Role of neoadjuvant/adjuvant therapy in patients with localized Renal Cell Carcinoma: the PROSPER (EA8143) trial and beyond

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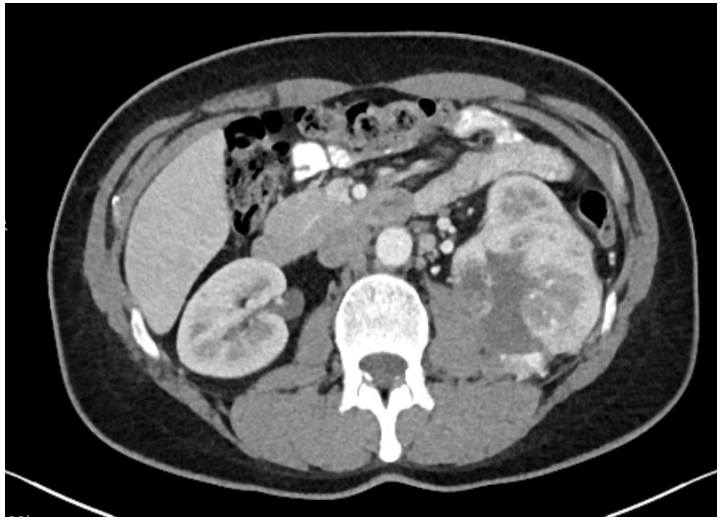
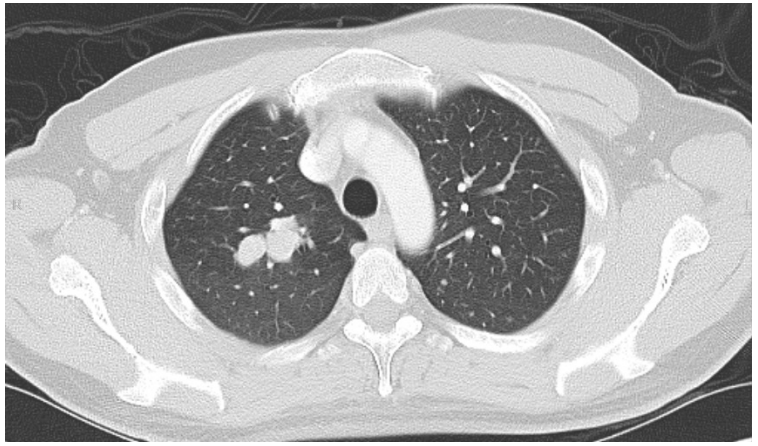
Jackson Hole Seminars 2024

Surgical Monotherapy Fails to Cure a Significant Proportion of Patients with “Localized” RCC



43yo male with 8cm ccRCC

2 years



Multiple lung metastases

Can we alter this outcome?

- Neoadjuvant
  - Control/treat distant disease at earliest time point
  - Shrink tumor to facilitate surgery / organ preservation
  - “Litmus test”
  - Systemic treatment given prior to postoperative recovery / complications
- Adjuvant
  - Treat micrometastatic disease
  - Prevent recurrence
  - Prolong survival

Key: Adjuvant hopes to identify those at highest risk for recurrence and spare lower risk patients toxicity

Neoadjuvant TKIs to Downstage Tumor Thrombus

- Numerous case reports and case series (largest series N=25)
- Different agents used
- ~40% of patients experience decrease in thrombus size
- Rare to change “level” of thrombus or to impact surgical approach (eg avoid sternotomy)
- Toxicity is not insignificant in this high-risk surgical group

Cost et al. Eur Urol, 2011, Bigot et al., World Journal of Urology, 2014

Neoadjuvant TKIs to Facilitate Surgical Resection and PN

- Retrospective series and Phase II trials demonstrating feasibility
- Tumor size reduction ~25%
- PN ~50+%
- How do you determine resectability prior to therapy? A self-fulfilling prophecy in non-randomized studies?

Karam et al., Eur Urol 2014

Rini et al., J Urol 2015

History of Adjuvant Trials in RCC (NEGATIVE)

Author, y	Intervention	Patient Population	N	Outcome[a]
Kjaer,[24] 1987	Radiation	Stages II-III	65	**26-mo survival:** 50%
	Observation			**26-mo survival:** 62%
Pizzocaro,[26] 1987	Medroxyprogesterone	All M0	136	**Relapse:** 32.7%
	Observation			**Relapse:** 33.9%
Galligioni,[33] 1996	Tumor cells + BCG	Stages I-III	120	**DFS:** 63%
	Observation			**DFS:** 72%
Pizzocaro,[28] 2001	IFN-α	T3 N0 M0, T2/3N1-3M0	247	**5-y OS:** 66%
	Placebo			**5-y OS:** 66%
Messing,[29] 2003	IFN-α	T3-4a N0-3 M0	283	**Median survival:** 5.1 y
	Observation			**Median survival:** 7.4 y
Clark,[30] 2003	IL-2	T3b-4 N0 M0, T(any) N1-3 M0	44	**2-y DFS:** 53% **2-y OS:** 86%
	Observation			**2-y DFS:** 48% **2-y OS:** 77%
Wood,[35] 2008	HSPPC-96	T1b-T4 N0 M0, T(any) N1-2 M0	819	**Recurrence:** 37.7%
	Observation			**Recurrence:** 39.8%
ARISER,[39] 2015	Girentuximab 50-mg loading dose followed by 20 mg/wk × 23 wk	pT1b-T2 N0 M0 (grade 3-4), pT3-T4 N0 M0, pT(any) N1 M0	864	**DFS:** HR, 0.99; *P*=.74 **OS:** HR, 1.01; *P*=.94 **DFS (high CA9 expression):** HR, 0.55; *P*=.01
	Placebo			

Patel et al., Clinical Advances in Hematology and Oncology, 2016

Phase III TKI Adjuvant Trials

Trial (sponsor)	Randomization	Duration of therapy (years)	*N*	Start date	End date[a]	Primary endpoint	Clear cell required?	Details
ASSURE (ECOG)	Sunitinib vs. sorafenib vs. placebo	1	1,943	April 2006	September 2010	DFS	No	• Eligibility: pT1bN0M0 (grades 3–4) or pT2-4N1-3M0 RCC • Histology: Any • Cardiac safety substudy reported
ATLAS (Pfizer)	Axitinib vs. placebo	3	592	April 2012	June 2017	DFS	Yes	• Eligibility: pT2-4N0M0 or pTxN1M0 RCC
EVEREST (SWOG)	Everolimus vs. placebo	1	1,218	April 2011	October 2021	DFS	No	• Eligibility: pT1bN0M0 (grades 3–4) or pT2-4N1-3M0 RCC • Histology: Any • Accrual ~50% complete
PROTECT (GSK)	Pazopanib vs. placebo	1	1,500	November 2010	April 2016	DFS	Yes	• Eligibility: pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 RCC
SORCE (MRC)	Sorafenib vs. placebo	3	1,420	June 2007	December 2012	DFS	No	• Eligibility: Intermediate- or high-risk RCC (Leibovich score, 3–11)
S-TRAC (Pfizer)	Sunitinib vs. placebo	1	720	July 2007	November 2015	DFS	Yes	• Eligibility: High-risk RCC (modified UISS criteria) pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 RCC

