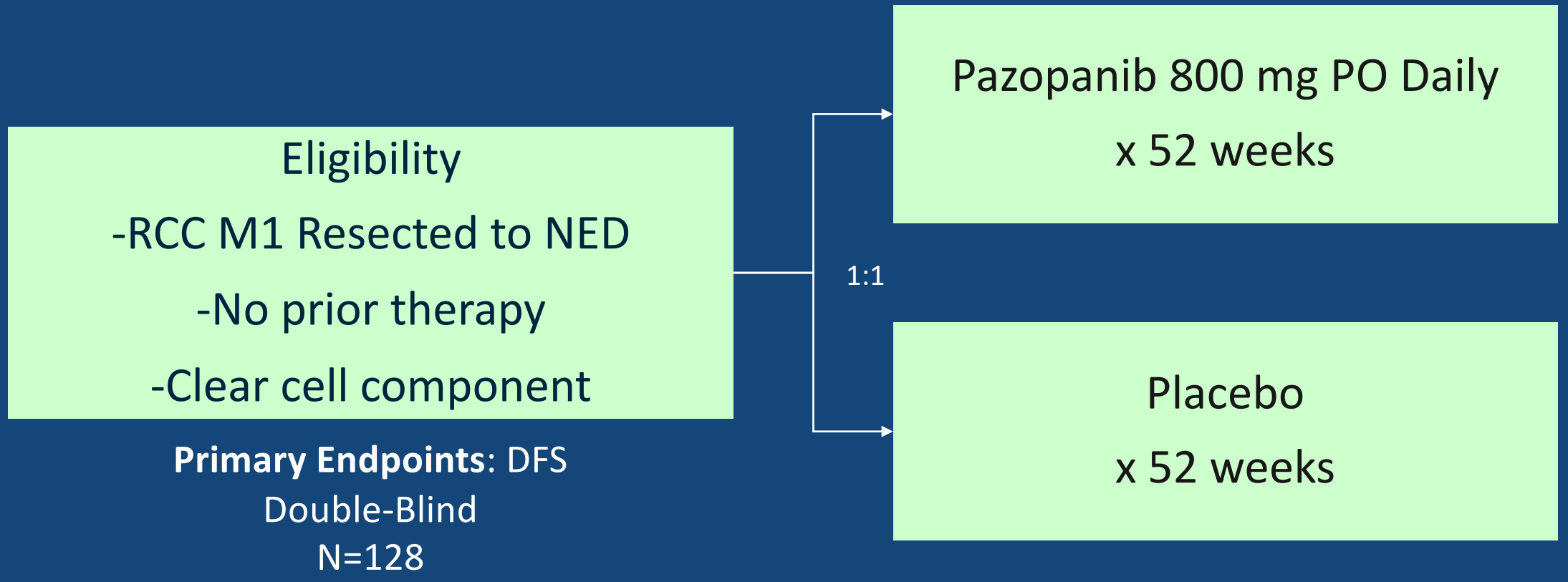
# Summary of Reported Adjuvant TKI Studies

| | ASSURE (n=1943) | STRAC (n=615) | PROTECT (n=1538) | ATLAS* (n=724) |
|---|---|---|---|---|
| Arms | Sunitinib vs. Sorafenib vs. Placebo x 1 year | Sunitinib vs. Placebo x 1 year | Pazopanib vs. Placebo x 1 year | Axitinib vs. Placebo x 3 years |
| Start Dose Reduction | Yes | No | Yes | No |
| Non-Clear Cell | Yes | No | No | No |
| Eligibility | pT1bG3-4N0, pT2-4GxN0, TxGxN+ | pT3-4GxN0-x, TxGxN1-2 | pT2G3-4N0M0, pT3-4N0M0, pTxN1M0 | pT2-4N0M0, pTxN1M0 |
| Median DFS (years) | 5.8 vs. 6.1 vs. 6.6 | 6.8 vs. 5.6 | NR vs. NR | NR vs. NR |
| Hazard Ratio (CI) | Sunitinib – 1.02 (97.5% CI 0.85-1.23) Sorafenib – 0.97 (97.5% CI 0·80-1.17) | 0.76 (95% CI 0.59-0.98) | 0.94 (95% CI 0.77-1.14) | 0.87 (95% CI 0.660-1.147) |

*Closed due to futility.

TKI=Tyrosine kinase inhibitor; G=Grade; DFS=Disease-free survival; CI=Confidence interval; NR=Not reached.

