Neues aus der Uroonkologie
ASCO 2022

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Praxis für Hämatologie und Onkologie Koblenz

Übersicht

1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

#5028: Impact of PSMA PET/CT on prostate cancer salvage radiotherapy management: Results from the prospective randomized phase 3 trial [PSMA SRT NCT03582774].

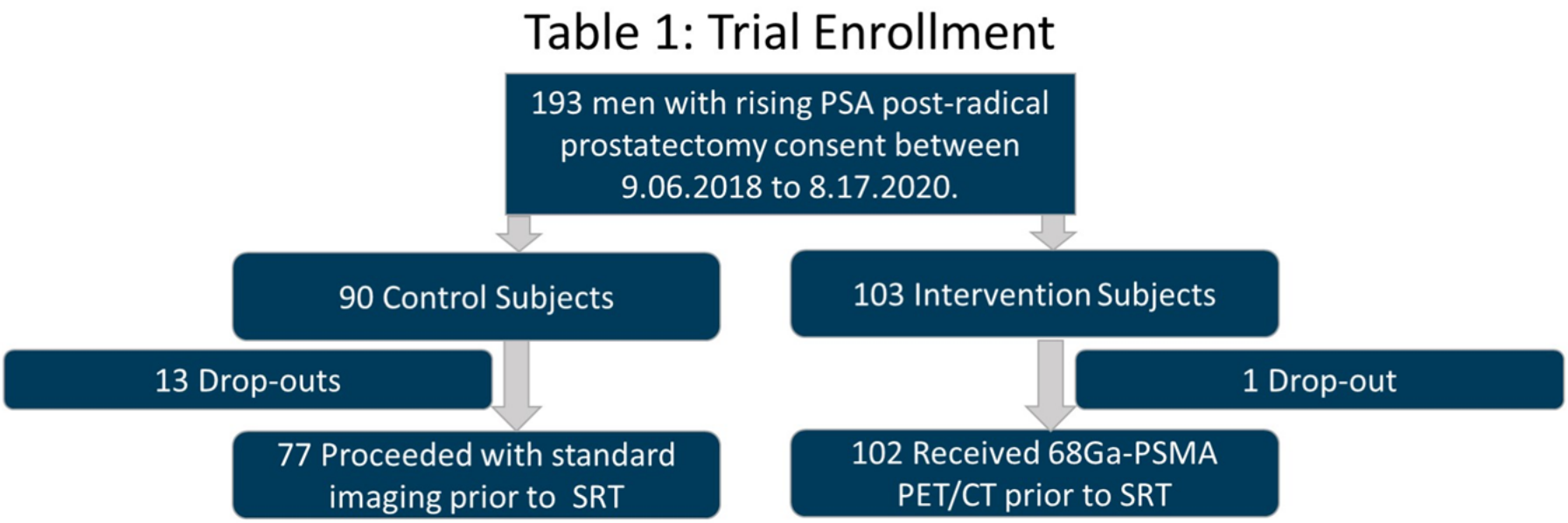
Wesley R Armstrong, et al.

Hintergrund

- Etwa 50% der high-risk Prostatakarzinompatienten erleiden ein biochemisches Rezidiv nach salvage radiotherapy (SRT)

- PSMA-PET CT kann auch bei niedrigen PSA Werten Prostatakarzinombefall ausserhalb des Strahlenfeldes nachweisen.

Studiendesign



-Mediane Zeit von Prostatektomie bis Einschluß waren 20.3 Monate für die Kontrollgruppe und 28.3 Monate für die PSMA-PET CT Gruppe

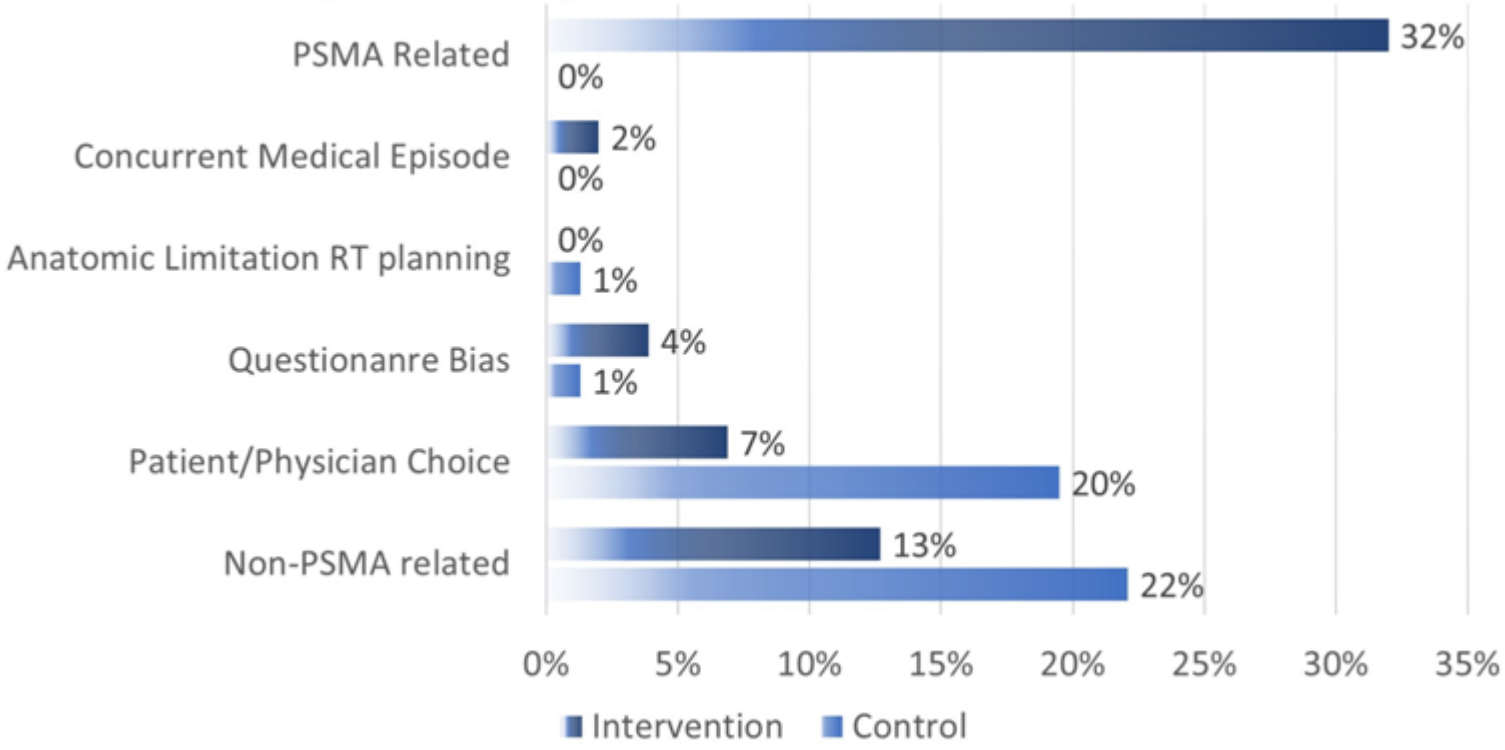
- Medianer PSA-Wert: 0.3 ng/ml (Kontrollgruppe) und 0.23 ng/ml (PSMA-PET-CT)

Patienten mit M1 Status, ADT Therapie in den letzten 3 Monaten oder Kontraindikationen gegen eine Satrahlentherapie wurden nicht eingeschlossen

Ergebnisse

- Wesentliche Änderungen zwischen SRT Plan vor Randomisiserung und RT Ausführung erfolgten in 45% in der PSMA-PET-CT Gruppe und in 22% in der Kontrollgruppe

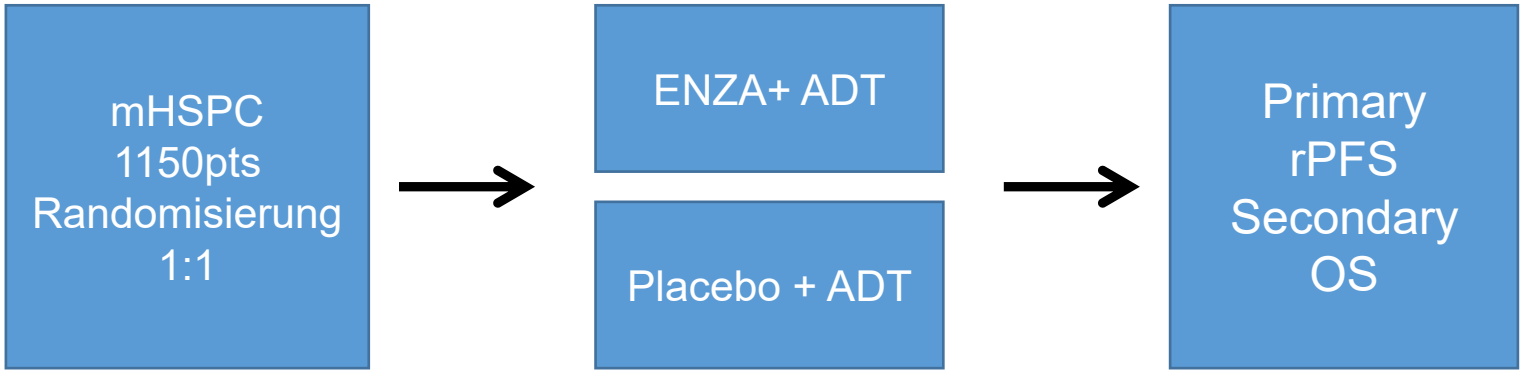
Table 2: Change in Management



#5072: Radiographic progression in the absence of prostate-specific antigen (PSA) progression in patients with metastatic hormone-sensitive prostate cancer (mHSPC): Post hoc analysis of ARCHES.

Andrew J. Armstrong, et al.