[a]Study completion date reflects estimated primary completion date cited at http://www.clinicaltrials.gov or actual date of complete enrollment.
Abbreviations: DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; GSK, GlaxoSmithKline; MRC, Medical Research Council; OS, overall survival.

DFS Benefit
OS Negative

Haas et al., *The Lancet* 2016 Ravaud et al., NEJM, 2016

Pal SK, Haas NB. Oncologist 2014;19:851-9.

Adjuvant TKI Therapy: Bottom Line

Brief Correspondence

Updated European Association of Urology Guidelines Regarding Adjuvant Therapy for Renal Cell Carcinoma

Axel Bex[a,], Laurence Albiges[b], Börje Ljungberg[c], Karim Bensalah[d], Saeed Dabestani[e], Rachel H. Giles[f,g], Fabian Hofmann[h], Milan Hora[i], Markus A. Kuczyk[j], Thomas B. Lam[k,l], Lorenzo Marconi[m], Axel S. Merseburger[n], Michael Staehler[o], Alessandro Volpe[p], Thomas Powles[q]*

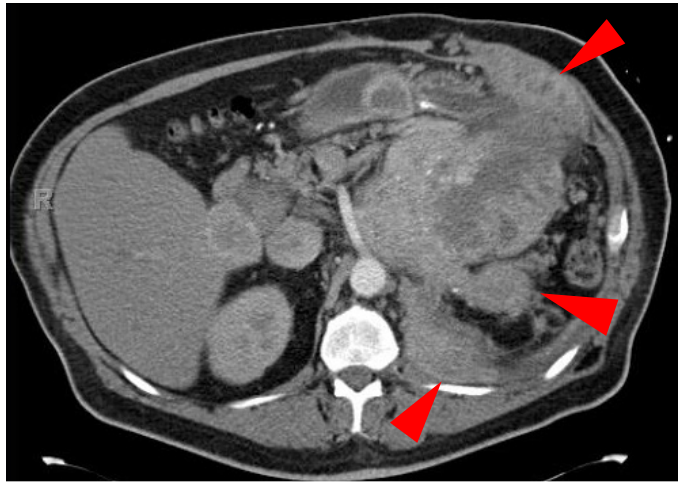
Despite having been diagnosed with high-risk disease, many patients remain without recurrence, and the side effects of sunitinib are high. Therefore, the panel members, including patient representatives, do not recommend sunitinib after tumour removal in these patients.

Adjuvant Sunitinib approved for adjuvant use based on S-TRAC. Positive DFS, Negative OS

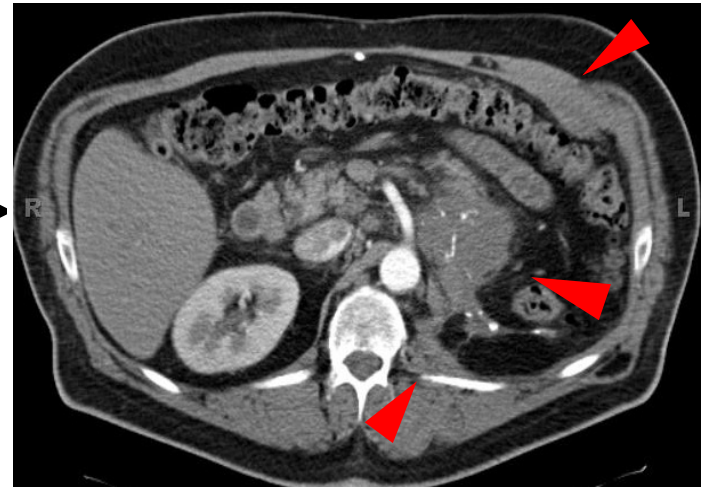
Bex et al., Eur Urol, 2016

Thoughts on Adjuvant TKI Therapy

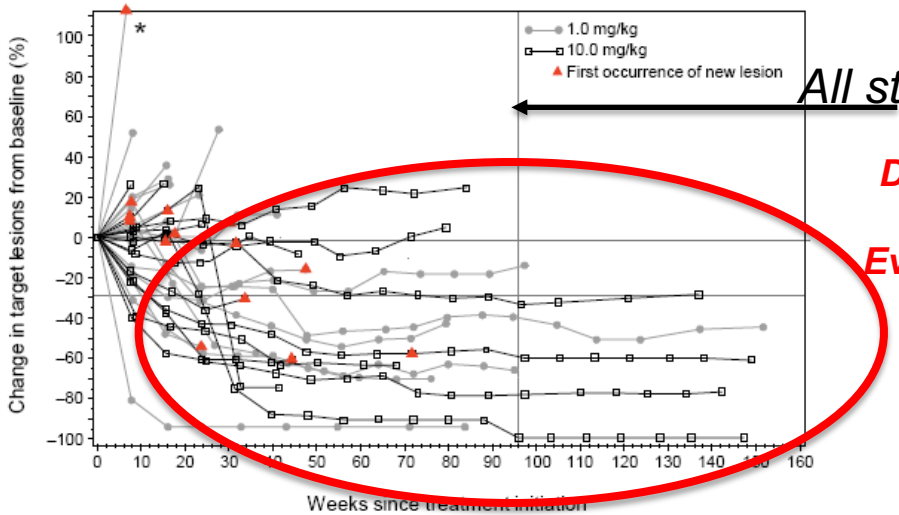
- TKIs are rarely if ever curative in the metastatic setting
- Toxicity is high
- Efficacy of Treatment AFTER Disease Progression May be Worse in Treatment Arms
- Unlike conventional chemotherapy (eg Cisplatin), TKIs are usually given until progression in advanced cancer
- Revascularization occurs in days in animal models when TKI is stopped
- Withdrawal may promote metastases



