Optimal first line therapy for non-clear cell kidney cancer variants

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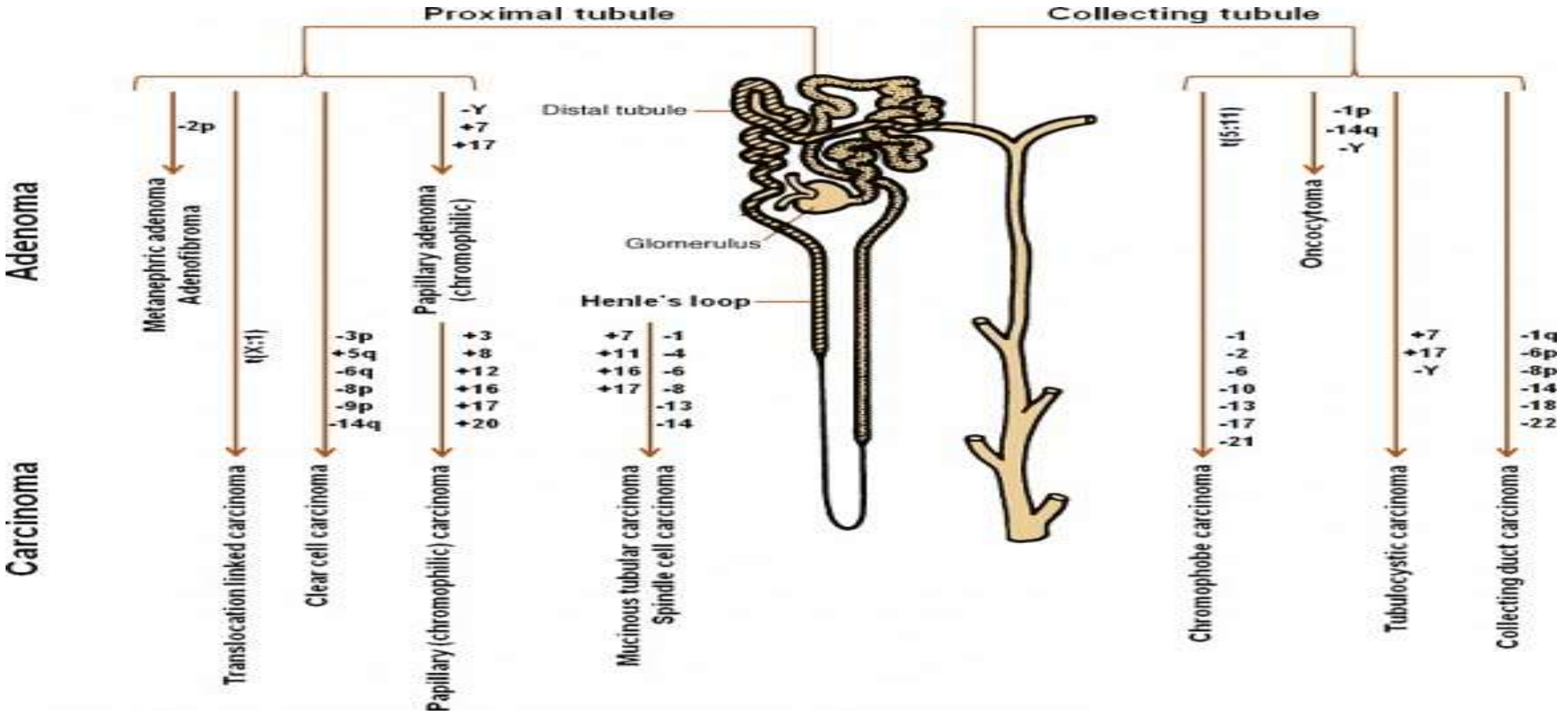
NCI Designated Comprehensive Cancer Center

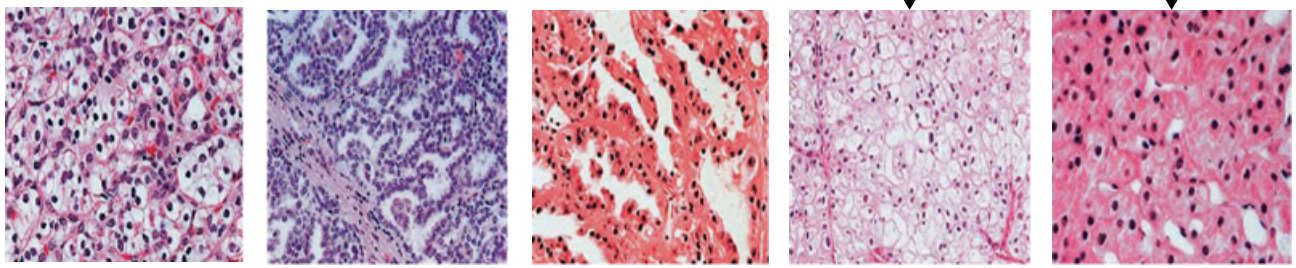
Non-clear cell RCC

Uniquely distinct subtypes (biology, morphology, clinical behavior)



Oosterwijk, Eur Urol 2011

Kidney cancer is not a single disease

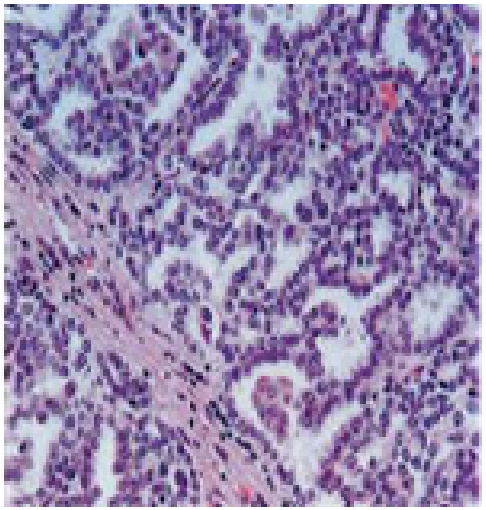


	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
	75%	*5%*	*10%*	*5%*	*5%*
	VHL	*MET*	*FH*	*FLCN*	*FLCN*
Sporadic mutations	***VHL (89%)***	*MET (13%)*	*TBD*	*TBD*	*TBD*

FLCN= folliculin; BHD= Birt-Hogg-Dubé; FH = fumarate hydratase; MET = mesenchymal epithelial transition factor; VHL = von Hippel-Lindau.

Pfaffenroth, et al. *Expert Opin Biol Ther.* 2008; Linehan, *Semin Cancer Biol* 2012

Papillary RCC



- Represents 5-15% of RCC
  - Histologic subtypes: I and II
  - Type II more common than Type I
  - Type II more likely to metastasize
- Type I resembles a hereditary form of kidney cancer
  - Germline activating mutation in *MET*
  - Somatic *MET* mutations found in 5-13%
- Trisomy 7 (*MET*) and 17 (*MET ligand HGF*) common in both type I and II tumors
- High MET protein expression common for both subtypes
- MET mRNA expression higher for pRCC type I and II (vs. clear cell)

Schmidt, L., Oncogene 1999; Albiges CCR 2014.