Hintergrund ARCHES



- Enzalutamid und ADT zeigten eine signifikante Verbesserung des rPFS und OS im Vergleich zu Placebo beim mHSPC
- Radiologische Progression ohne PSA Anstieg wurde bereits unter Therapie mit Enzalutamid + ADT beobachtet

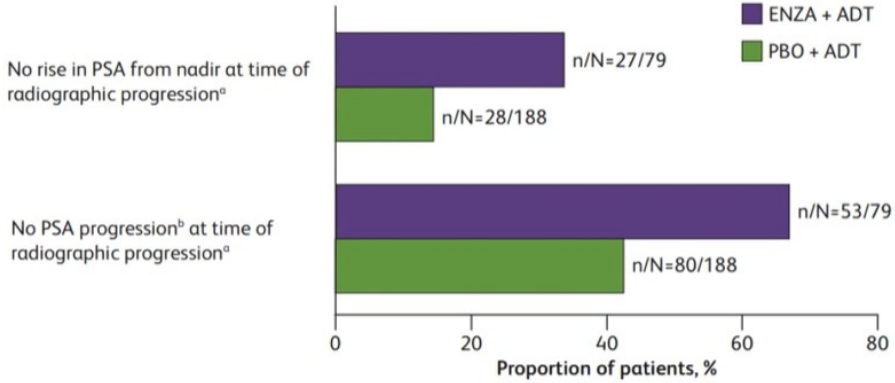
→ Post-hoc-Analyse zur Untersuchung der Konkordanz von PSA Progression und Radiologischer Progression

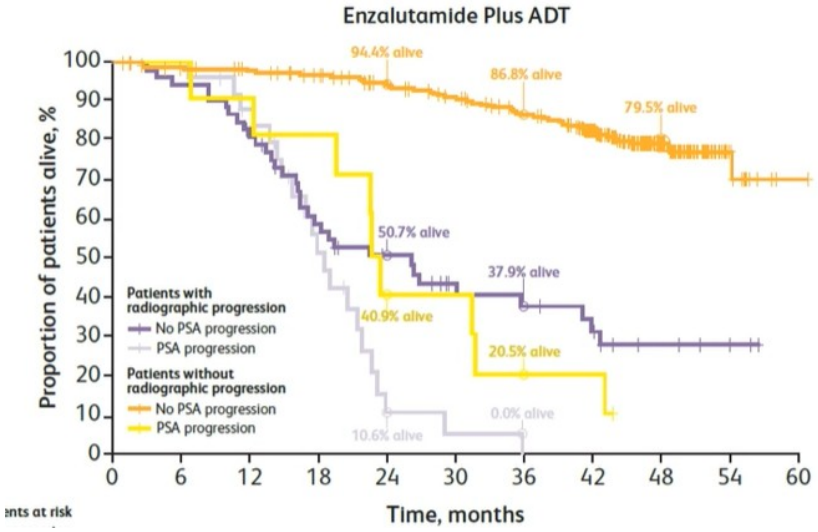
Ergebnisse

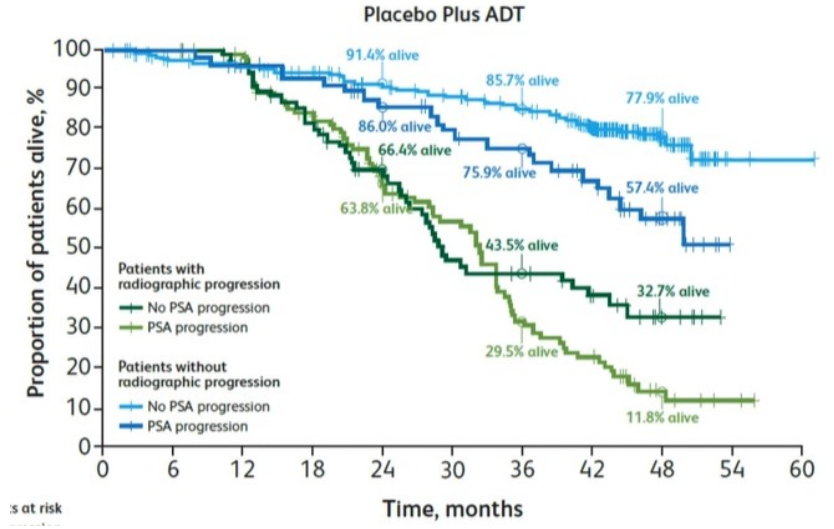
Median PSA at Radiographic Progression and Change in PSA From Nadir to Radiographic Progression

Parameter	ENZA + ADT (n=79)	PBO + ADT (n=188)
Median PSA at radiographic progression, ng/mL (range)	2.25 (0–1062.3)	17.47 (0–1779.5)
Median absolute rise in PSA from nadir to radiographic progression,[a] ng/mL (range)	0.77 (0–1053.9)	12.23 (0–1675.3)
Median percentage rise in PSA from nadir to radiographic progression, % (range)	200.00 (0–42,450.0)	366.86 (0–94,411.1)

Co-Occurrence of Radiographic Progression and Increasing PSA







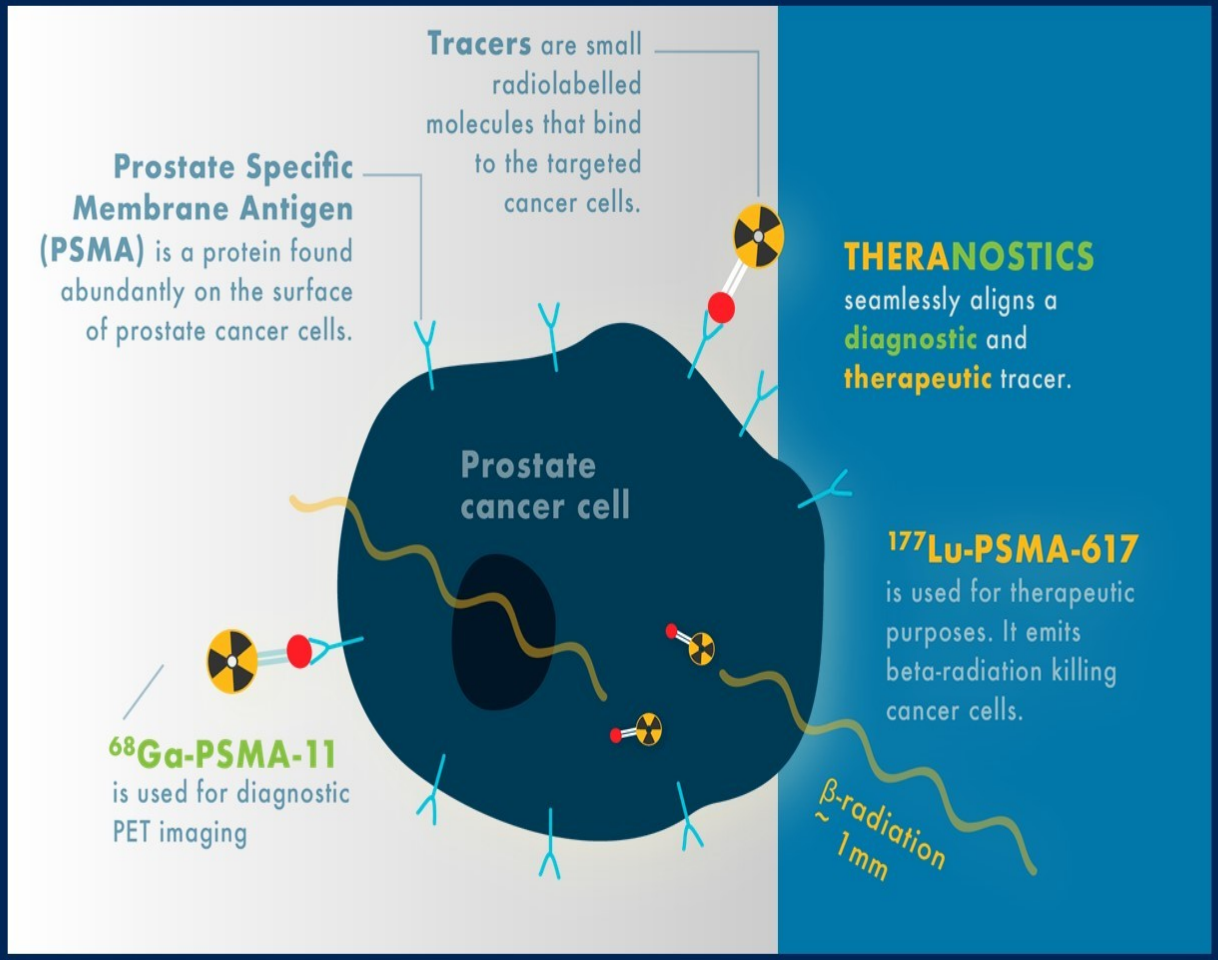
Fazit

- Radiologische Progression ohne PSA-Progression kommt häufig in der Kombination ADT+Enzalutamid vor
- Regelmässige Bildgebungen sollten unabhängig vom PSA Verlauf unter laufender Therapie mit Androgenrezeptor Signalweg Inhibitoren +ADT wie z.B. ENZALUTAMID erfolgen

#5000: TheraP: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603).

Michael s Hofman,et al.

^{177}Lu-PSMA-617: ↑OS and QoL in mCRPC[1]



[1] Sartor O et al, NEJM 2021; 385

Aim: report secondary endpoint of OS

ANZUP Cancer Trials Group Limited

N=291 registered

^{68}Ga-PSMA-11 + FDG PET/CT
- PSMA SUVmax > 20 at any site
- No FDG positive/PSMA negative sites of disease
- Centrally reviewed

N=91 ineligible
- Low PSMA expression (n=29)
- FDG discordant disease (n=51)
- Other (n=11)

28% unsuitable →followed-up for OS

R

N=200

^{177}Lu-PSMA-617
8.5 ↓ 0.5GBq IV q6 weekly
Up to 6 cycles
median 5
exceptional response 7

N=99
Died prior to Rx (n=1)

CABAZITAXEL
20mg/m^2 IV q3 weekly,
Up to 10 cycles
median 8

N=101
Met exclusion criterion (n=1)
Withdrawal of consent (n=15)