Pre-Nivolumab

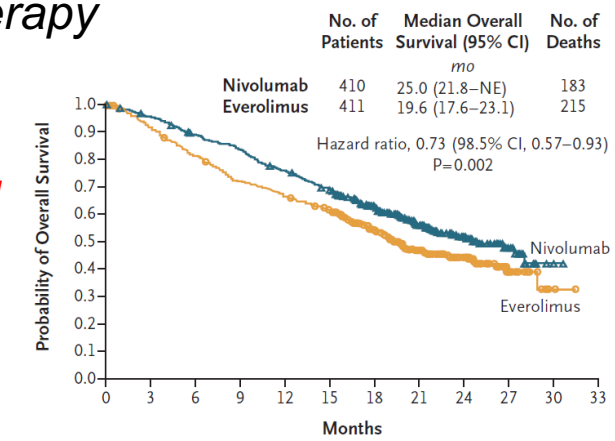


Post-Nivolumab



All stopped therapy

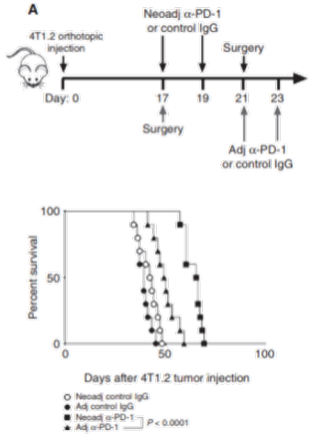
Durability of Response Even Off Drug

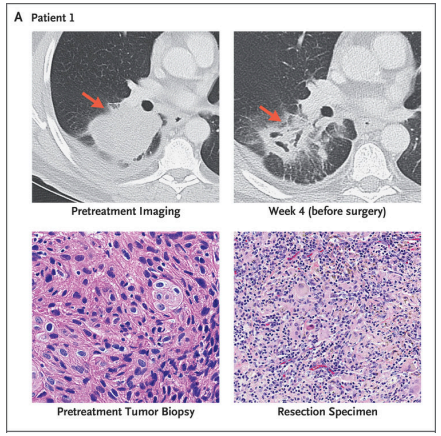


Topalian et al., N Engl J Med 2012; 366:2443-245
Motzer RJ et al., NEJM 2015: 373, 1803
Drake ASCO 2013

Rationale for Neoadjuvant

- “Priming the immune system preoperatively with continued postoperative engagement”



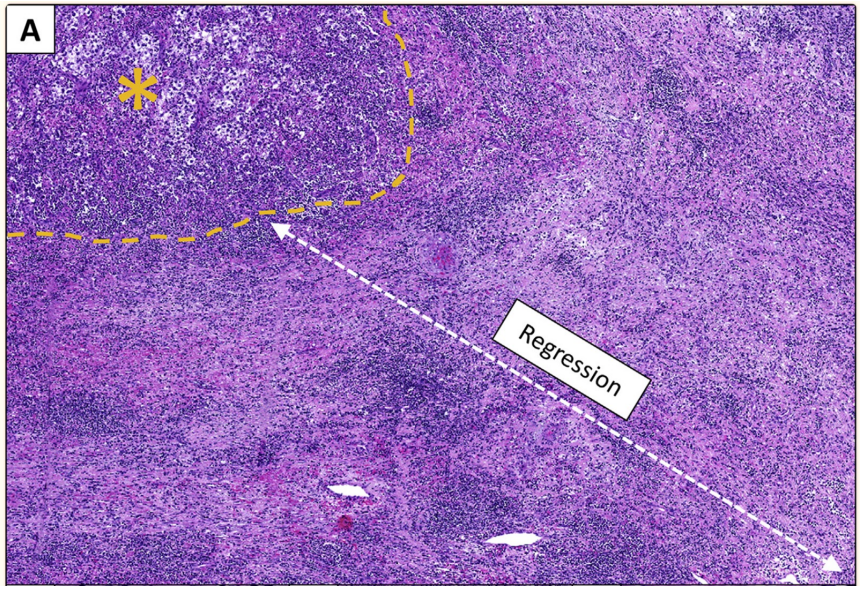


- In Preclinical model: Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease (Liu et al., Cancer Discovery, Dec 2016)
- Neoadjuvant nivolumab in lung, melanoma, and breast with good pathological response (Forde et al., NEJM 2018)

Neoadjuvant Nivolumab in Patients with High-risk Nonmetastatic Renal Cell Carcinoma

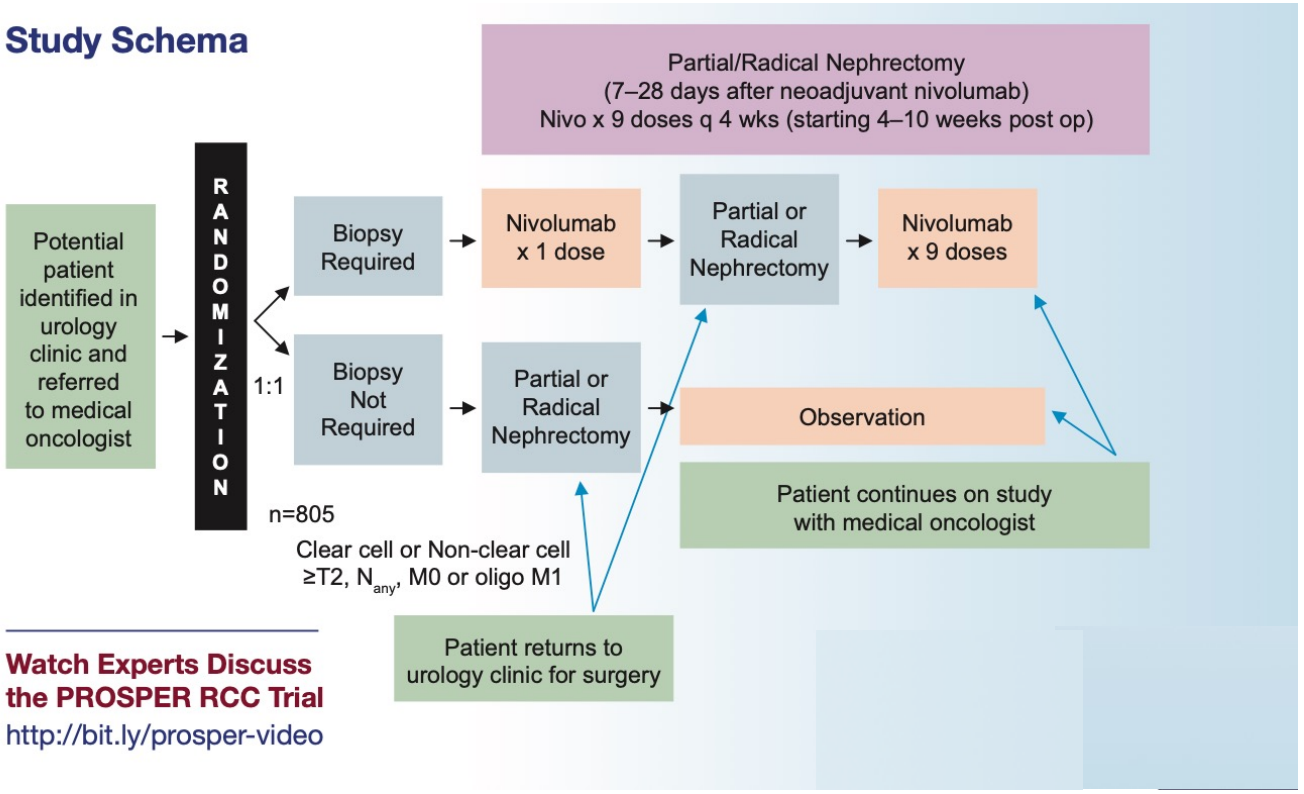
Michael A. Gorin [a b c †], Hiten D. Patel [a †], Steven P. Rowe [a b], Noah M. Hahn [a c], Hans J. Hammers [d], Alice Pons [c e], Bruce J. Trock [a], Phillip M. Pierorazio [a c], Thomas R. Nirschl [c e], Daniela C. Salles [f], Julie E. Stein [f], Tamara L. Lotan [f], Janis M. Taube [e f], Charles G. Drake [g], Mohamad E. Allaf [a c]