# E2180 Phase III Randomized Double-Blind Study

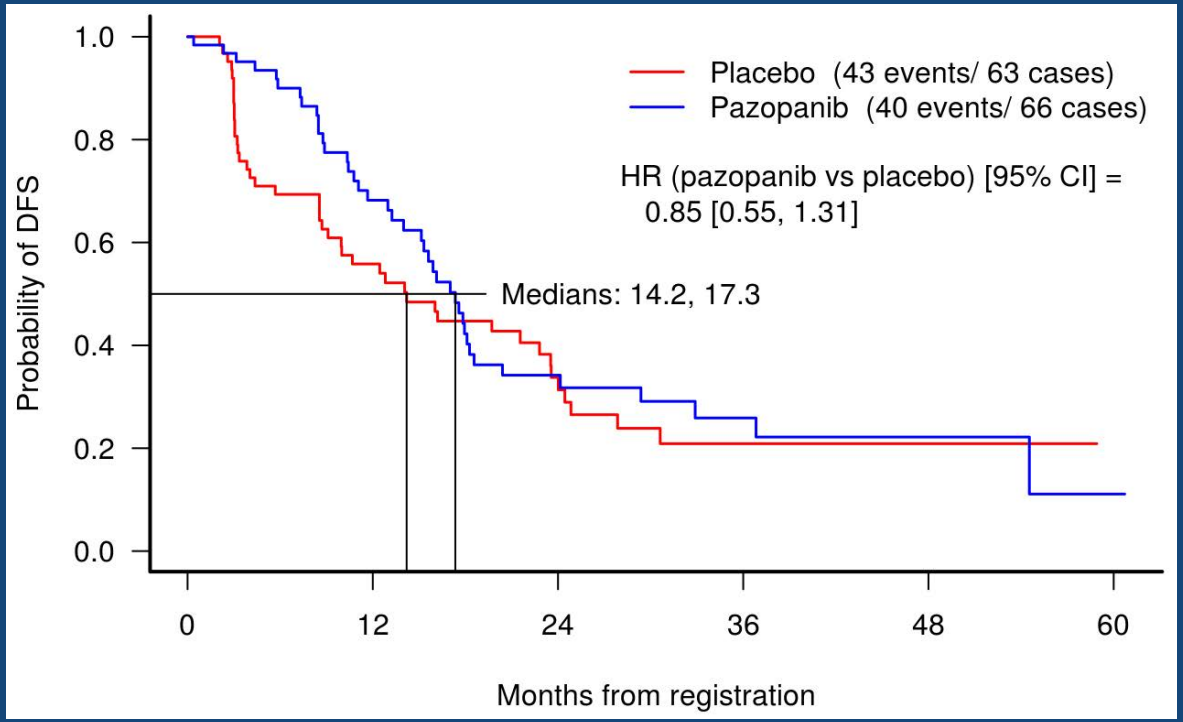



**Primary Endpoints**: DFS
Double-Blind
N=128

Stratified by disease-free interval (< or > 1 year) and number of sites resected (1 versus > 1).
RCC=Renal cell carcinoma; NED=No evidence of disease; PO=Orally; DFS=Disease-free interval.

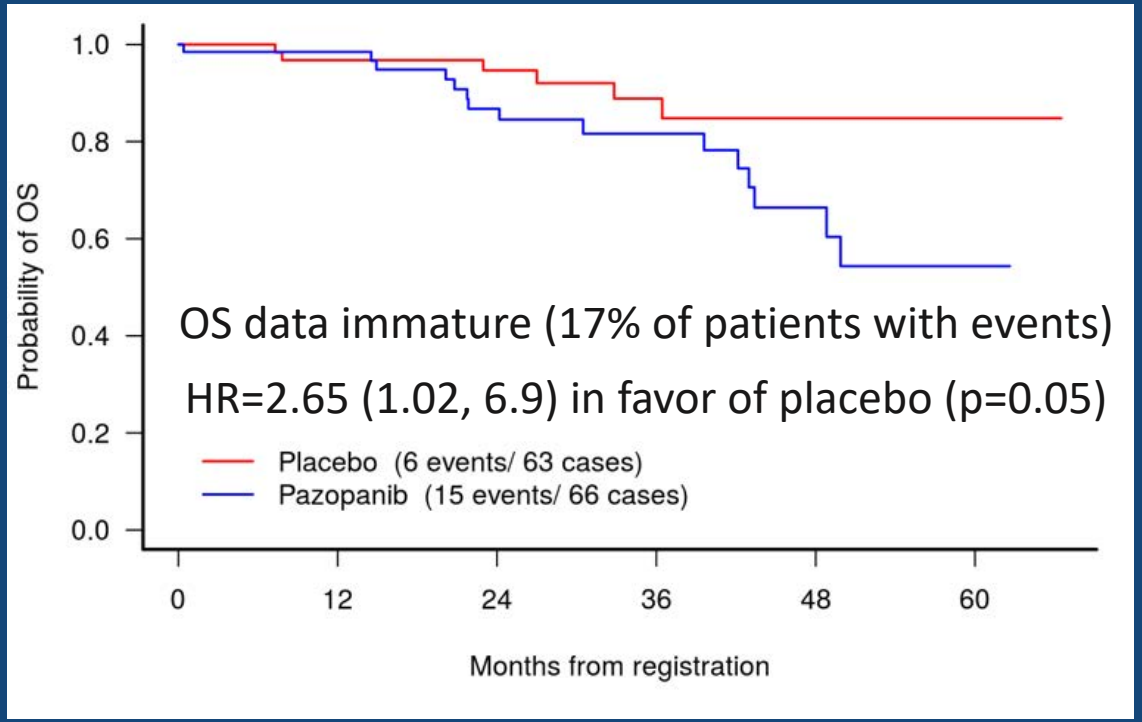
# E2810 Phase III Study

## Disease-Free Survival




Pazopanib did not improve DFS

## Overall Survival




Non-significant trend toward better OS in placebo arm
Given unblinding post-progression, subsequent therapies may have impacted OS

DFS=Disease-free interval; OS=Overall survival; HR=Hazard ratio.

# Conclusions – Abstract 4502

- VEGF targeted therapies have limited impact on micrometastatic disease even in the highest risk individuals and this remains an unmet need for patients

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