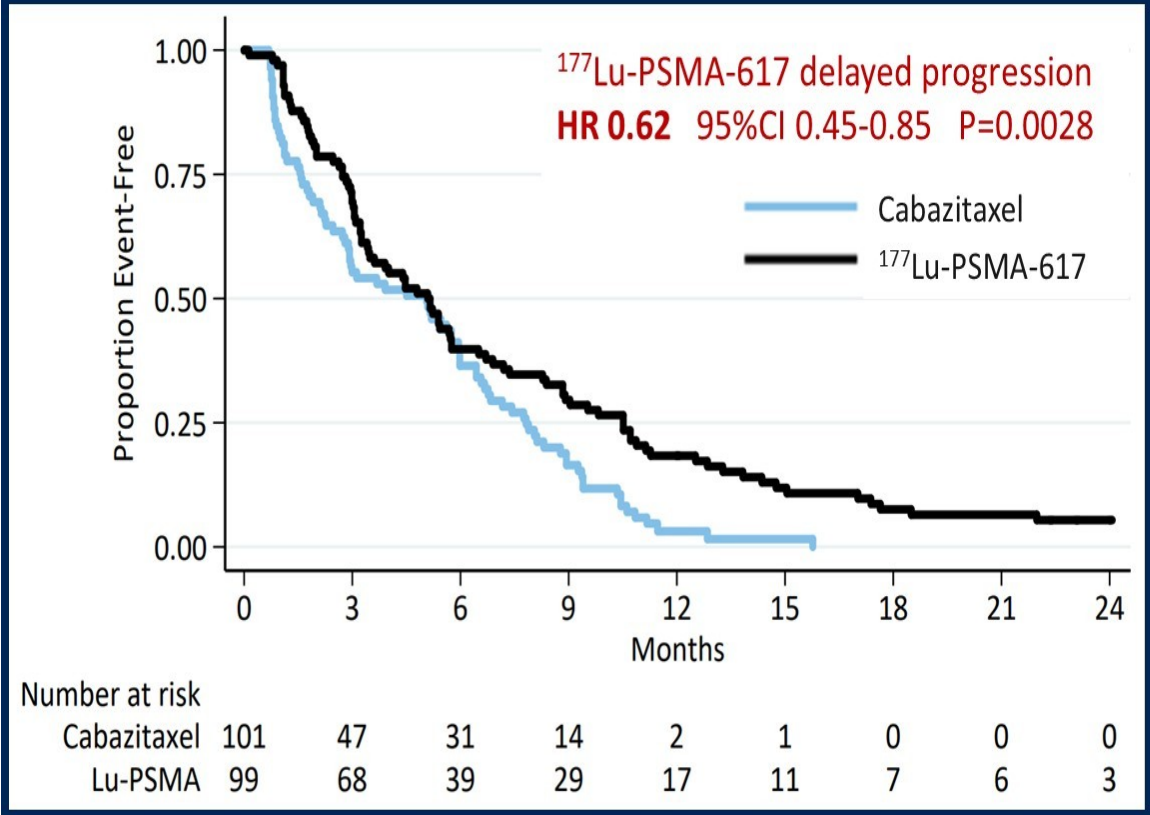
POST PROTOCOL SYSTEM TREATMENT

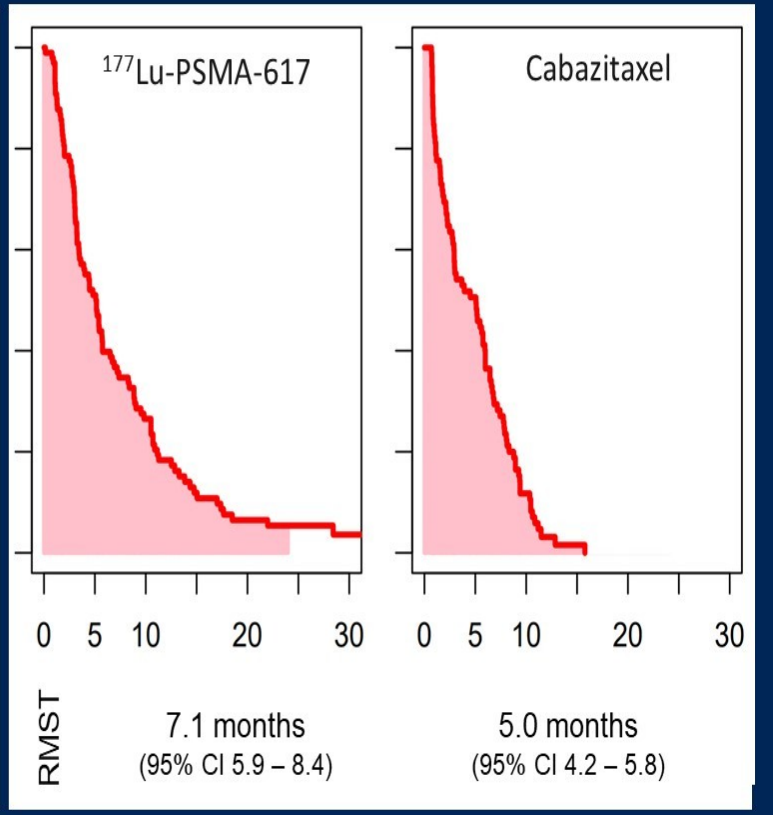
Cabazitaxel (32)
LuPSMA (5)
Abiraterone (5)
Enzalutamide (2)

Cabazitaxel (21)
LuPSMA (20)
Abiraterone (7)
Enzalutamide (9)

PRESENTED BY: Michael Hofman, MBBS @DrMHofman

Progression Free Survival (PSA and radiographic)





- Treatment effect not constant with respect to time → restricted mean survival time (RMST)
- 177 progression events. Cut-off 31 DEC 2020 for non-OS endpoints.
- Similar HR for rPFS (0.65) and PSA-PFS (0.60), and in per-protocol sensitivity analyses

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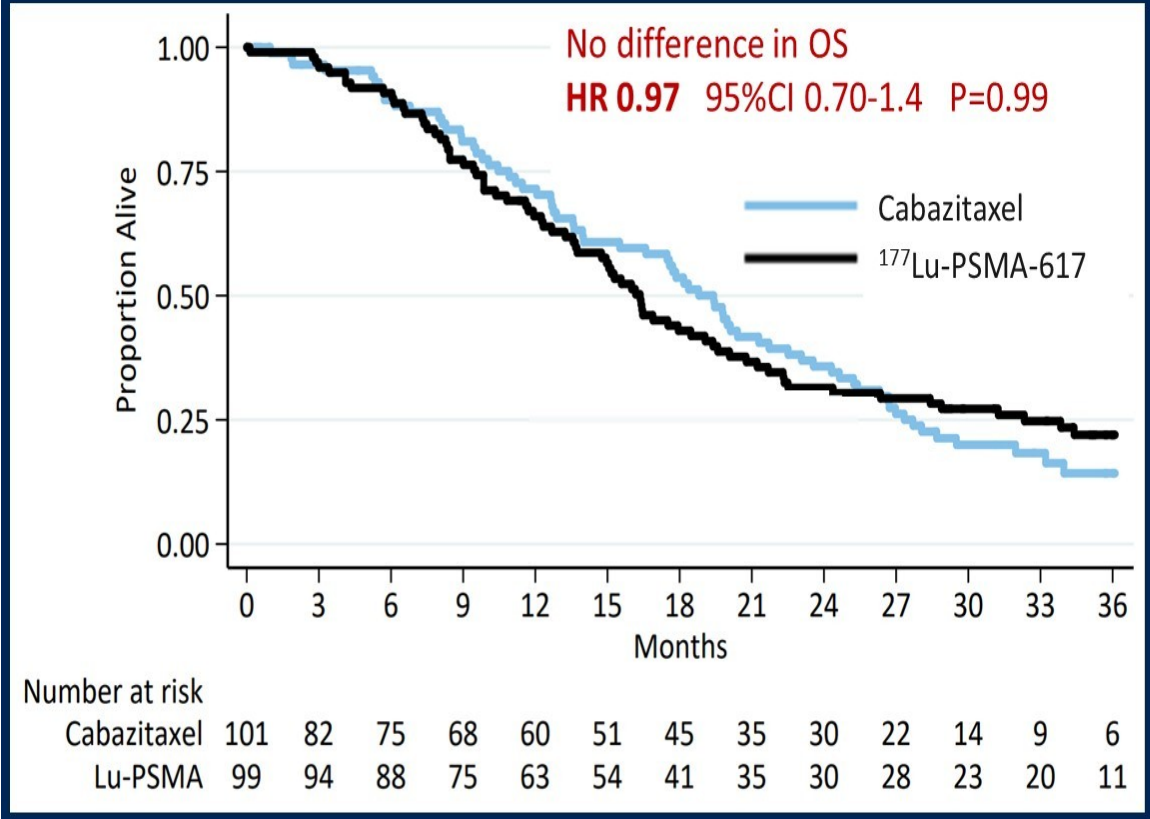
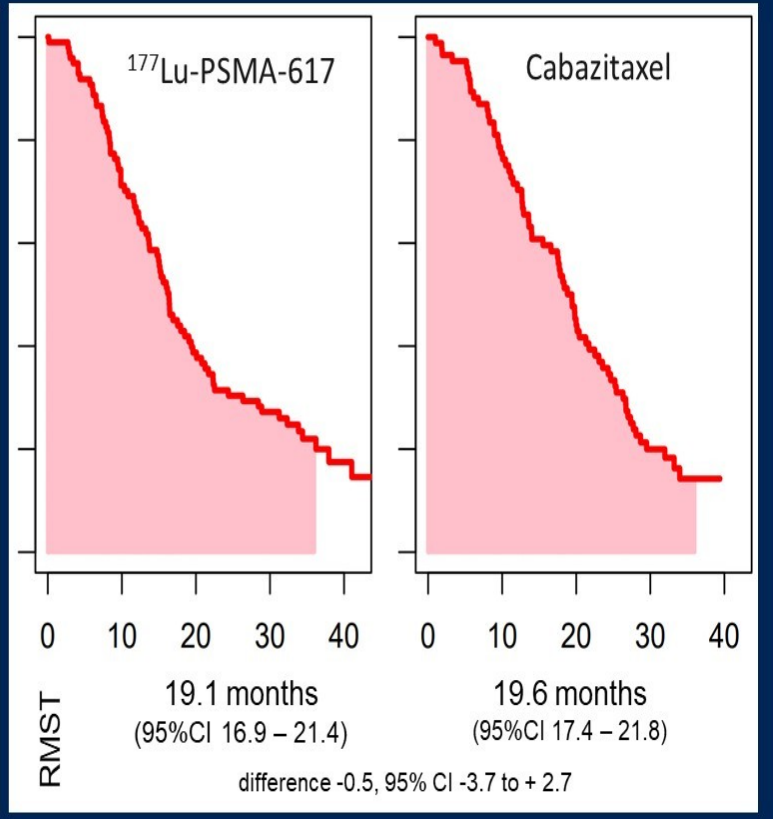
Overall survival (ITT)





- Cut-off 31 DEC 2021 for OS
- At 36 months follow-up, death reported in 147/200; 70/101 assigned cabazitaxel vs. 77/99 assigned LuPSMA
- Per-protocol analysis: no difference in OS
- No additional safety signals with longer follow-up.