- 17 patients, localized “high risk” resectable ccRCC
- 6 neoadjuvant Nivolumab doses
- No safety signal, some efficacy!



Eur Urol Onc 2022

Study Schema (PROSPER)



Study Schema

Key Points

- **Patient Advocates aided in this trial design**
- No placebo given
- Open label study
- Renal mass biopsy mandated in Surgery+Nivo arm
  - Biopsy encouraged in Surgery+Observation arm
  - Non-diagnostic biopsy is considered a good faith effort
- Bilateral renal masses allowed if can be treated at the same time or within 12 weeks
- M1 allowed if resectable at same time or within 12 weeks and patient rendered NED
- Nivolumab dosage = 480mg monthly

Study Design Summary

- **Primary Endpoint:** Recurrence Free Survival (RFS) defined as time from randomization to disease recurrence or death, whichever comes first. *Patients who did not get surgery or were not disease-free post surgery were considered as an event at Day 1.*

- **Secondary Endpoints:** Overall Survival, RFS for clear cell RCC, Safety/Tolerability, Patient Reported Outcomes, Correlative Science

- Study with 84.2% power targeting 11.7% absolute improvement of 5yr RFS
- Accrual Goal=805 patients

Patient Characteristics at Enrollment

- Enrollment based on clinical stage
- ~ 50% of pts cT1/T2
- ~ 15% of pts cN1
- ~ 3% cM1
- ~ 75% pts ECOG PS 0

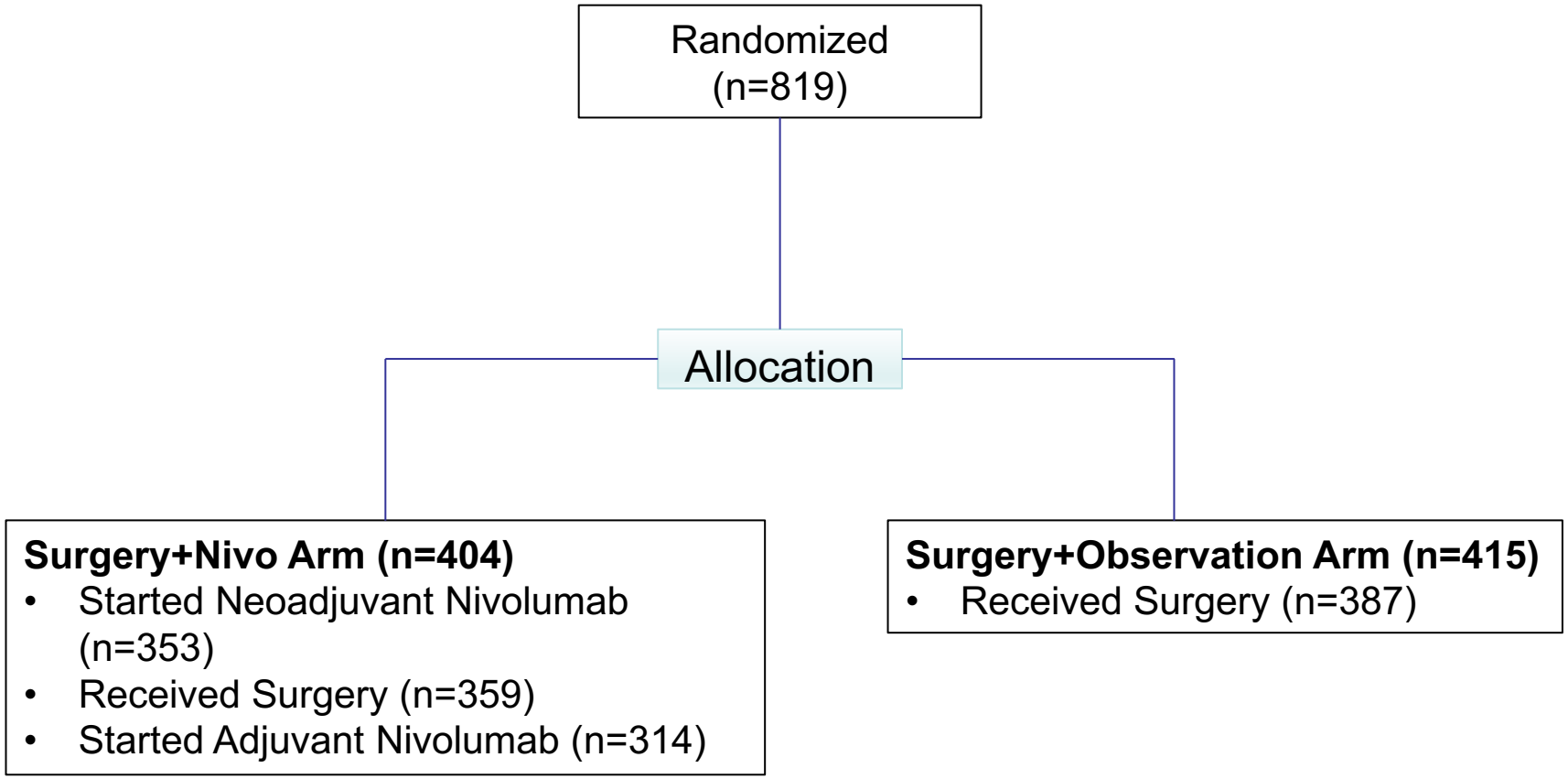
	Surgery+Nivo arm n = 404	Surgery+Observation arm n = 415	Total n = 819
	N (%)	N (%)	N (%)
Age (year)			
Median	60	61	61
Sex			
Female	120 (30)	128 (31)	248 (30)
Race			
Black or African American	31 (8)	30 (8)	61 (8)
White	332 (88)	340 (88)	672 (88)
Clinical T stage			
T1	12 (3)	13 (3)	25 (3)
T2	204 (50)	194 (47)	398 (49)
T3 or T4	186 (46)	208 (50)	394 (48)
Clinical N stage			
Nx/N0	342 (85)	355 (86)	697 (85)
N1	62 (15)	59 (14)	121 (15)
Clinical M stage			
Mx/M0	391 (97)	399 (96)	790 (97)
M1	12 (3)	15 (4)	27 (3)
ECOG PS			
0	289 (76)	312 (77)	601 (77)
1	89 (24)	95 (23)	184 (23)