Med Oncol (2009) 26:202–209
DOI 10.1007/s12032-009-9177-0

ORIGINAL PAPER

Effect of temsirolimus versus interferon-α on outcome of patients with advanced renal cell carcinoma of different tumor histologies

Overall Survival

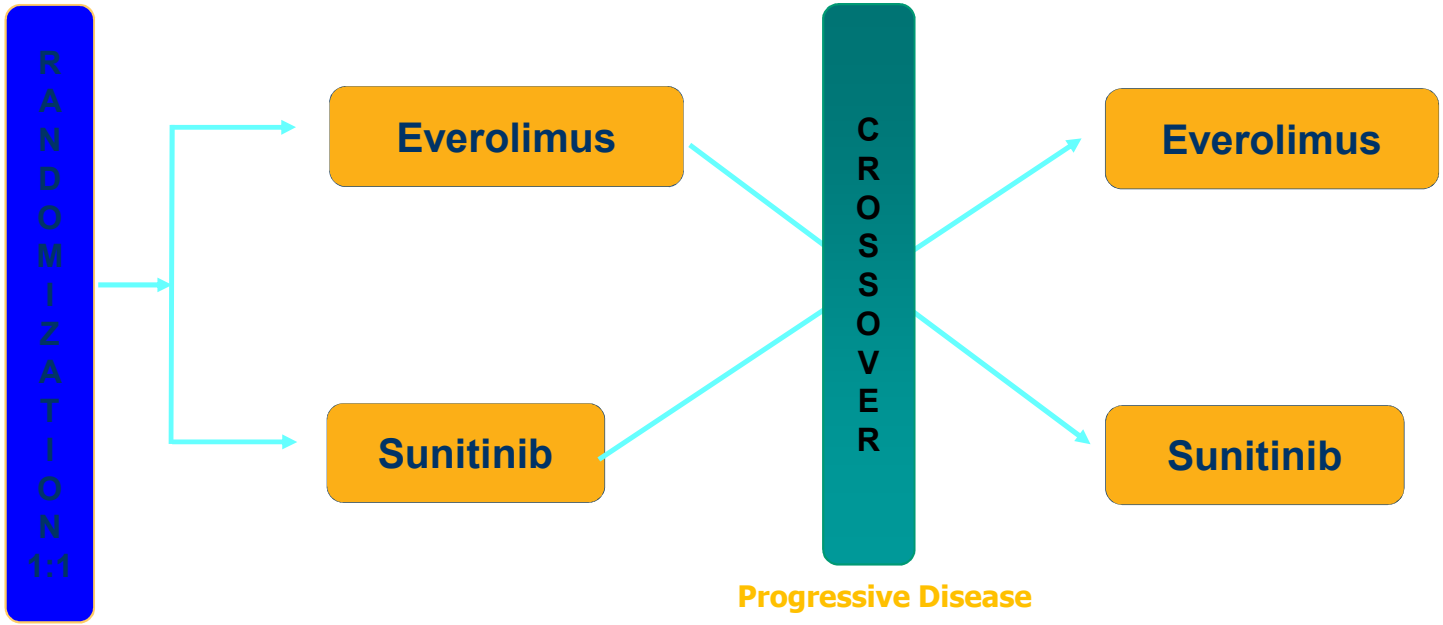
Histology type	Temsirolimus versus IFN[b]	
	Hazard ratio	95% CI[a]
Primary cell type		
Clear cell	0.82	0.64, 1.06
Other	0.49	0.29, 0.85
Papillary subtype		
Contains	0.50	0.27, 0.94
Does not	0.80	0.63, 1.03

Dutcher, et al., 2009

Everolimus versus Sunitinib Prospective Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma (The ESPN Trial)

ELGIBILITY CRITERIA:
Histology
- Papillary
- Chromophobe
- Unclassified
- Translocation
- Clear-cell w/ ≥ 20% sarcomatoid

•PS 0/1
•Measurable disease
•Adequate organ function
•No prior systemic therapy
•No uncontrolled brain metastasis



Stratification:
1. **MSKCC risk group**
2. **Papillary vs other**

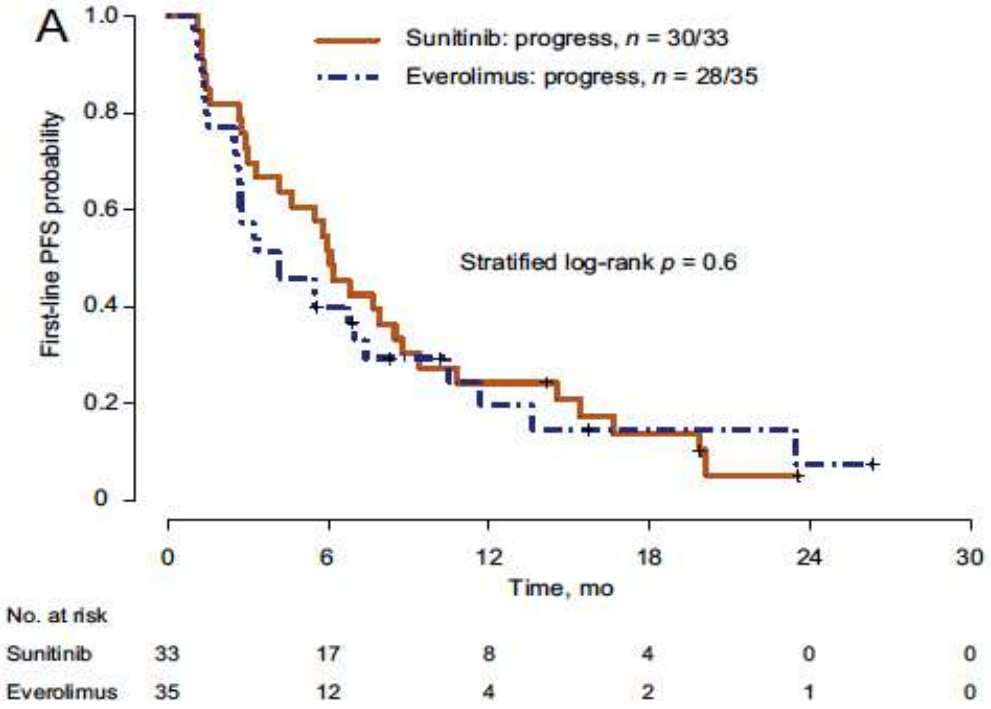
N=108 (68 accrued before closure); One-sided type I error 0.05, 80% power; improvement of median PFS from 12 weeks with sunitinib to 20 weeks with everolimus

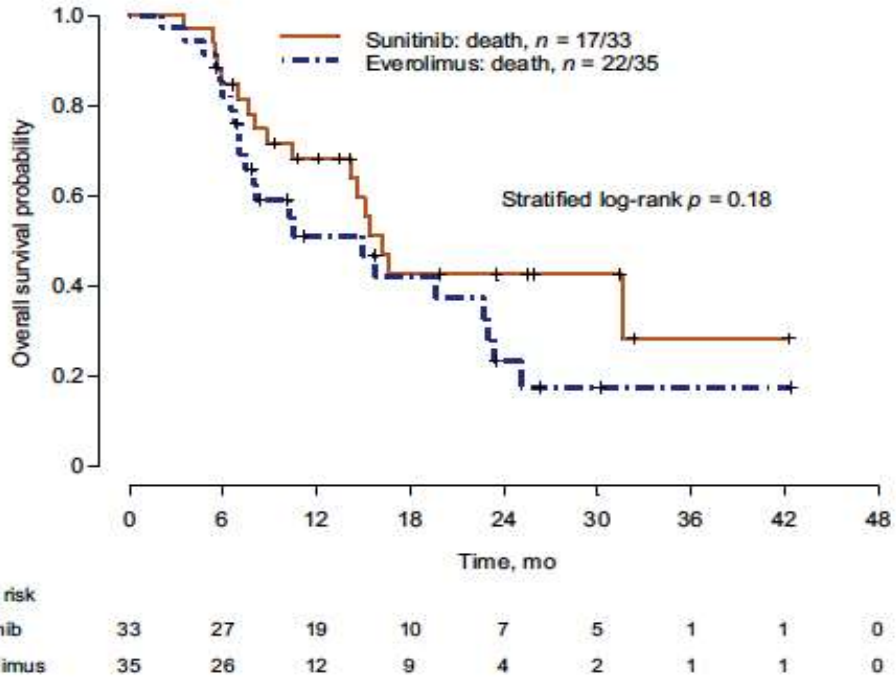
Tannir, Eur Urol 2016

Patient Characteristics (N=68)