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Discussion

Strengths

- Prospective, randomized, multi-center
- 3 years follow-up
- Active control arm[1] (vs. VISION)

Limitations

- Post protocol cross-over confounds OS
- Withdrawal post randomization in cabazitaxel arm
- OS a 2º endpoint (underpowered)

Clinical Implications

- LuPSMA: >greater activity PSA50-RR, RECIST, rPFS, PSA-PFS
- Similar OS to cabazitaxel, a life prolonging treatment[1]
- Fewer AEs, better patient reported outcomes

[1] de Wit R et al, NEJM 2019; 381

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Conclusion

The TheraP data support the choice of ^{177}Lu-PSMA-617 over cabazitaxel for patients with PSMA-positive, progressive mCRPC after docetaxel and androgen-receptor pathway inhibitor, on the basis of its higher PSA response rate, greater PFS benefit, QoL benefits, favorable safety profile and dosing schedule, and similar survival outcomes.

Survival was considerably shorter for patients excluded on PSMA/FDG-PET with either low PSMA-expression, or discordant disease.

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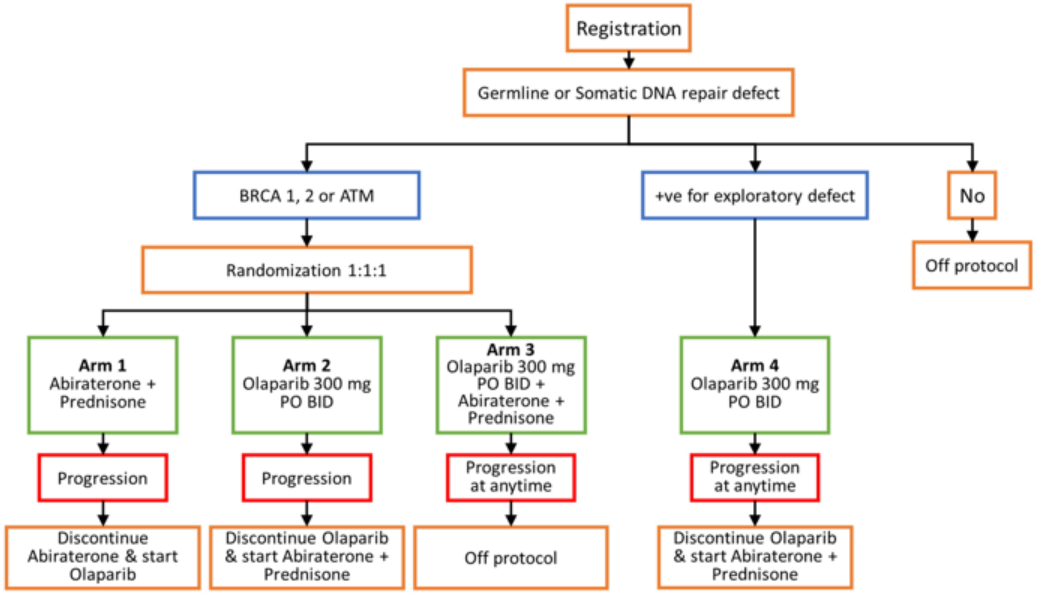
#5018: BRCAAWAY: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) with DNA repair defects.

Maha H. A. Hussain, et al.

STUDY BACKGROUND AND SCHEMA

- The PARP-inhibitor olaparib is approved for mCRPC patients with deleterious germline or somatic homologous recombination repair gene mutations (HRRm).
- PARP1 interacts with androgen signaling, and castration-resistant tumor cells exhibit increased PARP1 activity.
- Preclinically PARP1-inhibition synergizes with androgen receptor (AR) targeted therapy.
- BRCAAway is a biomarker selected, randomized, open-label, multicenter phase 2 trial evaluating efficacy of targeting AR vs PARP vs combination in first line mCRPC patients with germline and/or somatic HRRm in BRCA1, BRCA2, or ATM.



Primärer Endpunkt: OS
Sekundäre Endpunkte: Response Rate (RR) nach RECIST, PSA-RR
Cross-Over: erlaubt für Arme 1 und 2

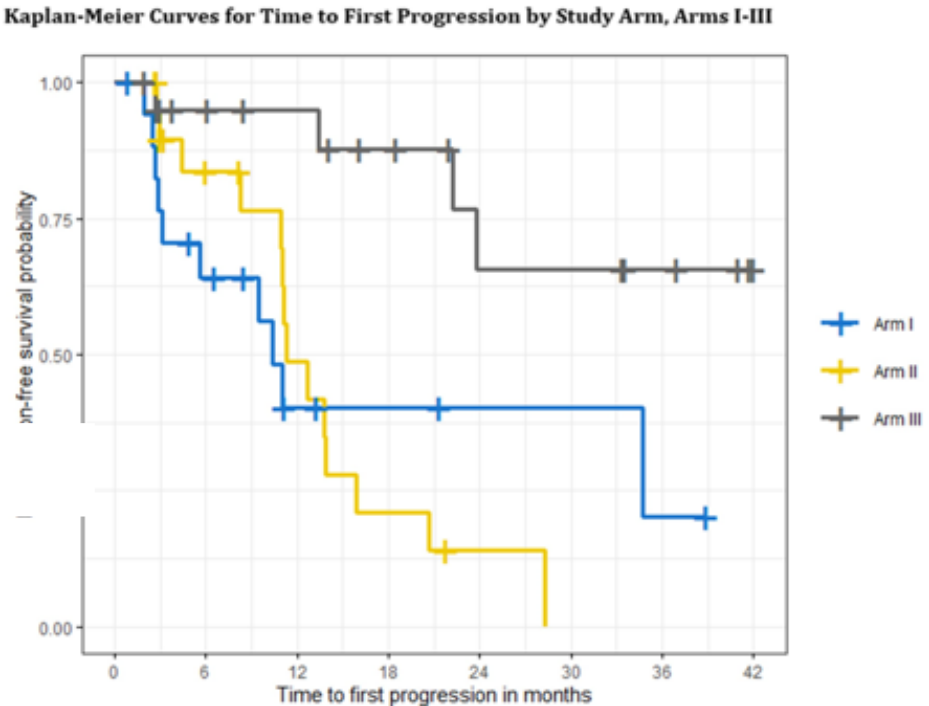
BASELINE CHARACTERISTICS

Characteristic	Overall, N = 61	Arm I, N = 19	Arm II, N = 21	Arm III, N = 21	p-value[3]
Age (Years)[1]	67.0 (42.0, 85.0)	63.0 (42.0, 85.0)	67.0 (50.0, 77.0)	69.0 (48.0, 80.0)	0.35
Ethnicity[2]					1.00
Hispanic or Latino	1 (1.6%)	0 (0%)	0 (0%)	1 (4.8%)	
Not Hispanic or Latino	60 (98%)	19 (100%)	21 (100%)	20 (95%)	
Race[2]					1.00
Black or African American	6 (9.8%)	2 (11%)	2 (9.5%)	2 (9.5%)	
White	55 (90%)	17 (89%)	19 (90%)	19 (90%)	
Baseline ECOG[2]					0.25
0	41 (67%)	10 (53%)	15 (71%)	16 (76%)	
1	20 (33%)	9 (47%)	6 (29%)	5 (24%)	
Baseline PSA[1]	14.4 (0.1, 4,036.8)	13.6 (0.1, 4,036.8)	13.5 (1.9, 143.9)	15.0 (0.9, 212.0)	0.92
Baseline Disease[2]					0.43
Bone and Soft Tissue	13 (21%)	5 (26%)	3 (14%)	5 (24%)	
Soft Tissue Only	17 (28%)	3 (16%)	9 (43%)	5 (24%)	
Bone Only	31 (51%)	11 (58%)	9 (43%)	11 (52%)	
Germline/Somatic Mutation[2]					0.64
Germline	33 (54%)	9 (47%)	13 (62%)	11 (52%)	
Somatic	28 (46%)	10 (53%)	8 (38%)	10 (48%)	
Baseline Mutation[2]					0.42
ATM Only	11 (18%)	4 (21%)	2 (9.5%)	5 (24%)	
BRCA1 Only	3 (4.9%)	2 (11%)	0 (0%)	1 (4.8%)	
BRCA2 Only	46 (75%)	13 (68%)	18 (86%)	15 (71%)	
Multiple	1 (1.6%)	0 (0%)	1 (4.8%)	0 (0%)	

[1]median (min-max)
[2]n (%)
[3]Kruskal-Wallis rank sum test; Fisher's exact text; Chi-squared test

RESULTS

Arm (evaluable patients)	Undetectable PSA n (%)	Median PFS (95% CI) in Months	12-month PFS rate (95% CI)	Unadjusted hazard ratio (Arm 3 vs Arms 1 and 2)
1: Abi/pred (19)	5 (26%)	10.4 (5.6, NA)	40% (0.21, 0.77)	0.17 (95% CI: 0.05, 0.56)
2: Olaparib (21)	4 (19%)	11.3 (11.0, NA)	49% (0.29, 0.82)	0.15 (95% CI: 0.05, 0.49)
3: Abi/pred + olaparib (21)	7 (33%)	NA (23.8, NA)	95% (0.86, 1.0)	-



ADVERSE EVENTS: OVERALL

	N = 61					
Adverse Event (System Organ Class)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Overall
Blood and lymphatic system disorders	7 (11)	4 (6.6)	3 (4.9)	—	—	14 (23)
Cardiac disorders	2 (3.3)	—	1 (1.6)	—	—	3 (4.9)
Ear and labyrinth disorders	3 (4.9)	1 (1.6)	—	—	—	4 (6.6)
Endocrine disorders	—	1 (1.6)	—	—	—	1 (1.6)
Eye disorders	1 (1.6)	—	—	—	—	1 (1.6)
Gastrointestinal disorders	29 (48)	11 (18)	—	—	—	40 (66)
General disorders and administration site conditions	26 (43)	7 (11)	3 (4.9)	—	—	36 (59)
Hepatobiliary disorders	—	—	1 (1.6)	—	—	1 (1.6)
Infections and infestations	3 (4.9)	7 (11)	3 (4.9)	2 (3.3)	1 (1.6)	16 (26)
Injury, poisoning and procedural complications	1 (1.6)	3 (4.9)	1 (1.6)	—	—	5 (8.2)
Investigations	11 (18)	5 (8.2)	3 (4.9)	—	—	19 (31)
Metabolism and nutrition disorders	10 (16)	5 (8.2)	4 (6.6)	—	—	19 (31)
Musculoskeletal and connective tissue disorders	17 (28)	14 (23)	1 (1.6)	—	—	32 (52)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	—	1 (1.6)	2 (3.3)	—	—	3 (4.9)
Nervous system disorders	23 (38)	3 (4.9)	2 (3.3)	—	—	28 (46)
Psychiatric disorders	10 (16)	—	—	—	—	10 (16)
Renal and urinary disorders	3 (4.9)	6 (9.8)	2 (3.3)	—	1 (1.6)	12 (20)
Reproductive system and breast disorders	2 (3.3)	4 (6.6)	—	—	—	6 (9.8)
Respiratory, thoracic and mediastinal disorders	10 (16)	4 (6.6)	—	—	—	14 (23)
Skin and subcutaneous tissue disorders	10 (16)	1 (1.6)	—	—	—	11 (18)
Vascular disorders	8 (13)	9 (15)	8 (13)	—	—	25 (41)

CONCLUSIONS

In mCRPC patients with inactivating BRCA1, BRCA2 and/or ATM alterations, abiraterone/prednisone + the PARP-inhibitor olaparib was well tolerated and resulted in longer PFS and better PSA response vs either agent alone.