Patient Characteristics Post Surgery

- >60% had pT3/T4 tumors
- >60% had high grade tumors
- ~80% had clear cell RCC
- ~ 5% in each group underwent partial nephrectomy
- ~3% of RCC patients that had surgery were not disease-free post surgery
- ~ 5% were non-RCC cases that were excluded from the primary analysis

	Surgery+Nivo arm n = 404	Surgery+Observation arm n = 415	Total n = 819
	N (%)	N (%)	N (%)
Pathologic T-stage			
T1	35 (10)	42 (11)	77 (10)
T2	83 (24)	81 (21)	164 (22)
T3 or T4	233 (66)	261 (68)	494 (67)
Pathologic N-stage			
Nx/N0	316 (90)	355 (92)	671 (91)
N1	36 (10)	30 (8)	66 (9)
Pathologic M-stage			
Mx/M0	340 (97)	368 (96)	708 (96)
M1	12 (3)	16 (4)	28 (4)
Surgery Type			
Radical	344 (96)	375 (95)	719 (95)
Surgery Histology			
Clear cell	278 (78)	306 (77)	584 (77)
Papillary	27 (8)	20 (5)	47 (6)
Chromophobe	24 (7)	21 (5)	45 (6)
Sarcomatoid features			
Yes	30 (8)	49 (12)	79 (11)
Fuhrman grade			
1	14 (4)	10 (3)	24 (4)
2	89 (28)	96 (27)	185 (28)
3	136 (42)	146 (41)	282 (42)
4	81 (25)	100 (28)	181 (27)

Enrollment


Randomized
(n=819)
Allocation
Surgery+Nivo Arm (n=404)
• Started Neoadjuvant Nivolumab (n=353)
• Received Surgery (n=359)
• Started Adjuvant Nivolumab (n=314)
Surgery+Observation Arm (n=415)
• Received Surgery (n=387)

Interim Analysis for Futility

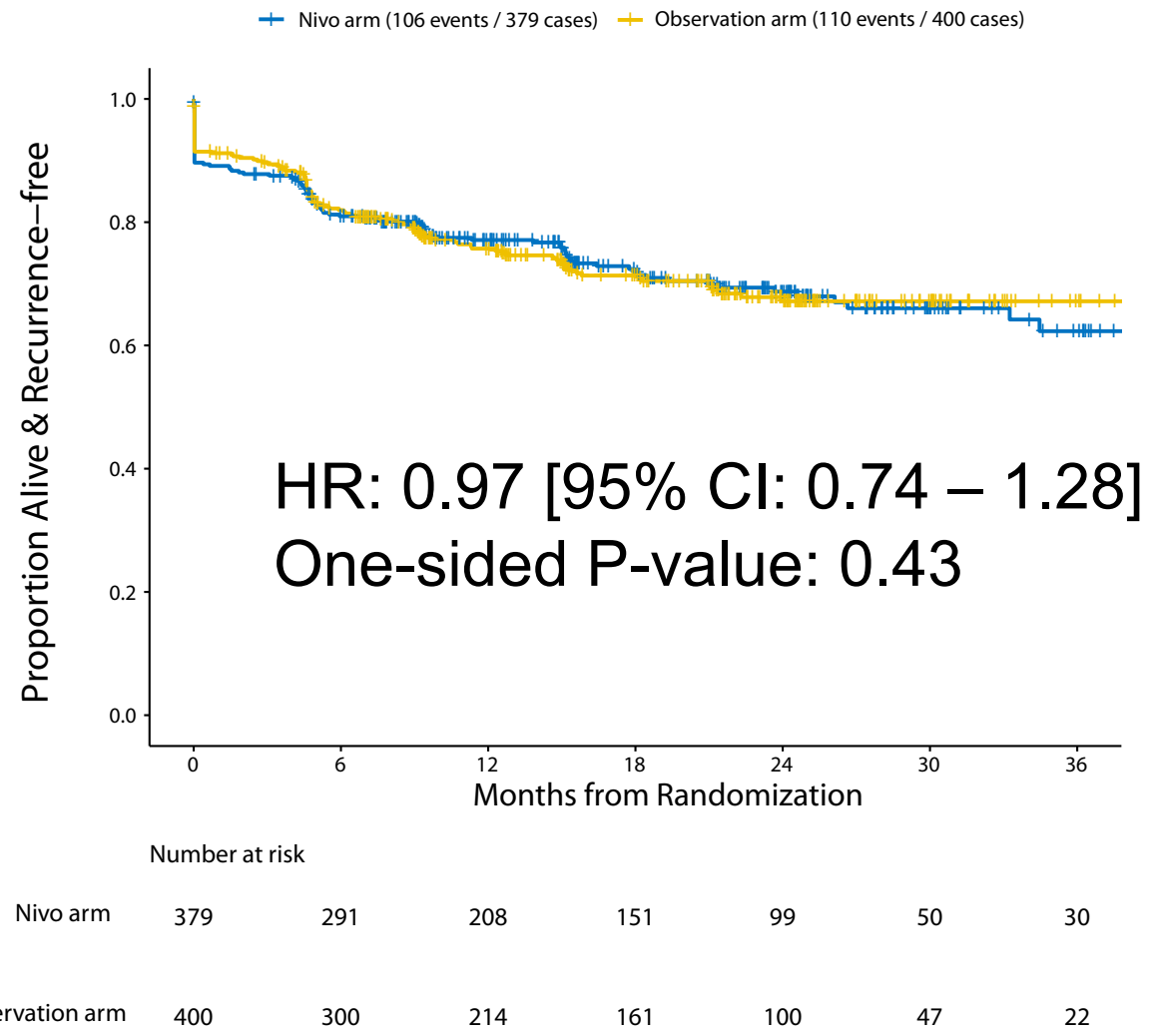
ECOG-ACRIN Data Safety Monitoring Committee (DMSC)