	Everolimus n=35	Sunitinib n=33	P-value
Age (median, range)	58 (23-73)	60 (28-76)	0.72
Gender (M:F)	24:11	19:14	
Race Caucasian Hispanic Black	 28 3 2	 25 5 3	0.59
Nephrectomy	27	25	1.0
Histology **Papillary** **cc Sarcomatoid** **Chromophobe** **Unclassified** **Xp11.2**	 **13** **6** **6** **6** **4**	 **14** **6** **6** **4** **3**	**0.97**
ECOG Performance Status 0 1	 15 20	 18 15	

PFS and OS: First-line setting





Tannir, Eur Urol 2016

Exploratory Analysis: OS and PFS by Histology

Table 2 – Overall survival and first-line progression-free survival by treatment arm and histologic subtype

Subtype	Everolimus			Sunitinib		
	n	Median OS, mo (95% CI)	Median PFS, mo (95% CI)	*n*	Median OS, mo (95% CI)	Median PFS, mo (95% CI)
Papillary	13	14.9 (7.1–22.7)	4.1 (1.5–7.4)	14	16.6 (5.9–NA)	5.7 (1.4–19.8)
Chromophobe	6	25.1 (4.7–NA)	NA	6	31.6 (14.2–NA)	8.9 (2.9–20.1)
Unclassified	6	NA	4.7 (2.6–NA)	4	15.4 (NA)	9.4 (3.3–15.4)
Translocation	4	8.1 (5.5–23)	3.0 (1.3–NA)	3	16.2 (8.8–NA)	6.1 (6.0–8.8)
Clear cell with >20% sarcomatoid features	6	11.1 (2.0–NA)	1.9 (1.0–23.4)	6	7.0 (5.4–10.4)	3.5 (1.3–7.7)

CI = confidence interval; NA = not assessable; OS = overall survival; PFS = progression-free survival.

In pRCC, outcomes with sunitinib are numerically superior

Tannir, Eur Urol 2016

ASPEN Trial Schema

NCT01108445

18 global sites: 10 USA, 5 UK, 3 in Canada

Metastatic RCC

- Non-clear cell pathology: papillary, chromophobe, unclassified
- No prior therapy
- Measurable disease

Stratified by Histology, MSKCC Risk Group

n=108

RANDOMIZE

Everolimus 10 mg orally once daily
Days 1-42
Cycle = 6 weeks

Sunitinib 50 mg orally
Days 1-28
Cycle = 6 weeks

Radiographic PFS Primary Endpoint

No planned crossover

Duke Cancer Institute was coordinating center and central biorepository for this multinational randomized open label trial, monitoring by inVentiv Health clinical

PRESENTED AT: ASCO Annual '15 Meeting

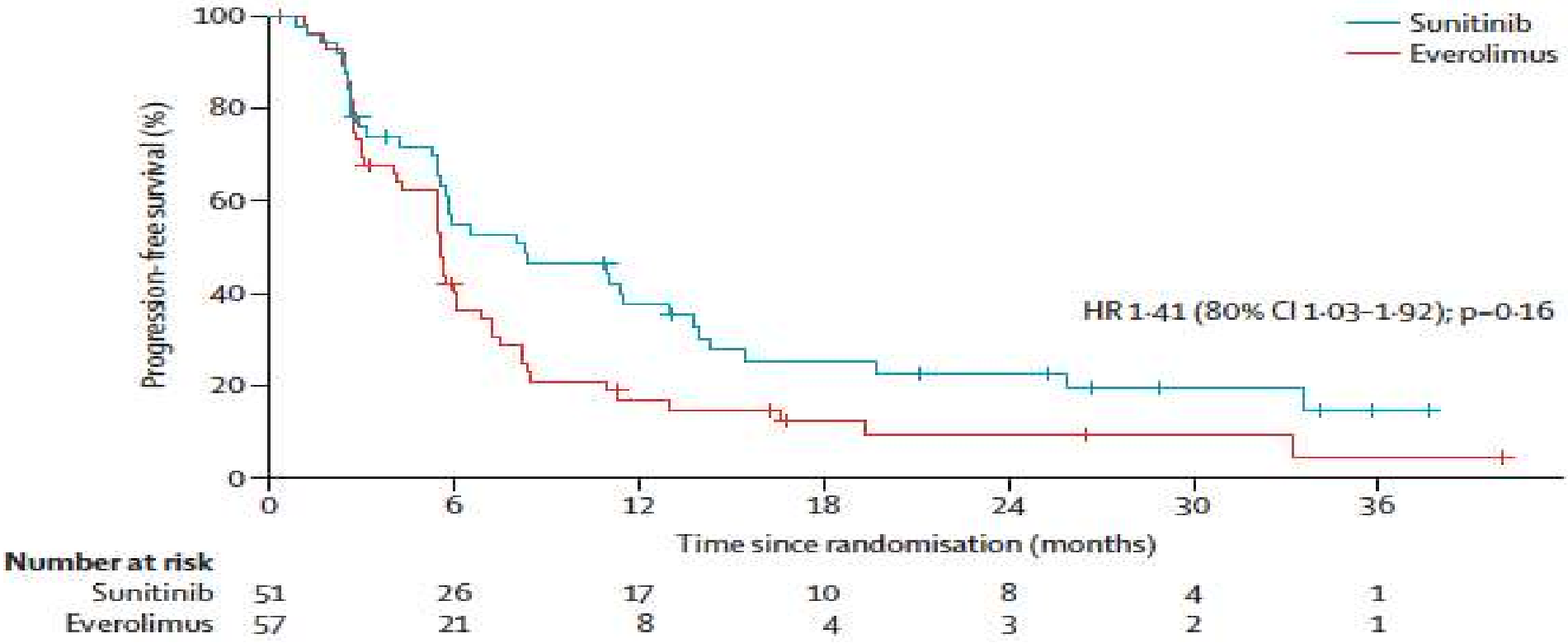
Armstrong, et al. Lancet Oncol 2016

Presented By Andrew Armstrong at 2015 ASCO Annual Meeting

Baseline Characteristics

Characteristic	Sunitinib (n=51)	Everolimus (n=57)
Years of age, median (range)	59 (24-100)	64 (29-90)
Gender (male %)	73	77
Race, Caucasian [white/black %]	82/14	91/9
Papillary histology, n (%)	65	65
type 1 papillary, n (%)	8	4
Chromophobe, n (%)	20	11
Unclassified histology, n (%)	16	23
Translocation carcinoma, n (%)	12	4
Sarcomatoid differentiation (%)	11	27
Prior nephrectomy (%)	80	79
Elevated LDH (%)	27	25
Liver/lung/bone metastases, (%)	31 / 59 / 24	26 / 44 / 26
MSKCC Risk Group (%)		
0	29	25
1-2	63	56
≥ 3	8	19