1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

LBA4500: EVEREST: Everolimus for renal cancer ensuing surgical therapy—A phase III study (SWOG S0931, NCT01120249).

Christopher W Ryan, et al.

Introduction

- One-third of patients with RCC develop recurrence after nephrectomy
- Surveillance alone after surgery remained standard management for years
- A new generation of adjuvant trials began in 2006

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New Generation Adjuvant RCC Trials*

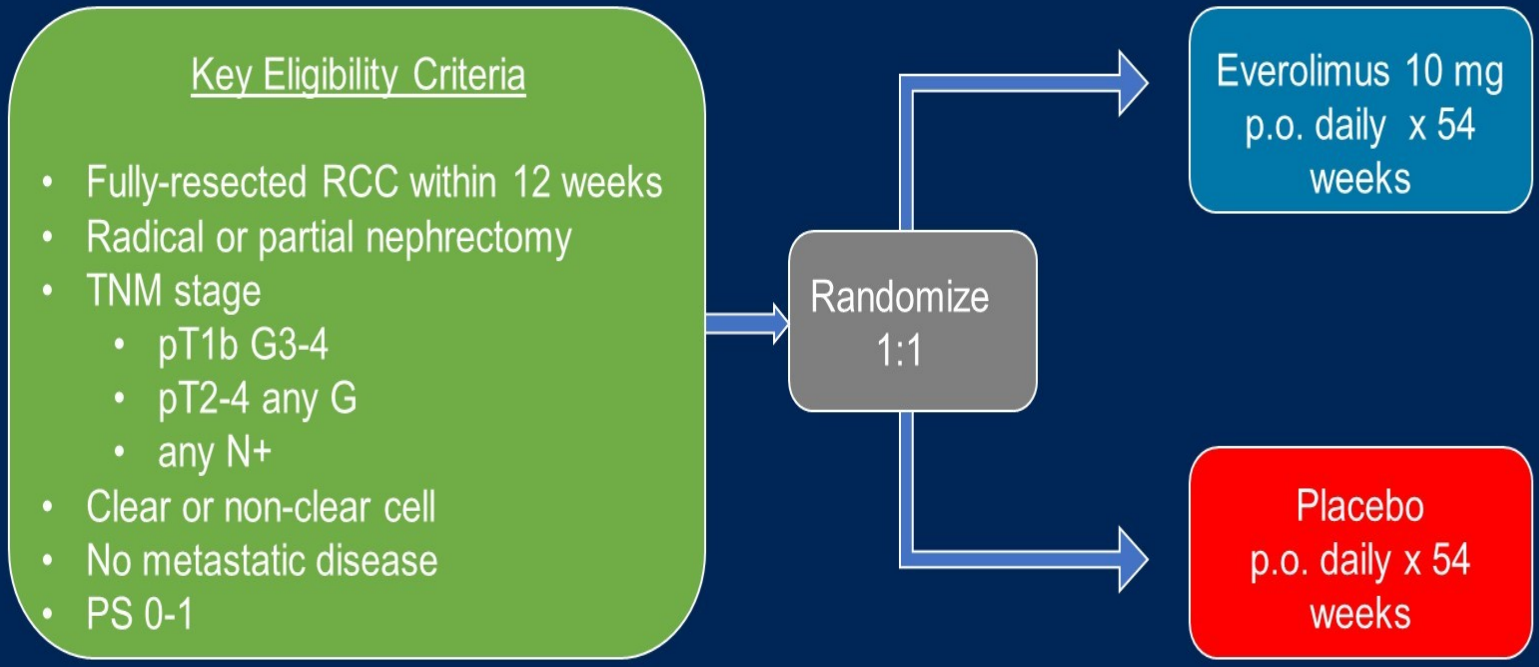
Trial	Agent	DFS HR	95% CI	P-value	OS
ASSURE	Sunitinib	1.02	0.85 - 1.23	P=0.80	NS
	Sorafenib	0.97	0.80 – 1.17	P=0.72	NS
SORCE	Sorafenib 3 yr	1.01	0.83 – 1.23	P=0.95	NS
	Sorafenib 1 yr	0.94	0.77 – 1.14	P=0.51	NS
PROTECT	Pazopanib	0.86	0.70 – 1.06	P=0.17	NS
ATLAS	Axitinib	0.87	0.66 – 1.15	P=0.32	NR
S-TRAC	Sunitinib	0.76	0.59 – 0.98	P = 0.03	NS
KEYNOTE-564	Pembrolizumab	0.63	0.50 - 0.80	P<0.0001	NS

* All placebo-controlled, DFS primary endpoint

Haas NB *Lancet* 2016; Eisen T *JCO* 2020; Motzer RJ *JCO* 2017 and *Eur Urol 2021* ; Gross-Goupil M *Ann* Oncol 2018; Rauvad A *N Engl J Med* 2016 and *Eur Urol* 2018; Choueiri TK *N Engl J Med* 2021 and GU ASCO 2022

PRESENTED BY:
Christopher W. Ryan, MD

Study Design



Stratification Factors:
Risk Group (Intermediate-High vs. Very High)
Histology (Clear cell vs. non-Clear Cell)
Performance Status (0 vs. 1)

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Objectives

- Primary
  - Recurrence-free survival – time from randomization to first documentation of RCC recurrence or death due to any cause
- Secondary
  - Overall survival
  - Toxicity
  - Bank biospecimens for future analysis
  - Investigate steady state everolimus trough levels and association with AEs[1]

1. Synold TW et al. *Kidney Cancer* 3:111-118, 2019

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S0931 Risk Stratification*

Intermediate High Risk			Very High Risk		
pT1b	pT2	pT3a	pT3a	pT3b-c, T4	Any pT
Grade 3-4	Any Grade	Grade 1-2	Grade 3-4	Any Grade	Any Grade
N0	N0	N0	N0	N0	N+

* Modified UCLA Integrated Staging System

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Baseline Characteristics

Characteristic	Everolimus (N=755)	Placebo (N=744)
Age, median (yrs)	58.7	58.4
Male	69%	70%
Performance Status		
0	80%	79%
1	20%	21%
Race		
White	91%	90%
Black	5%	4%
Asian	1%	3%
Other/Unknown	3%	3%

Characteristic	Everolimus (N=755)	Placebo (N=744)
Risk Group		
Very High	55%	55%
Intermediate High	45%	45%
Nephrectomy		
Radical	91%	89%
Partial	9%	11%
Histology		
Clear Cell	83%	84%
Non-Clear Cell	17%	16%
Papillary	8%	7%
Chromophobe	7%	6%
Other	2.5%	3.2%

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Treatment Delivery

	Everolimus (N=755)	Placebo (N=744)
Median time on treatment, months	9.3	12.6
Dose reductions	37%	7%
Discontinuation, not due to progression or death %	47%	17%

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Most Frequent Adverse Events

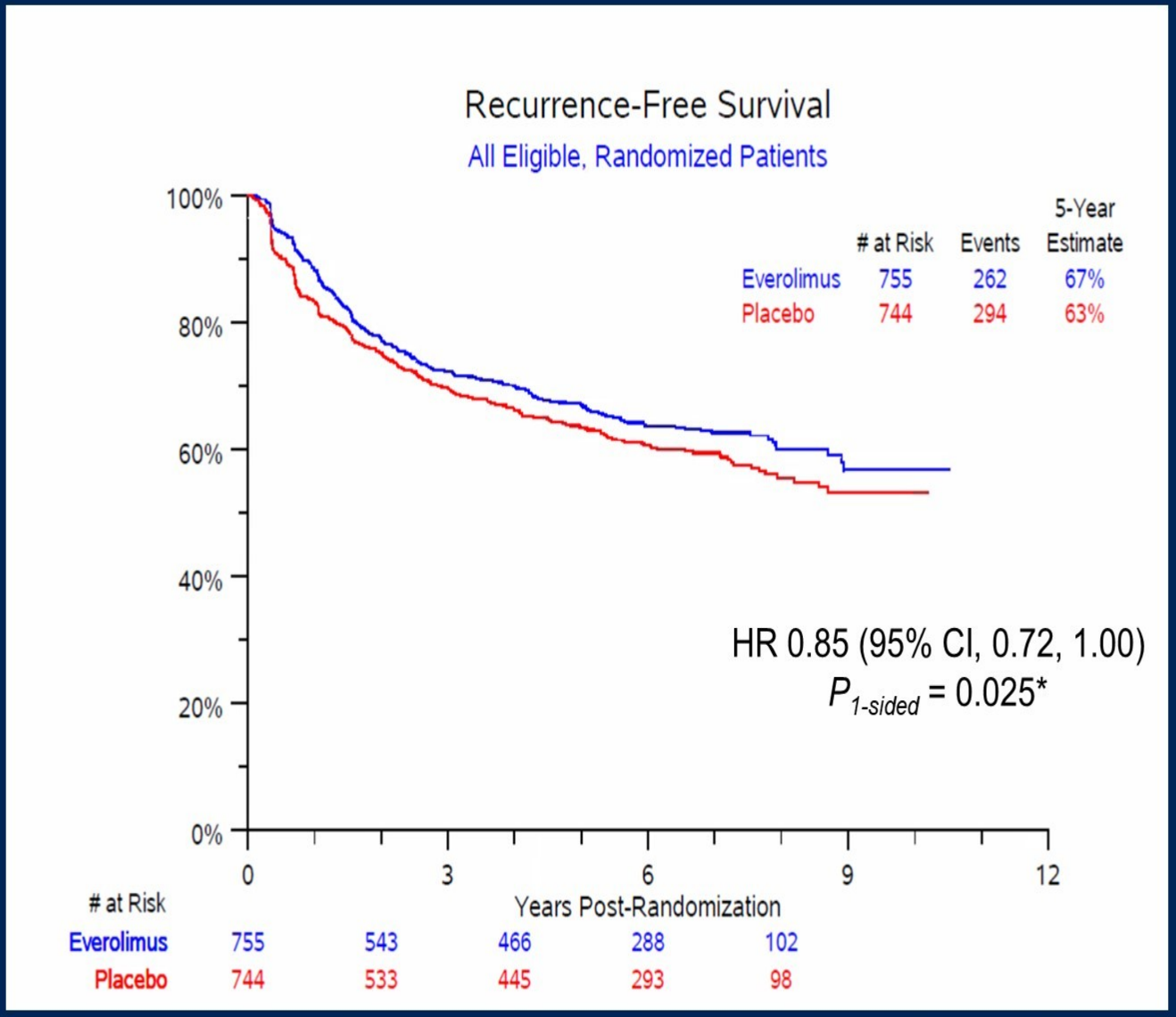
Adverse Event*	Everolimus (N=740)		Placebo (N=723)	
	All Grades	G3+	All Grades	G3+
Any AE**	96%	46%	81%	11%
Gastrointestinal				
Mucositis oral	64%	14%	19%	0%
Diarrhea	33%	1%	15%	1%
Nausea	24%	0	17%	0
Skin				
Rash maculo-papular	31%	2%	8%	0
Rash acneiform	29%	2%	5%	0
Pruritus	18%	1%	8%	0
Dry skin	17%	1%	8%	0