- Full information: 209 follow-up events
- Analyses timepoints are follow-up event driven (only counting recurrences and deaths)
  - Efficacy analyses planned at 65%, 85%, 100% information time
  - Inefficacy/futility interim analyses planned to start at 44% information and then again every time there is an increase in at least 10% of information
- **At 71.8% information time, inefficacy analysis results were presented to DMSC and recommendation was to release result for futility (stratified hazard ratio for RFS exceeded threshold of 0.96)**

Interim Analysis for Futility: No Difference in RFS

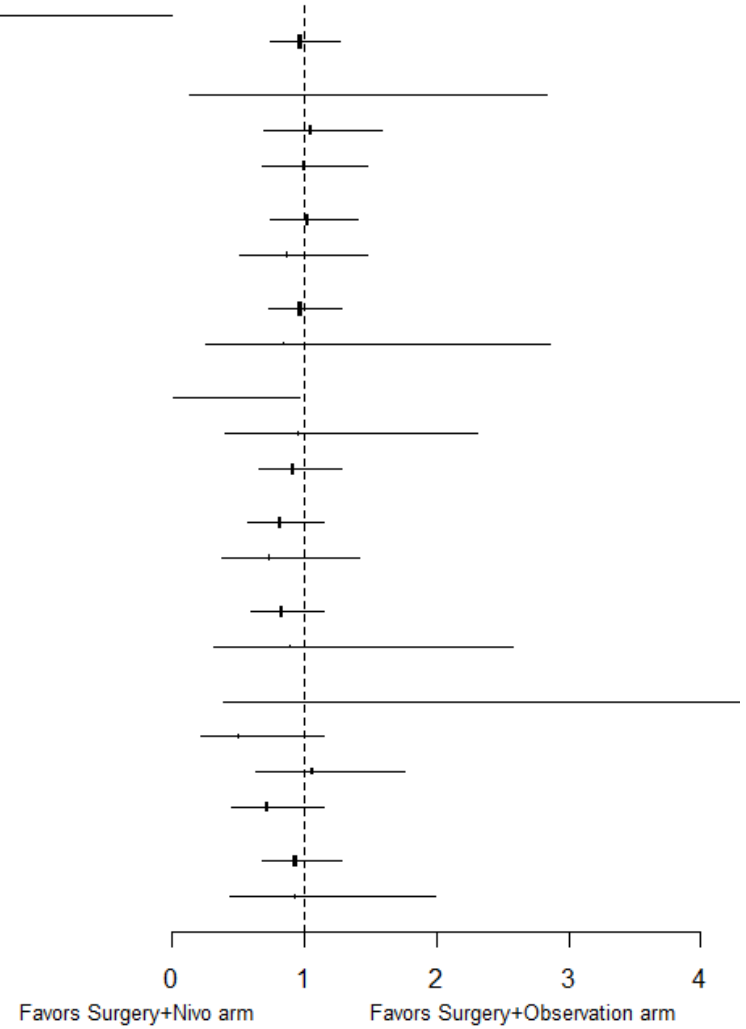
- At interim analysis, DSMC stopped trial for inefficacy
- Median Follow-up=16months
- No difference in RFS between arms
- OS data not mature

- **Conditional power for primary and sensitivity analyses <30%**
- **Trial was quickly approaching full-information when this decision was made (71.8% information)**



Forest Plot of RFS According to Subgroup

Sub-group	N	HR	95% CI
All RCC Patients	779	0.97	(0.74, 1.27)
cT1	25	0.61	(0.13, 2.83)
cT2	398	1.05	(0.69, 1.59)
cT3 or cT4	394	1.00	(0.68, 1.47)
cNx or cN0	697	1.02	(0.74, 1.40)
cN1	121	0.87	(0.51, 1.47)
cMx or cM0	790	0.97	(0.73, 1.28)
cM1	27	0.85	(0.25, 2.86)
pTx or pT1	79	0.12	(0.01, 0.96)
pT2	164	0.96	(0.40, 2.31)
pT3 or pT4	494	0.91	(0.65, 1.28)
pNx or pN0	671	0.81	(0.57, 1.14)
pN1	66	0.73	(0.37, 1.41)
pMx or pM0	708	0.83	(0.60, 1.14)
pM1	28	0.89	(0.31, 2.57)
Fuhrman Grade 1	24	3.37	(0.38, 30.18)
Fuhrman Grade 2	185	0.50	(0.21, 1.15)
Fuhrman Grade 3	282	1.06	(0.63, 1.76)
Fuhrman Grade 4	181	0.72	(0.45, 1.14)
Clear-cell	625	0.93	(0.68, 1.28)
Non-clear cell	128	0.93	(0.44, 1.99)



Adverse Events

- More AEs in Nivolumab Arm

Event	Surgery+Nivo arm n = 356	Surgery+Observation arm n = 387
	no. of patients with event (%)	
Any-cause adverse events		
Adverse event of any grade	332 (93)	230 (59)
Adverse event of grade 3-4 as the highest grade**	118 (33)	51 (13)
Discontinuation of treatment due to any grade adverse event	51 (14)	N/A
Adverse event of grade 5	14 (4)	10 (3)
Treatment-related adverse events, as assessed by investigator		
Adverse event of any grade	276 (78)	103 (27)
Adverse event of grade 3-4 as the highest grade**	54 (15)	16 (4)
Discontinuation of treatment due to any grade adverse event	46 (13)	N/A
Adverse event of grade	9 (3)	4 (1)