Primary Endpoint: PFS

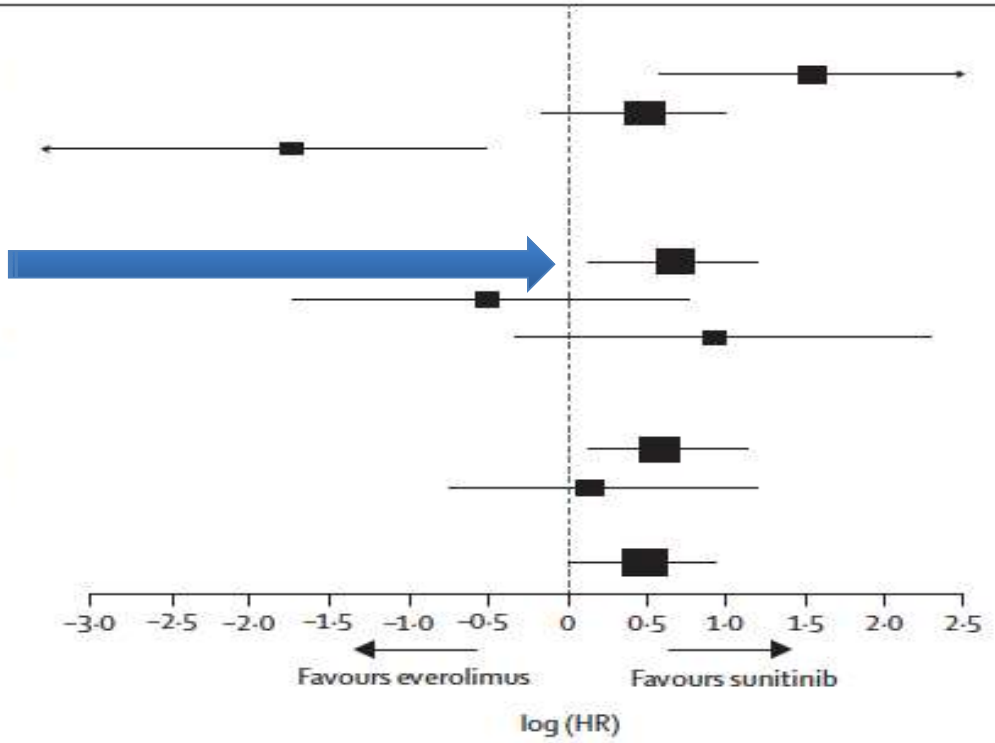


Armstrong, et al. Lancet Oncol 2016

Forest Plot: ASPEN trial

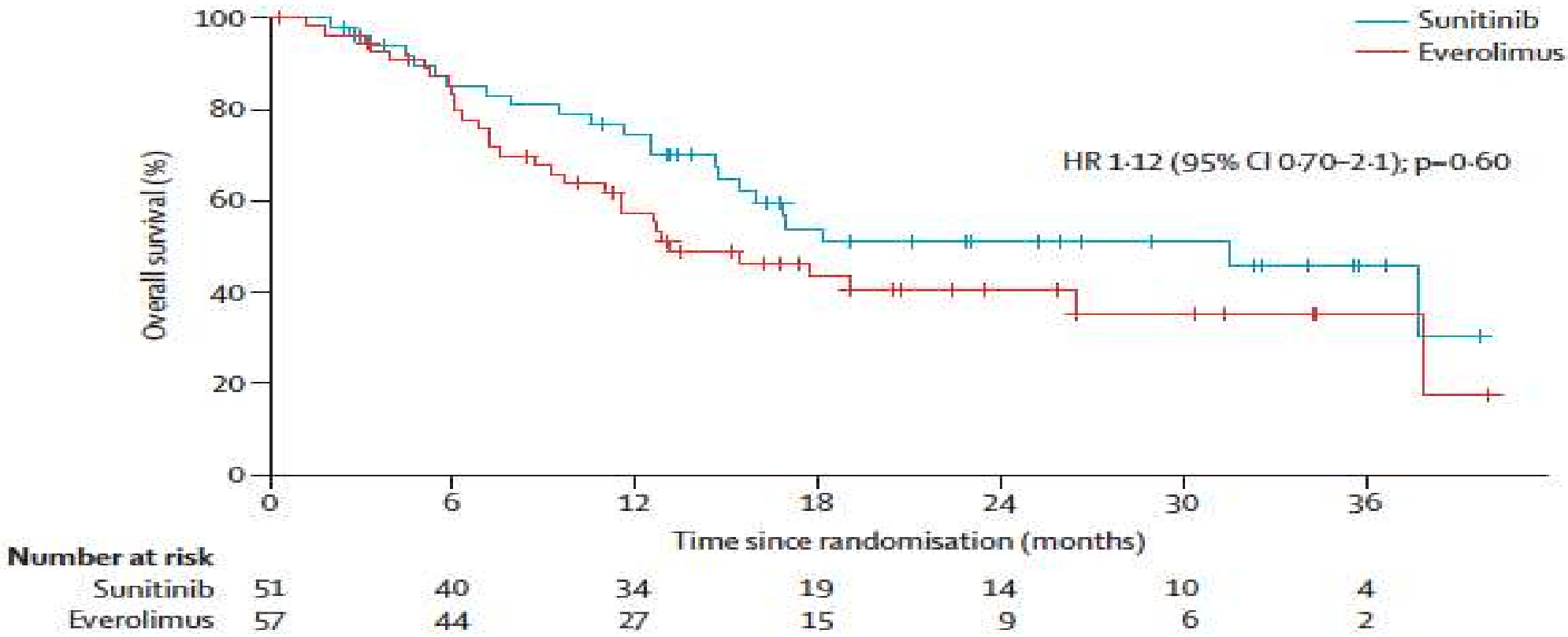
In pRCC, sunitinib superior to everolimus

	Events/ patients	Median progression-free survival (months; 80% CI)		Hazard ratio (80% CI)
		Sunitinib	Everolimus	
MSKCC risk group				
Good	21/29	14 (11·5–19·7)	5·7 (5·6–8·4)	2·9 (1·5–5·7)
Intermediate	51/64	6·5 (5·7–11·0)	4·9 (3·0–5·6)	1·4 (0·9–2·0)
Poor	15/15	4·0 (0·9–5·8)	6·1 (3·1–7·3)	0·3 (0·1–0·7)
Histology				
Papillary	60/70	8·1 (5·8–11·1)	5·5 (4·4–5·6)	1·6 (1·1–2·3)
Chromophobe	12/16	5·5 (3·2–19·7)	11·4 (5·7–19·4)	0·7 (0·3–1·7)
Unclassified	15/22	11·5 (5·3–not reached)	5·7 (2·8–7·2)	1·9 (0·8–4·9)
Baseline LDH				
≤ULN	62/75	8·4 (5·8–13·0)	5·6 (5·5–6·1)	1·5 (1·1–2·2)
>ULN	19/26	5·8 (3·2–15·4)	4·1 (2·6–6·0)	1·1 (0·6–2·3)
Total	87/108	8·3 (5·8–11·4)	5·6 (5·5–6·0)	1·4 (1·0–1·9)



Armstrong, et al. Lancet Oncol 2016

Key Secondary Endpoint: OS



Summary: Sunitinib in non-clear cell RCC

Study	N	Response Rate	PFS, months	Tumor types included
Tannir	57	5%	2.7	Papillary (n=27) and other non-clear cell types (n=30)
Lee	31	36%	6.4	All nccRCC except collecting duct
Molina	23	5%	5.5	Included 8 papillary, 5 unclassified
Ravaud	61	13% 11%	6.6 5.5	Type I papillary (n=15) Type II papillary (n=46)
ESPN	33	9%	6.1	Papillary and others
ASPEN	51	18%	8.3	Papillary and others