Adverse Event*	Everolimus (N=740)		Placebo (N=723)	
	All Grades	G3+	All Grades	G3+
Nervous System				
Headache	18%	0	11%	0
Vascular				
Hypertension	16%	4%	13%	3%
Nutrition				
Anorexia	16%	1%	5%	0
Respiratory				
Dyspnea	15%	1%	6%	0
Pneumonitis	13%	1%	0	0
General Disorders				
Fatigue	56%	4%	41%	1%
Edema limbs	15%	0	5%	0

* ≥10% incidence, any grade, treatment related

No grade 5 AEs

** Including lab abnormalities, worst grade for each patient



*did not cross prespecified p-value boundary for statistical significance of 0.022

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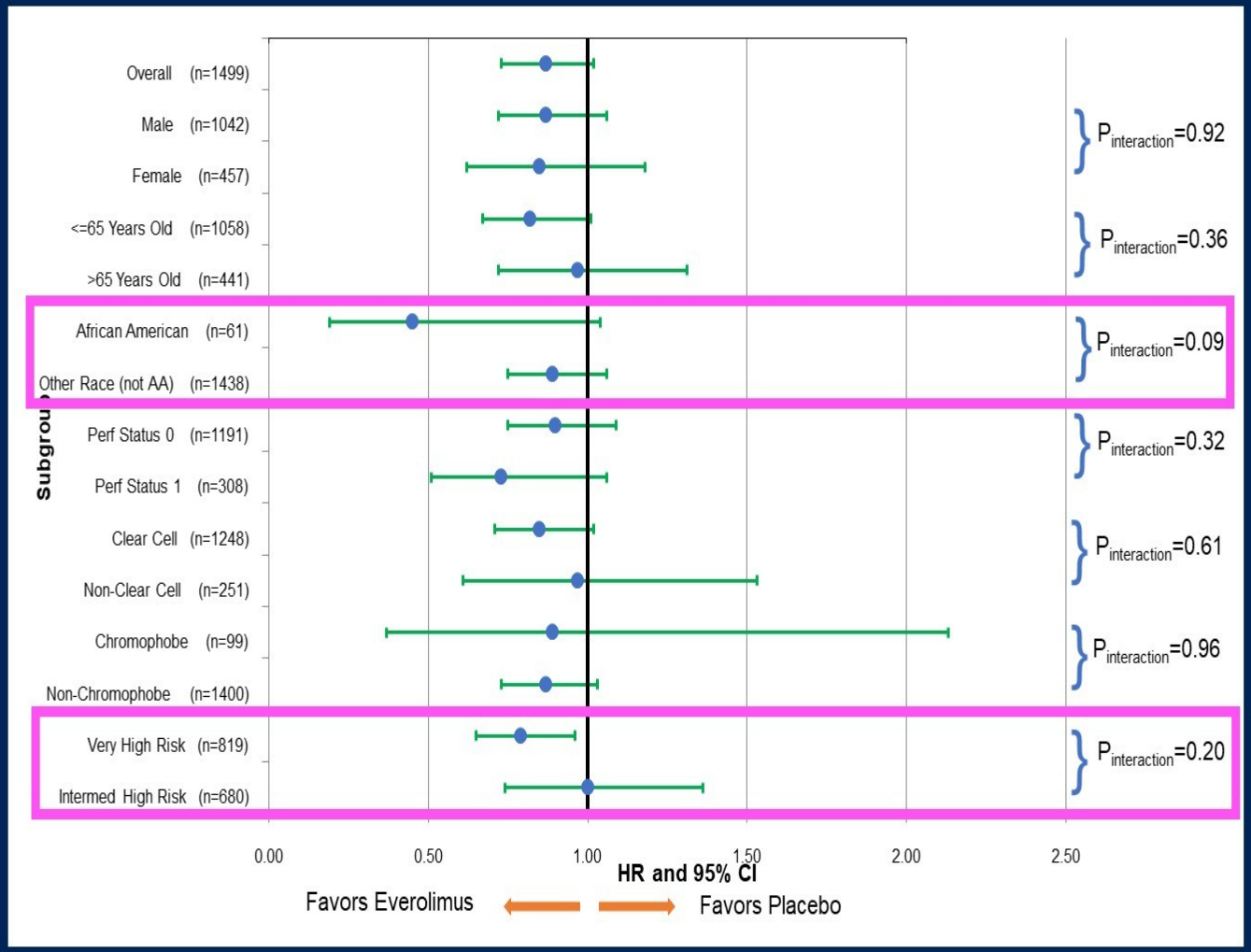
RFS Hazard Ratios and 95% CI by Subgroups



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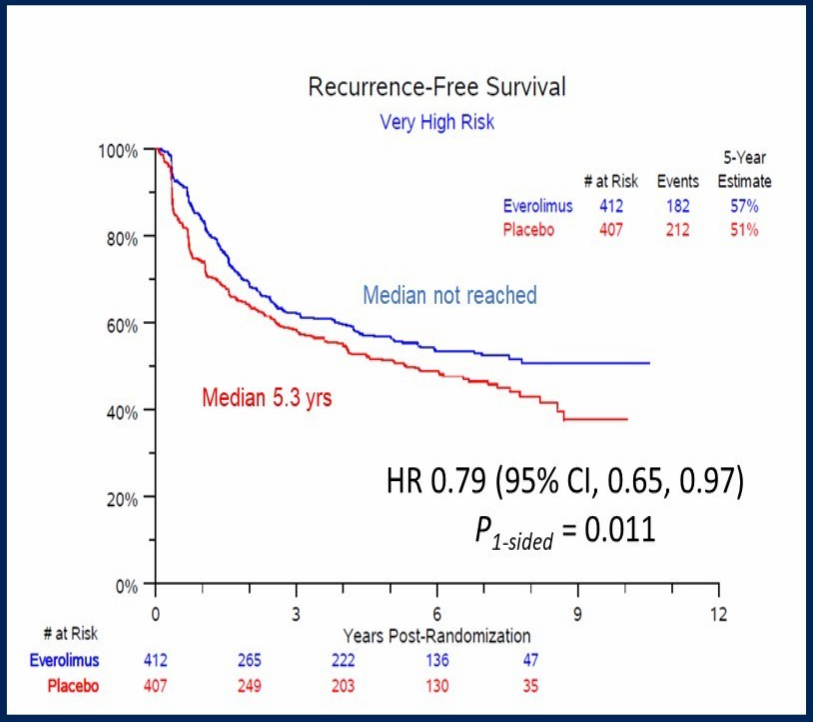
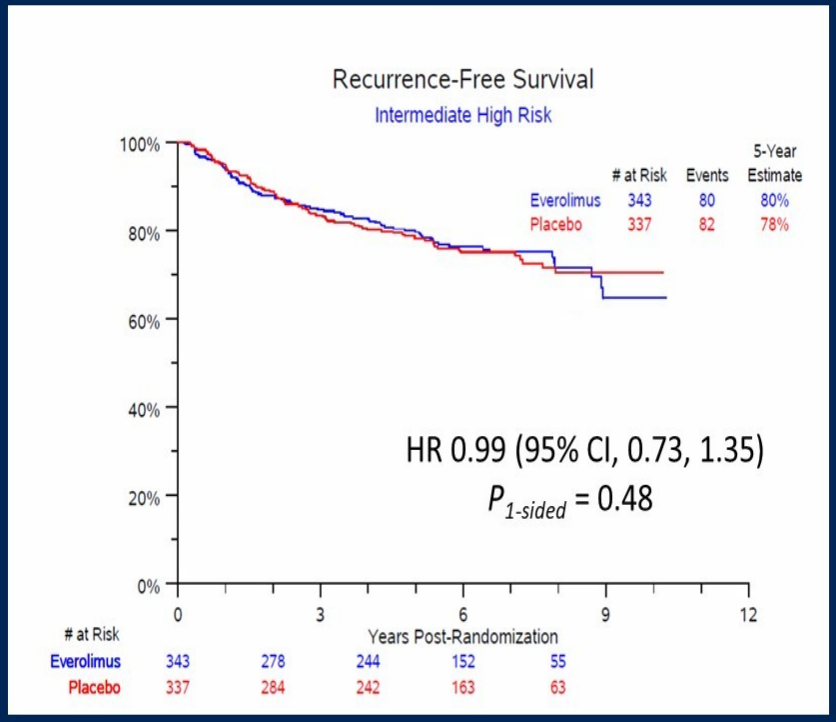
Christopher W. Ryan, MD