** = Statistically different between the two arms using the Fishers exact test

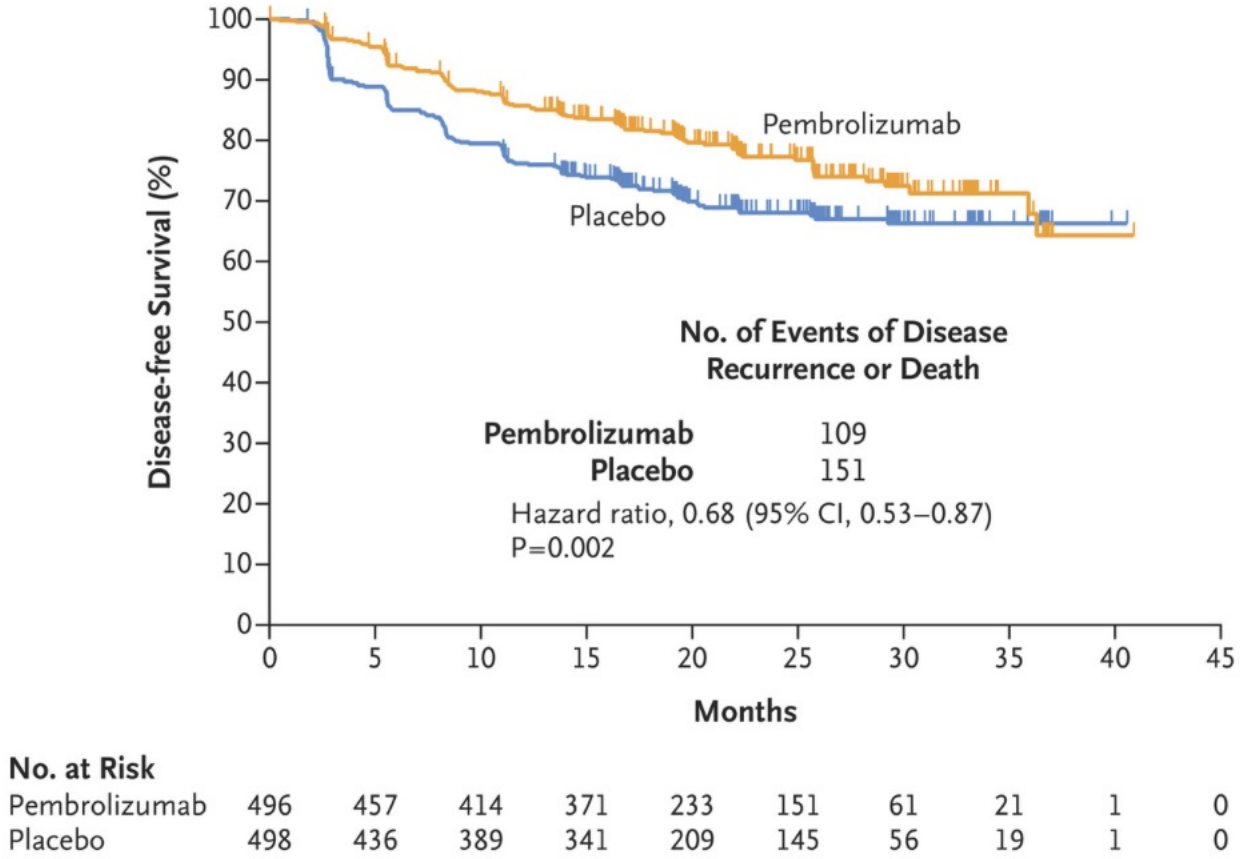
Grade 5 events: Acute kidney injury, cardiac arrest, cardiac disorder, death, injury to inferior vena cava, myasthenia gravis, progressive disease, respiratory failure, stroke

PROSPER Conclusions

- This is the first phase III neoadjuvant IO trial in renal cell carcinoma
- Perioperative nivolumab did not improve RFS in patients with renal cell carcinoma at high risk for recurrence
- Adverse events in the surgery+nivolumab arm were consistent with toxicity profile in other nivolumab trials
- Ongoing radiomic, pathomic and other biomarker analyses within this trial may inform the design of future neoadjuvant renal cell carcinoma trials
- Further analysis of patient subsets within this unique trial design should help inform future research

	EA8143 PROSPER RCC Nivo vs. **Observation**[5]	IMmotion010 Atezo vs. **Placebo**[6]	KEYNOTE-564 Pembro vs. **Placebo**[7]
Recurrence Assessment	Investigator	Central	Investigator
Metastatectomy	YES	YES	YES
Allow non-clear cell RCC	YES (15%)	NO (Sarcomatoid with any subtype)	NO (Sarcomatoid)
Intravenous Placebo?	**NO (Observation)**	**YES**	**YES**
Risk Group	High Risk	Higher Risk	Higher Risk
Neoadjuvant?	**YES**	**NO**	**NO**
Preoperative Biopsy	YES	NO	NO