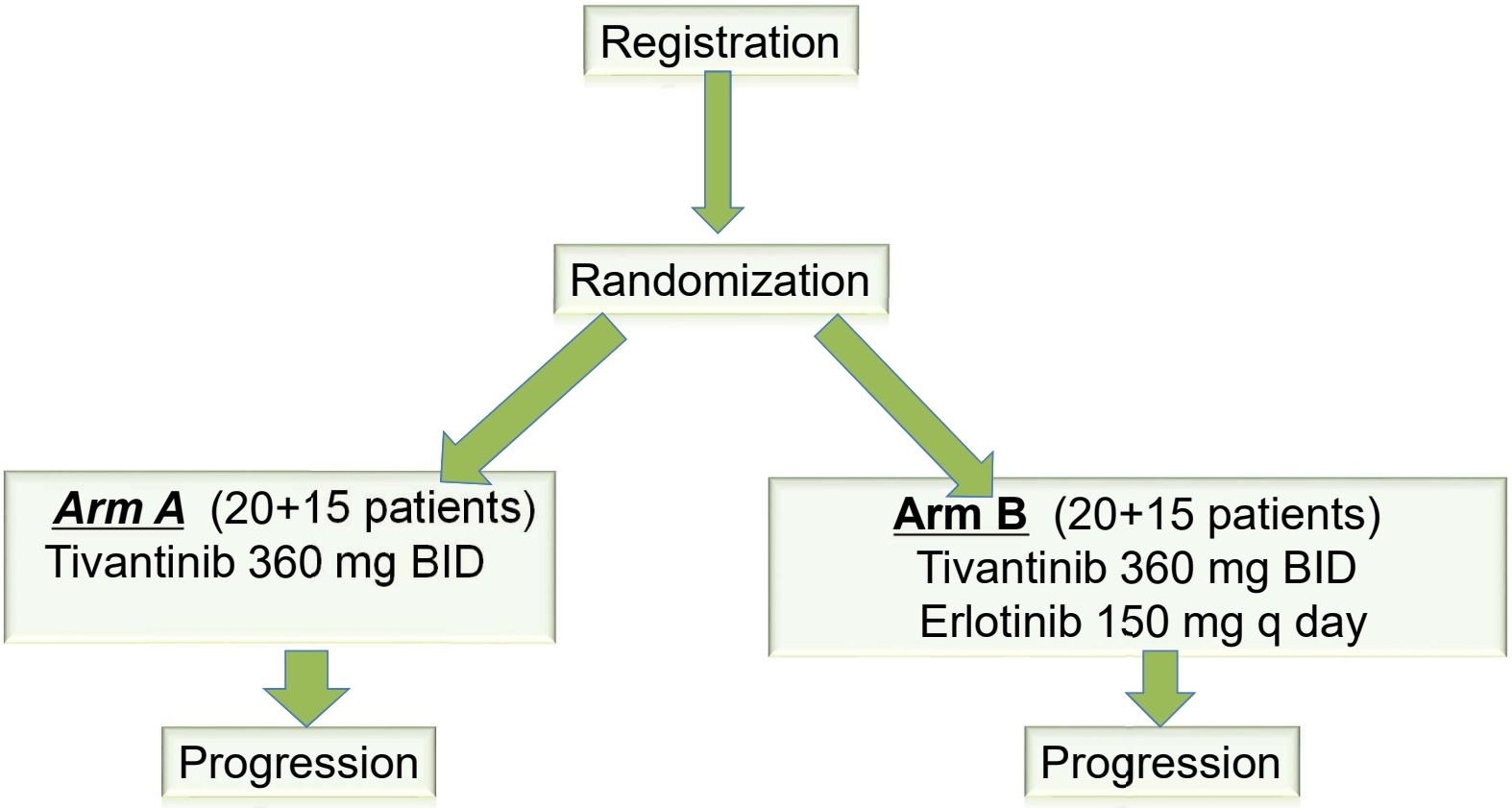
Modest activity: mPFS ~6 months

Tannir et al Eur Urol. 2012; Lee et al, Ann Oncol 2012; Molina, Invest New Drugs 2013; Ravaud et al Ann Oncol. 2012;23(Suppl 9)

Historical Phase II Trials of EGFR/MET Inhibitors in Papillary RCC

Agent	N	Reference	Results
Erlotinib	52	Gordon et al (J Clin Oncol 2009) (SWOG 0317)	• RR of 11% • 6-month PFS 29% • Median OS 27 months
Foretinib	74	Choueiri et al (J Clin Oncol 2013)	• RR of 13.5% • PFS of 9.3 mos • OS not reached

SWOG 1107: Parallel (Randomized) Phase II Evaluation of Tivantinib and Tivantinib in Combination with Erlotinib in Papillary Renal Cell Carcinoma



PI: Twardowski, P

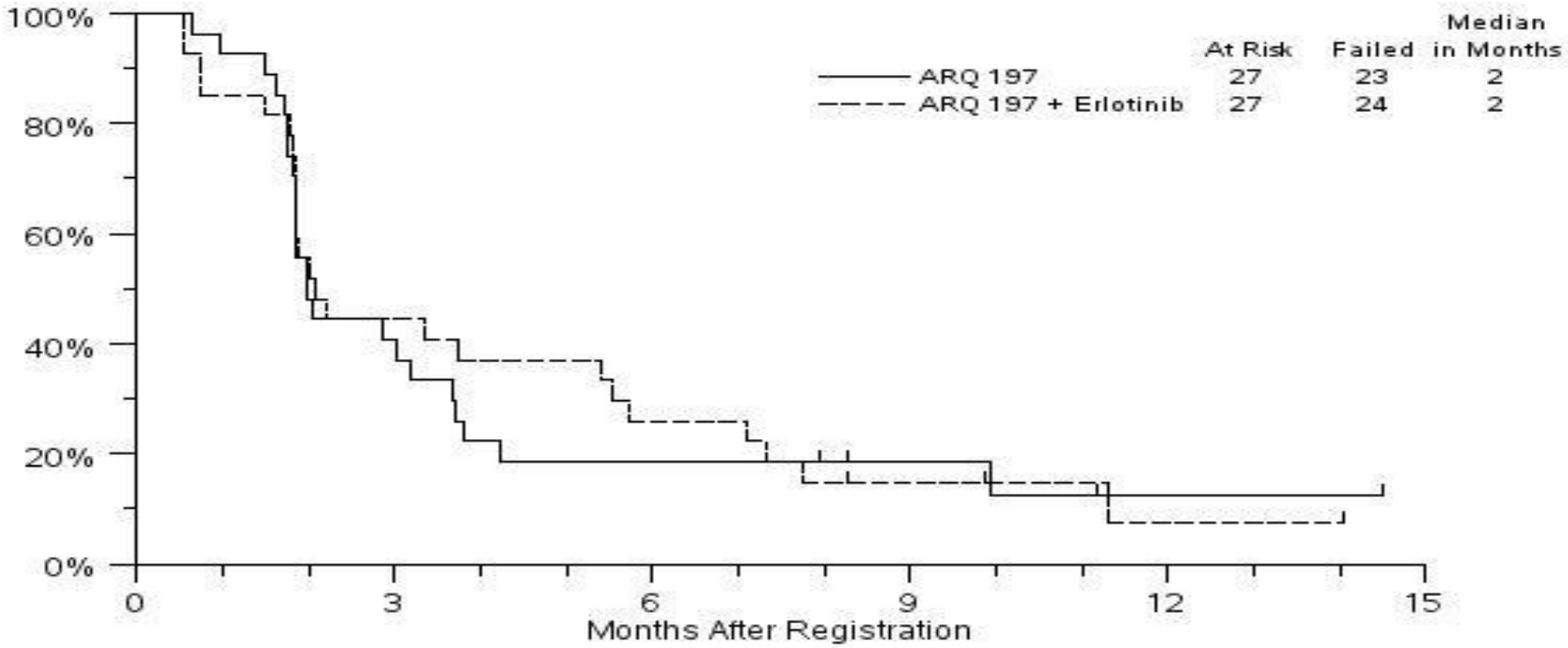
S1107: Parallel (Randomized) Phase II Evaluation of Tivantinib and Tivantinib in Combination with Erlotinib in Papillary Renal Cell Carcinoma