RFS Treatment Effect by Risk Group





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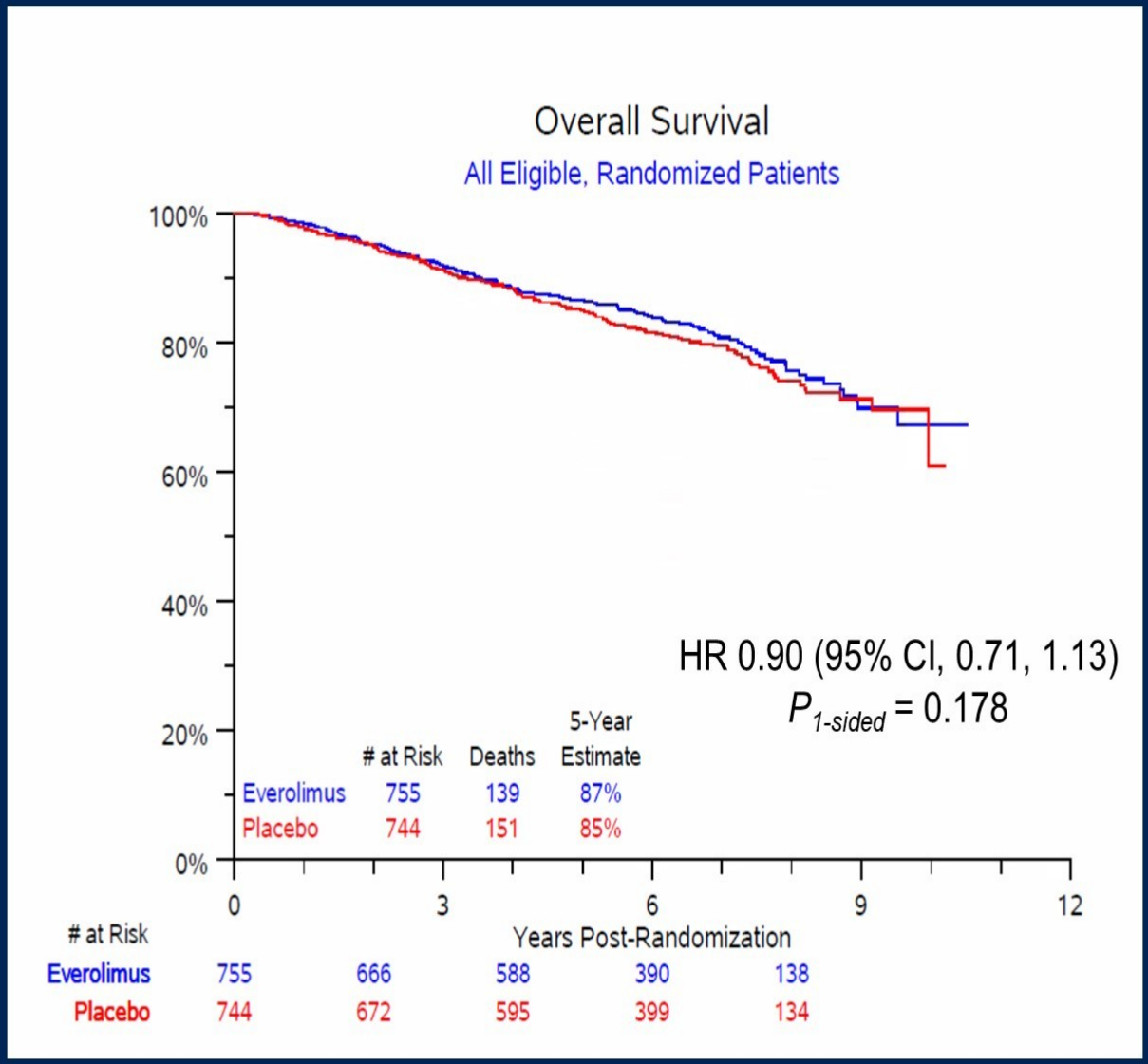

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Conclusions

- Adjuvant everolimus improved RFS in RCC patients after nephrectomy, but nominal significance level not reached
- The effect of everolimus was especially pronounced in patients with very high risk disease
- Adverse events were consistent with safety profile of everolimus, but there was a high discontinuation rate in this population
- The results of EVEREST warrant further investigation into the adjuvant role of everolimus and subsets that may benefit most

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1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

LBA4505: A randomised, double blind, phase II clinical trial of maintenance cabozantinib following chemotherapy for metastatic urothelial carcinoma (mUC): Final analysis of the ATLANTIS cabozantinib comparison.

Robert J Jones, et al.

Background and Rationale

- Until January 2021, standard treatment for advanced urothelial cancer in Europe was combination platinum-based chemotherapy followed by surveillance until progression[1]
- Though highly supportive of precision-medicine trials in urothelial cancer, our patient research partners advised that 'biomarker-negative' patients should, where possible, be offered inclusion in clinical trials
- Cabozantinib is a tyrosine kinase inhibitor for VEGFR, AXL, MET and RET which has shown clinical activity in platinum-pretreated progressive urothelial cancer[2]
- We therefore investigated cabozantinib in patients unsuitable for inclusion in the precision medicine arms of a maintenance-therapy platform trial in advanced urothelial cancer

[1]https://www.ema.europa.eu/; [2]Apolo, A et al. Lancet Oncol 2020 Aug;21(8):1099-1109.

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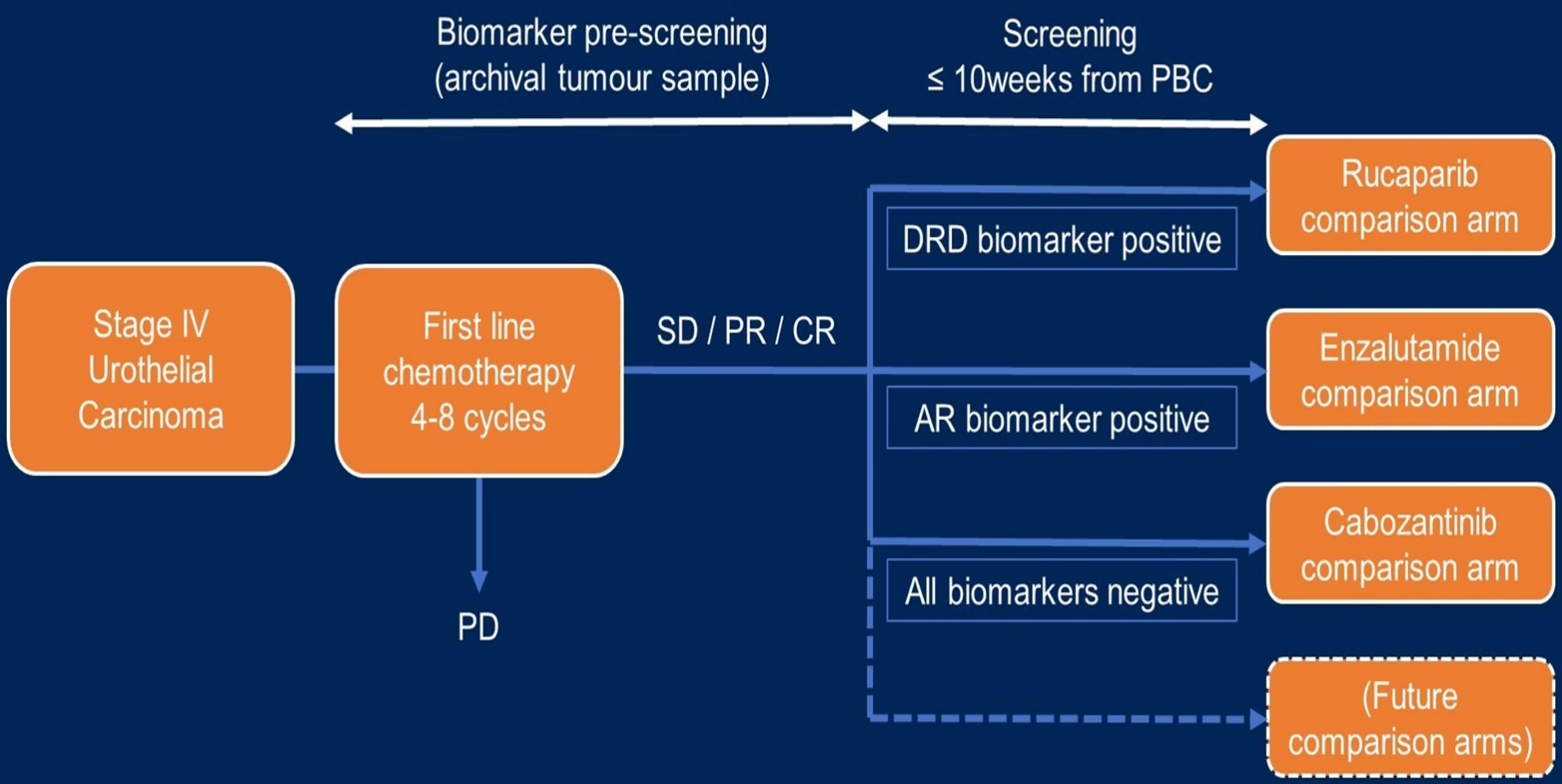
The ATLANTIS trial platform[1]



[1]Fulton et al, Trials. 2020 Apr 19;21(1):344

SD, stable disease; PR, partial response; CR, complete response; PD, progressive disease; DRD, DNA repair deficiency; AR, androgen receptor

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Cabozantinib comparison arm trial design[1]

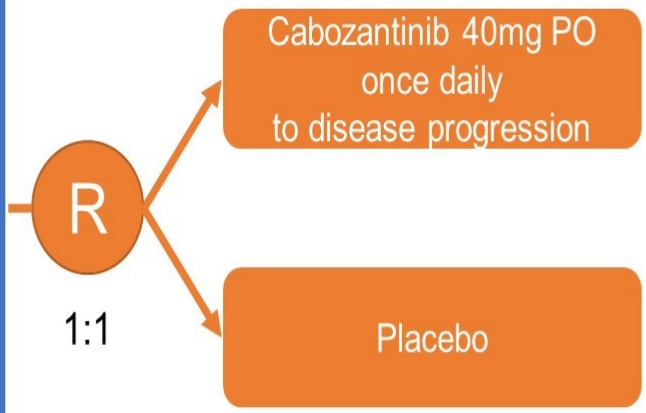
Patient population

Inclusion:

- Urothelial carcinoma
- T4b and/or N1-3 and/or M1
- ≤10 weeks from 4 to 8 cycles of chemotherapy
- ECOG performance status 0 to 2

Exclusion:

- Disease progression during chemotherapy



Primary endpoint:

- Progression free survival**

Secondary endpoints:

- Overall survival
- Confirmed response rates (RECIST v1.1)
- Safety and tolerability (CTCAE v4.03)

Population was enriched for patients who were excluded from other comparisons which required the following molecular characteristics:

- ≥10% genome-wide loss of heterozygosity
- Somatic alteration in any of: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*
- Androgen receptor positive by immunohistochemistry