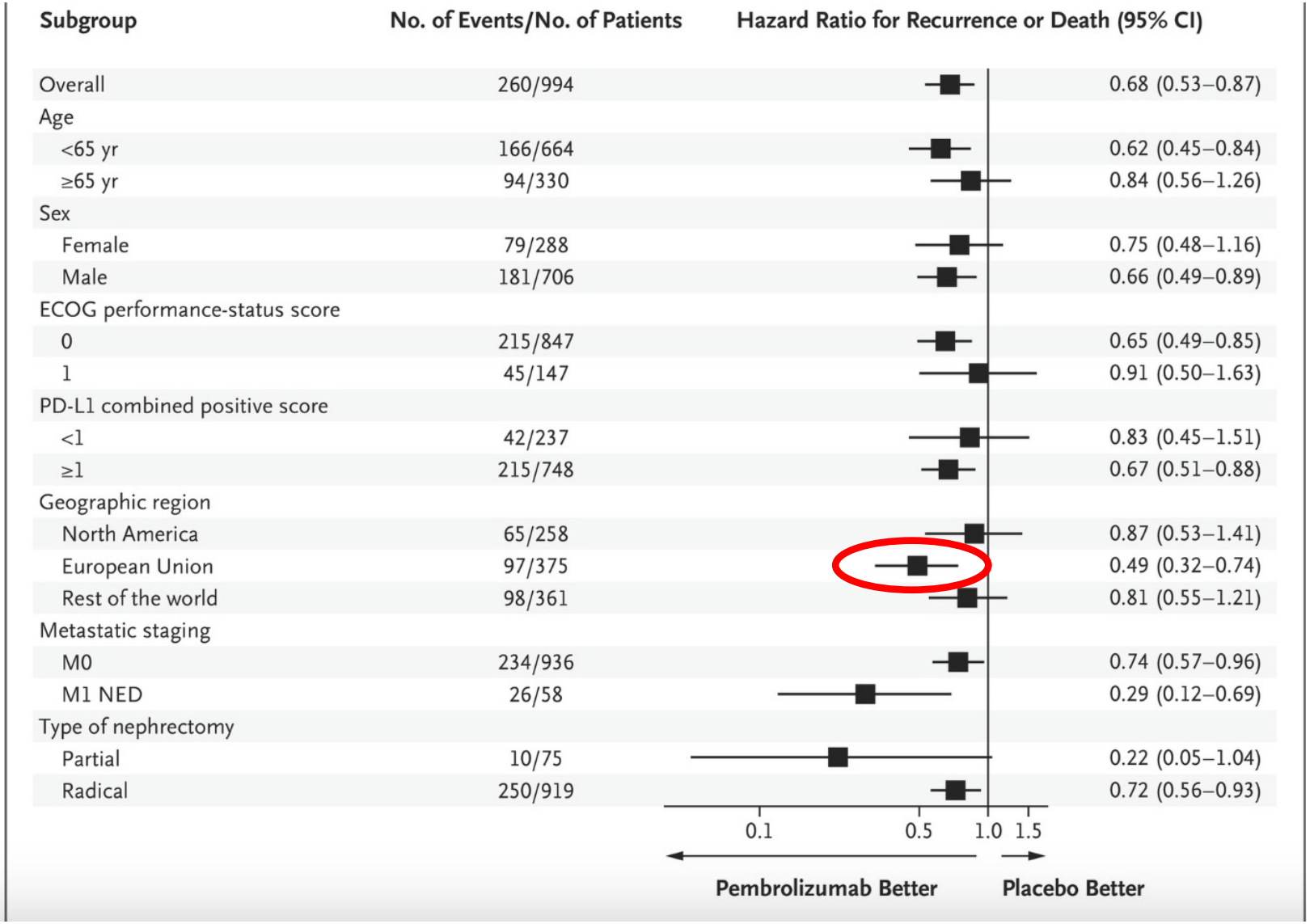
Checkmate-914
Ipi/Nivo vs. Placebo



November 2021
FDA Approved for adjuvant therapy for those with intermediat—high or high risk for recurrence

November 2023
Press Release

KEYTRUDA® (pembrolizumab) Significantly Improved Overall Survival (OS) Versus Placebo as Adjuvant Therapy for Certain Patients With Renal Cell Carcinoma (RCC) Following Nephrectomy


Subgroup
No. of Events/No. of Patients
Hazard Ratio for Recurrence or Death (95% CI)
Overall 260/994 0.68 (0.53–0.87)
Age
<65 yr 166/664 0.62 (0.45–0.84)
≥65 yr 94/330 0.84 (0.56–1.26)
Sex
Female 79/288 0.75 (0.48–1.16)
Male 181/706 0.66 (0.49–0.89)
ECOG performance-status score
0 215/847 0.65 (0.49–0.85)
1 45/147 0.91 (0.50–1.63)
PD-L1 combined positive score
<1 42/237 0.83 (0.45–1.51)
≥1 215/748 0.67 (0.51–0.88)
Geographic region
North America 65/258 0.87 (0.53–1.41)
European Union 97/375 0.49 (0.32–0.74)
Rest of the world 98/361 0.81 (0.55–1.21)
Metastatic staging
M0 234/936 0.74 (0.57–0.96)
M1 NED 26/58 0.29 (0.12–0.69)
Type of nephrectomy
Partial 10/75 0.22 (0.05–1.04)
Radical 250/919 0.72 (0.56–0.93)
0.1
0.5
1.0
1.5
Pembrolizumab Better
Placebo Better

Ongoing Trials

LITESPARK 002
Belzutifan + Pembro vs. **Pembro**

N=1600

RAMPART
Durvalumab vs. Durvalumab + Tremelimumab vs. Placebo

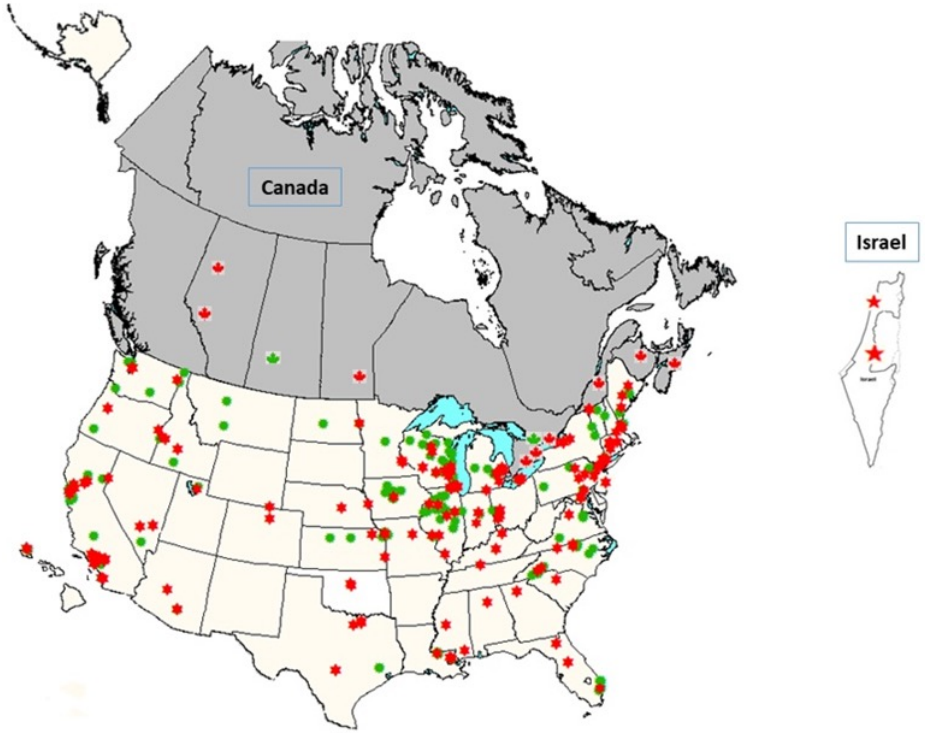
N=1700

Conclusions

- Sunitinib and Pembrolizumab are both FDA approved in the adjuvant setting
- Pembrolizumab first agent to demonstrate DFS and OS benefit
- Unclear why Keynote-564 was positive and all other trials negative
- Neoadjuvant therapy trials are feasible and safe
- Additional trials and correlative work in progress to help move the field forward

Participating Sites and Acknowledgements

JOHNS HOPKINS MEDICINE



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SUO-CTC and a number of AAGUS members

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ECOG-ACRIN cancer research group

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