- Eligibility: Patients with advanced papillary renal cell carcinoma (1 prior systemic therapy for advanced disease allowed but not required)
- Primary Endpoint: Response Rate (30% considered significant)
- Secondary Endpoint: Progression Free Survival
- Correlative studies: tissue c-MET mutation and amplification status, analysis of subsets of pRCC (type 1, 2), sporadic vs hereditary

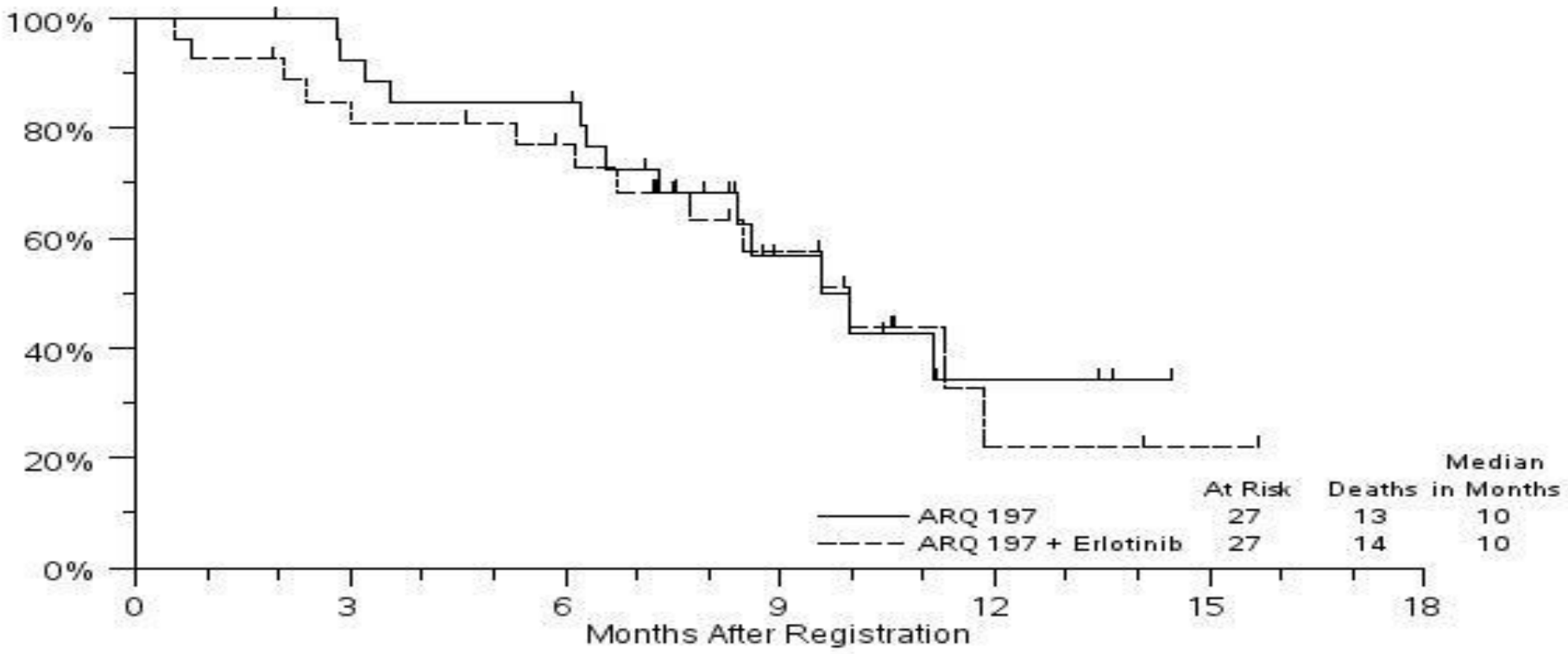
S1107: PATIENT CHARACTERISTICS

	ARQ 197 (n=27)		ARQ 197 + Erlotinib (n=27)	
AGE				
Median	62.1		63.6	
Minimum	20.3		22.8	
Maximum	76.1		81.9	
SEX				
Males	20	74%	17	63%
Females	7	26%	10	37%
HISPANIC				
Yes	1	4%	1	4%
No	25	93%	23	85%
Unknown	1	4%	3	11%
RACE				
White	21	78%	19	70%
Black	6	22%	6	22%
Multi-Racial	0	0%	1	4%
Unknown	0	0%	1	4%
HISTOLOGIC GRADE				
Unknown	11	41%	11	41%
1	0	0%	0	0%
2	3	11%	5	19%
3	9	33%	7	26%
4	4	15%	4	15%
HISTOLOGIC SUBSET				
Pure papillary	22	81%	24	89%
Mixed histology	5	19%	3	11%
HISTOLOGIC TYPE				
Not Assigned	12	44%	16	59%
Type 1	2	7%	1	4%
Type 2	13	48%	10	37%
PRIOR NEPHRECTOMY				
No	4	15%	8	30%
Yes	23	85%	19	70%
PRIOR SYSTEMIC THERAPY				
None	18	67%	19	70%
One	9	33%	8	30%
PERFORMANCE STATUS				
0	13	48%	11	41%
1	11	41%	13	48%
2	3	11%	3	11%

Progression-Free Survival by Treatment Arm



Overall Survival by Treatment Arm



S1107: Poor outcomes (harm?) seen with Tivantinib

- Rapid accrual (6-7 pts/month)
- **Primary endpoint RR = 0% (target > 30%)**
- Key secondary enpoints: OS (10 months) and PFS (2 months)
  - Substantially lower than what was seen in **SWOG 0317**
- Tumor tissue available from 34 patients
- TM Proposal (NCI-approved)
  - Deep exome sequencing to evaluate the rates of: VHL somatic mutation, MET somatic mutation, MET germline mutation, amplification of MET, EGFR mutation status, and fumarate hydratase mutation status.
  - Exploratory correlation of the genetic variants observed in pRCC to seek an initial understanding on their relevance to clinical outcomes of PFS, OS, and toxicity

Non-Clear Cell RCC: Recent Trials

Trial	Treatment	Randomized?	Number Enrolled	Histology Type	Overall Response Rate	Progression-Free Survival	Overall Survival
ESPN	Sunitinib vs. everolimus	Yes	68 patients	All non-clear cell	9% vs. 3%	6.1 vs. 4.1 months	16.2 vs. 14.9 months
ASPEN	Sunitinib vs. everolimus	Yes	108 patients	All non-clear cell	18% vs. 9%	8.3 vs. 5.6 months	31.5 vs. 13.2 months
RECORD-3	Sunitinib vs. everolimus	Yes	66 patients	All non-clear cell	N/A	7.2 vs 5.1 months	N/A
SUPAP	Sunitinib	No	61 patients	Papillary	13% (type I) and 11% (type II)	6.6 months (type I) and 5.5 months (type II)	17.8 months (type I) and 12.4 months (type II)

Pal, et al. ASCO Educ Book 2017

Completed Trials in Papillary RCC Only

Agent	No. of Patients	Phase	Population	Setting	PFS, months	RR, %	RR in MET+, %	Trial Name
Sunitinib	61	II	All mPRCC	First line	Type 1: 6.6 Type 2: 5.5	Type 1: 13 Type 2: 11	NA	NCT00541008[7]
Sunitinib *v* everolimus	70	II	All mPRCC	First line	8.1 *v* 5.5	24 *v* 5	NA	ASPEN[8]
Sunitinib *v* everolimus	27	II	All mPRCC	First line	5.7 *v* 4.1	NA	NA	ESPN[9]
Erlotinib	45	II	All mPRCC	First line	NA	11	NA	SWOG 0317[10]
Tivantinib *v* erlotinib + tivantinib	50	II	All mPRCC	First or second line	2.0 *v* 5.4	0	NA	SWOG 1107[11]
Foretinib	74	II	All mPRCC	Second line	9.3	14	50 (5 of 10)	NCT00726323[12]
Crizotinib	23	II	Type 1 mPRCC	NA	NA	9	50 (2 of 4)	CREATE[13]
Savolitinib	109	II	All mPRCC	Any line	6.2 *v* 1.4 by MET	7	18	NCT02127710[15]

Shuch, et al. JCO 2017

Ongoing Trials in Papillary and nccRCC

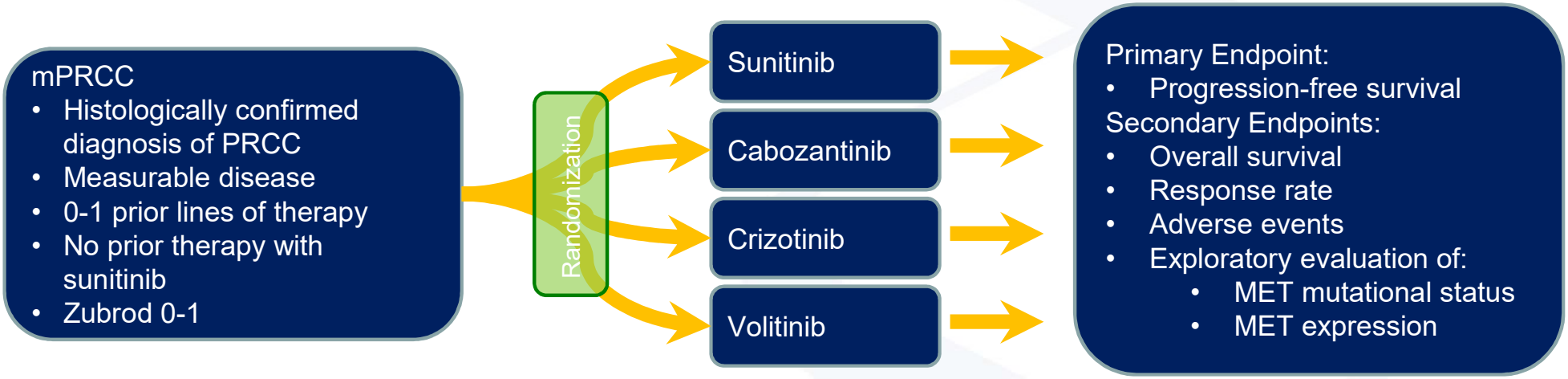
Ongoing Clinical Trials for mPRCC

Agent	No. of Patients	Phase	Population	Setting	Primary Outcome	Expected Completion Date
Sunitinib *v* cabozantinib *v* crizotinib *v* savolitinib	180	II	mPRCC	First or second line	PFS	March 2019
Savolitinib *v* sunitinib	180	III	mPRCC	Any line	PFS	February 2021
Axitinib	50	II	mPRCC	First line	PFS	January 2018
Capmatinib	22	II	mPRCC	Any line	ORR	January 2018
Everolimus + bevacizumab	55	II	Non–clear cell	First line	PFS	July 2018
Nivolumab + ipilimumab *v* sunitinib	306	II	Non–clear cell	First line	OS	December 2021
Lenvatinib + everolimus	31	II	Non–clear cell	First line	ORR	December 2018
Atezolizumab + bevacizumab	40	II	Non–clear cell	Any line	ORR	October 2019

Shuch, et al. JCO 2017

SWOG 1500: The PAPMET trial

Randomized Multi-Arm NCTN Phase II Trial of Met Inhibitors vs Sunitinib in Advanced Papillary RCC



- Designation of type I or type II or **papillary NOS** allowed
- SC: S. Pal (COH), P. Lara (UCD), N. Haas (ECOG), D Heng (NCIC)
- BISQFP funding for translational studies (TM PI: B. Shuch, M. Stein)
- NCI Coordination: John Wright

SWOG 1500: The PAPMET trial

Randomized Multi-Arm NCTN Phase II Trial of Met Inhibitors vs Sunitinib in Advanced Papillary RCC

Statistical Considerations

- Key assumptions:
  - **$PFS_{sunitinib}$ = 6 mos**, $PFS_{comparator}$ = 10.5 mos
  - $\beta = 0.85$, 1-sided $\alpha = 0.10$
- Requires **41** pts/arm → **164** pts total*
- Assuming 10% ineligibility, additional 4 pts/arm → **180 pts total**
- Limited enrollment of type II pts to 13 pts/arm (25%)
- If re-assessment at 1 year suggests lack of feasibility, will open enrollment to further type II pts

S1500: Translational Objectives

- To evaluate the prognostic and predictive value of MET alterations in patients with mPRCC treated with MET inhibitors

- To assess whether there is a greater treatment benefit of MET inhibitors among those with type 1 vs type 2 mPRCC.

Immune checkpoint inhibitor therapy is a reasonable strategy for nccRCC

One of the targets (PDL1) is expressed in nccRCC and is associated with poor prognosis

Retrospective study of PDL-1 positivity (n=101)

- Overall = 10.9%
- Chromophobe = 5.6%
- Papillary = 10%
- Xp11 = 30%
- Collecting duct = 20%

- PD-L1+ tumors have worse clinical outcomes

Choueiri et al. Ann Oncol 2014

Very smart people in this room (including one of the co-chairs) have already declared this to be true!

Koshkin VS, Barata PC, Zhang T, George DJ, Atkins MB, Kelly WJ, Vogelzang NJ, Pal SK, Hsu J, Appleman LJ, Ornstein MC, Gilligan T, Grivas P, Garcia JA, Rini BI. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. J Immunother Cancer 2018; 6(1):9.

"Nivolumab monotherapy demonstrated objective responses and was well tolerated in a heterogeneous population of patients with non-clear cell mRCC. In the absence of other data in this treatment setting, this study lends support to the use of nivolumab for patients with metastatic non-clear cell renal cell carcinoma."

There is now a growing body of evidence showing meaningful activity of CPI in nccRCC

From Case Reports…

Case Report

Check for updates

Rapid Deep Responses With Nivolumab Plus Ipilimumab in Papillary Renal Cell Carcinoma With Sarcomatoid Dedifferentiation

Gustavo Schvartsman,[1] Andre P.C.D. Carneiro,[1] Renee Z. Filippi,[1] Priya Rao,[2] Pavlos Msaouel[2]

Clinical Practice Points

- First-line treatment with nivolumab and ipilimumab for intermediate and high-risk patients with metastatic renal cell carcinoma (RCC) is standard-of-care.
- The United States Food and Drug Administration extended approval to all RCC histologies, despite enrollment of clear-cell RCC only.
- Sarcomatoid and rhabdoid dedifferentiation is associated with significantly worse prognosis and may lead to increased programmed death-ligand 1 upregulation.
- We present the first 2 cases, to our knowledge, of papillary RCC with sarcomatoid dedifferentiation with rapid and deep responses to the ipilimumab and nivolumab combination.

Clinical Genitourinary Cancer, Vol. 17, No. 4, 315-8
Keywords: Checkpoint inhibitors, CTLA-4, Immunotherapy, Kidney cancer, PD-1

Introduction

Immune checkpoint inhibition has been widely adopted in renal cell carcinoma (RCC) of clear cell histology, using anti-programmed cell death protein 1 (PD-1) therapy (nivolumab) either as a single agent or in combination with the anti-cytotoxic T-lymphocyte-associated protein 4 agent, ipilimumab.[1,2] However, the registration trials did not include non–clear-cell histologies,[1,2] and there are currently no data on the efficacy of combining nivolumab and ipilimumab in papillary RCC with sarcomatoid dedifferentiation, a rare but highly aggressive entity that is often refractory to targeted therapies approved for clear-cell RCC.[3] Papillary RCC is further subdivided in the genetically and morphologically distinct type 1 and type 2 subtypes.[4,5] Sarcomatoid dedifferentiation is found in ~2% of papillary RCC cases and is invariably associated with a worse prognosis.[6] In this report, we present 2 cases of patients with type 1 and type 2 papillary RCC with sarcomatoid dedifferentiation who experienced dramatic responses to the combination of nivolumab with ipilimumab.

Case Presentation

Patient 1

A 47-year-old Peruvian male with no past medical history incidentally discovered a tumor in his left kidney during routine check-up exams. The patient had never smoked, denied current or previous alcohol abuse, and performed physical activities regularly. He had no family history of malignancy. A routine total abdominal ultrasound showed a heterogeneous mass of 24 × 28 × 25 mm with poorly defined margins, localized in the upper third of his left kidney. A computed tomography (CT) scan of the abdomen/pelvis demonstrated a 43 × 40 mm left kidney mass, with regional lymph node involvement and no vascular compromise. CT of the chest did not show metastatic disease. He was then referred to a urologist, and 2 weeks later, he underwent a left radical nephrectomy. Pathology revealed a papillary type 2 RCC with sarcomatoid and rhabdoid dedifferentiation (Figure 1A, B). Fuhrman nuclear grade 4, measuring 4.7 cm in the greatest dimension, extending to the renal sinus. Margins were free of tumor. There were metastases in 3 lymph nodes of the renal hilum and in 1 ileo-renal lymph node.

G.S. and A.P.C.D.C. contributed equally to this work as first authors.

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1558-7673/$ - see front matter
https://doi.org/10.1016/j.clgc.2019.05.023

… to Prospective Clinical Trials!

CheckMate 374: Nivolumab in RCC

- 44 pts had nccRCC : Papillary (n = 24), chromophobe (n = 7), unclassified (n = 8), and other (n = 5).
- At a median follow-up of 11.1 months, median OS was 16.3 months. OS was similar regardless of baseline PD-L1 expression.
- ORR was 13.6% (95% CI 5.2–27.4)
  - One CR (chromophobe histology)
  - Five had PR (2 pts with papillary and 1 pt each with chromophobe, collecting duct, and unclassified histology).
  - Median DOR was 10.2 mo (95% CI 5.6–NE).

Vogelzang et al, ASCO GU 2019

There is now a growing body of evidence showing meaningful activity of CPI in nccRCC

KEYNOTE 427: Pembrolizumab in nccRCC

Table 2. Confirmed ORR in the Overall Population and in Patient Subgroups per RECIST v1.1 by BICR

	Overall N = 165	RCC Histology			IMDC Category		PD-L1 Status[a]		Sarcomatoid Features n = 38
		Papillary n = 118	Chromophobe n = 21	Unclassified n = 26	Favorable n = 53	Intermediate/Poor n = 112	CPS <1 n = 58	CPS ≥1 n = 102	
ORR, % (95% CI)	26.1 (19.5-33.5)	28.0 (20.1-37.0)	9.5 (1.2-30.4)	30.8 (14.3-51.8)	32.1 (19.9-46.3)	23.2 (15.8-32.1)	10.3 (3.9-21.2)	35.3 (26.1-45.4)	42.1 (26.3-59.2)
DCR, % (95% CI)[b]	40.6 (33.0-48.5)	44.1 (34.9-53.5)	33.3 (14.6-57.0)	30.8 (14.3-51.8)	43.4 (29.8-57.7)	39.3 (30.2-49.0)	25.9 (15.3-39.0)	49.0 (39.0-59.1)	52.6 (35.8-69.0)
Best objective response, %									
CR	6.1	5.9	4.8	7.7	11.3	3.6	5.2	6.9	7.9
PR	20.0	22.0	4.8	23.1	20.8	19.6	5.2	28.4	34.2
SD	30.9	33.1	47.6	7.7	32.1	30.4	41.4	24.5	18.4
PD	37.0	33,1	42.9	50.0	34.0	38.4	43.1	33.3	31.6
NE[c]	1.2	0.8	0.0	3.8	1.9	0.9	0.0	2.0	2.6
NA[d]	4.8	5.1	0.0	7.7	0.0	7.1	5.2	4.9	5.3

McDermott D et al. ASCO GU & ESMO 2019

There is now a growing body of evidence showing meaningful activity of IO-based combinations in nccRCC

- CALYPSO, a multi-arm study of various RCC histologies (clear cell, papillary and sarcomatoid variant).
- N=42 patients with metastatic pRCC (VEGF treatment naïve or refractory). 68% had no previous anti-tumor treatment.
- Treatment: Savolitinib 600mg and Durvalumab 1500mg Q4 weeks.
- The overall response rate was 27% (n=11), median PFS was 3.3. months, mOS not reached.
- A total of 22 of the 41 evaluable patients (54%) had a decrease in tumor burden.
- Of 11 patients with objective response, interim analysis showed duration of response approaching 6 months.
- No correlation between PD-L1 and MET biomarker expression and outcome was seen.

Powles, et al. ASCO GU 2019

There is now a growing body of evidence showing meaningful activity of IO-based combinations in nccRCC

Results of a phase II study of atezolizumab and bevacizumab in non-clear cell renal cell carcinoma (nccRCC) and clear cell renal cell carcinoma with sarcomatoid differentiation (sccRCC).

			Histology		Prior Systemic Therapy	
		Total N=52	sccRCC N=16	nccRCC N=36	No N=35	Yes N=17
ORR	N (%)	16 (31)	7 (44)	9 (25)	8 (23)	8 (47)
Stable Disease	N (%)	23 (44)	5 (31)	18 (50)	18 (51)	5 (29)

***"Conclusion:** In this study, we show that therapy with atezolizumab and bevacizumab was safe and demonstrated anti-tumor activity in nccRCC and sccRCC."*

Mckay, R. ASCO GU 2019

Do ”targeted therapies” really have meaningfully better activity than CPI in nccRCC?

	NIVOLUMAB	CABOZANTINIB*
RESPONSE RATE	21.6%	14.3%
COMPLETE RESPONSE RATE	8.8%	0%
MEDIAN OVERALL SURVIVAL	21.7 months	25 months

Koshkin VS, Barata PC, Zhang T, et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. J Immunother Cancer 2018; 6(1):9.

Campbell MT, Bilen M, Shah AY, et al. Cabozantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: A retrospective analysis. Eur J Cancer 2018

Conclusions

- In the absence of compelling Level 1 evidence that says otherwise, immunotherapy is a reasonable option for the treatment of people with advanced nccRCC
- Treatments directed towards the presumed driver molecular phenotype are likely to yield better outcomes
- Completion of ongoing trials testing agents directed against MET and other relevant targets in pRCC is essential
- Investigations that refine immunotherapic approaches (combinations with targeted therapies, other IO-agents, etc) should be pursued