Recruitment period Feb 2017 – March 2021

[1]Fulton et al, Trials. 2020 Apr 19;21(1):344. **Progression free survival, as assessed by investigator, was defined as time from randomisation until progressive disease (RECIST v1.1) or death from any cause

Patient characteristics

	Cabozantinib n=30		Placebo n=31	
Age				
Median (min, max)	70	(54, 83)	68	(40, 84)
Ethnicity, n (%)				
White	26	(87)	30	(97)
Asian	0	(0)	1	(3)
Other	4	(13)	0	(0)
Sex, n (%)				
Female	8	(27)	7	(23)
Male	22	(73)	18	(77)
ECOG PS, n (%)				
0	20	(67)	21	(68)
1	10	(33)	10	(32)
Smoking history, n (%)				
Current	5	(17)	3	(10)
Prior	11	(27)	15	(49)
Never	14	(47)	13	(42)
Histology, n (%)				
Pure TCC	26	(87)	28	(90)
Mixed TCC/SCC	4	(13)	3	(10)

	Cabozantinib n=30		Placebo n=31	
Bladder primary, n (%)				
Yes	23	(77)	23	(74)
No	7	(23)	8	(26)
Visceral metastases, n (%)				
Yes	10	(33)	12	(39)
No	20	(67)	19	(61)
First line chemotherapy, n (%)				
Cisplatin based	21	(70)	22	(71)
Carboplatin based	9	(30)	9	(29)
Best response to first line chemotherapy, n (%)				
SD	9	(30)	9	(29)
PR	17	(57)	17	(55)
CR	4	(13)	5	(16)

ECOG PS, Eastern Cooperative Oncology Group performance status; TCC, transitional cell carcinoma; SCC squamous cell carcinoma; SD, stable disease; PR, partial response; CR, complete response

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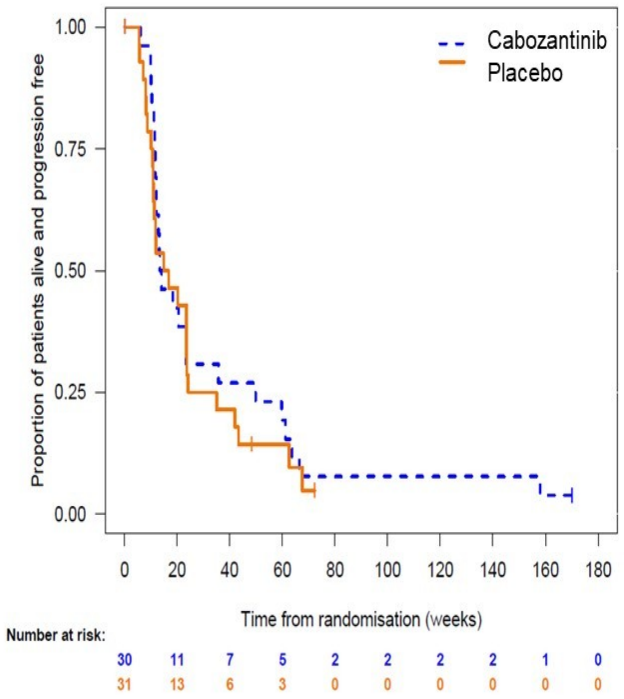
Progression free survival (primary endpoint)



	Cabozantinib	Placebo	p
PFS events	25 (83%)	26 (84%)	
Median PFS, weeks	13.7 (80% CI 12.1, 23.3)	15.8 (80% CI 11.3, 23.6)	
Hazard ratio*	0.89 (80% CI 0.61, 1.30)		0.35

*adjusted for minimisation factors

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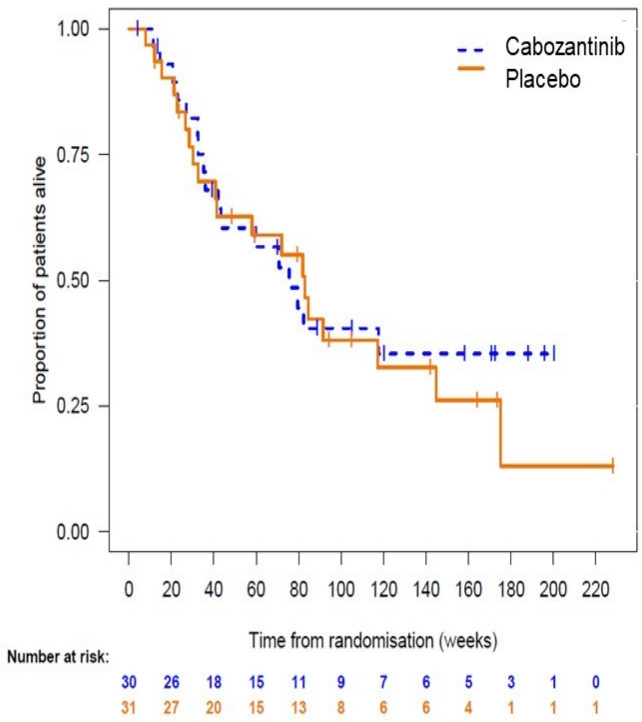
Overall survival (secondary endpoint)



	Cabozantinib	Placebo	p
OS events	17 (57%)	20 (65%)	
Median OS, weeks	75.5 (80% CI 43.4, 117.6)	82.9 (80% CI 58.0, 117.1)	
Hazard ratio*	0.80 (80% CI 0.52, 1.30)		0.25

*adjusted for minimization factors

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Response and duration of therapy

	Cabozantinib n=30	Placebo n=31
Median duration on treatment, cycles*	13	10
Confirmed objective responses		
Partial response	1	1
Complete response	0	1
Overall response rate	3.3%	6.5%

*Treatment cycles were of 28 days

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Robert Jones, University of Glasgow

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Safety*

	Cabozanitinib n=30(%)		Placebo n=31 (%)		p
	All grade	Grade ≥3	All grade	Grade ≥3	
Abdominal pain	6 (20)	-	2 (6.5)	-	0.16
Anorexia	**9 (30)**	**-**	**3 (9.7)**	**-**	**0.04**
Diarrhoea	**12 (40)**	**1 (3.3)**	**2 (6.5)**	**-**	**<0.01**
Fatigue	**17 (56.7)**	**0 (0)**	**10 (32.2)**	**-**	**0.02**
Headache	4 (13.3)	1 (3.3)	1 (3.2)	-	0.16
Hypertension	**13 (43.3)**	**7 (23.3)**	**4 (12.9)**	**-**	**<0.01**
Hyperthyroidism	6 (20)	-	1 (3.2)	-	0.06
Hypothyroidism	**6 (20)**	**-**	**1 (3.2)**	**-**	**<0.05**
Nausea	9 (30)	-	6 (19.4)	-	0.37
Pruritis	6 (20)	-	3 (9.7)	1 (3.2)	0.27
Rash	**8 (26.7)**	**1 (3.3)**	**1 (3.2)**	**-**	**0.01**
Vomiting	4 (13.3)	-	2 (6.5)	-	0.37

	Cabozantinib n=30		Placebo n=31		p
	Grade ≥2	Grade ≥3	Grade >2	Grade ≥3	
Anemia	2 (6.7)	-	5 (16.1)	-	0.26
Lymphocytopenia	3 (10)	-	6 (19.4)	-	0.69
Neutropenia	**4 (16.7)**	**2 (6.7)**	**1 (3.2)**	**-**	**0.03**
Hypoalbuminemia	3 (10)	-	1 (3.2)	-	0.30
Hypophosphatemia	10 (33.3)	1 (3.3)	4 (12.9)	3 (9.7)	0.10

Dose reductions	Cabozantinib n=30 (%)	Placebo n=31 (%)
0	17 (57)	28 (90)
1	13 (43)	3 (10)

*Treatment related adverse events occurring in ≥10% of patients within either treatment arm

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Conclusions

- Though underpowered, this study does not support further investigation of cabozantinib alone as a maintenance therapy after platinum-based chemotherapy in unselected patients with advanced urothelial cancer
- Negative patient selection for DRD and AR biomarkers may bias interpretation
- Placebo is no longer an acceptable control arm in this indication
- Future trials should consider combining novel agents with maintenance immunotherapy

DRD = DNA repair deficiency; AR = Androgen Receptor

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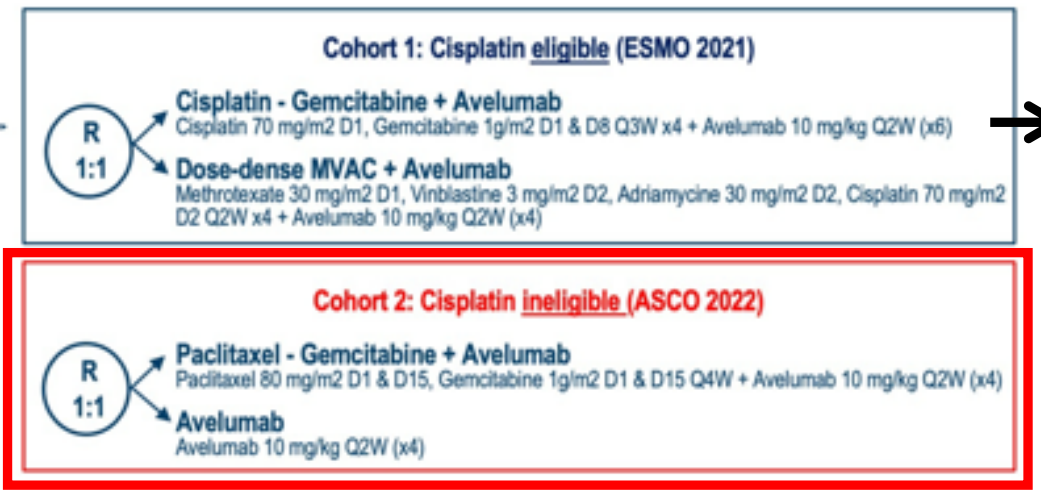
#4517: Avelumab as the basis of neoadjuvant regimen in platinum-eligible and -ineligible patients with nonmetastatic muscle-invasive bladder cancer: AURA (Oncodistinct-004) trial.

Nieves Martinez Chanza, et al.

Hintergrund und Studiendesign

- Cisplatin-basierte neoadjuvante Chemotherapie ist der Therapiestandard des muskelinvasiven Blasenkarzinoms
- Für Cisplatin ungeeigneten Patienten (etwa 50% der Patienten) existiert keine zugelassene Alternativtherapie
- Für Checkpointinhibitoren wurde in Studien vielversprechende Antitumoraktivität gezeigt
- Der CKI Avelumab wird bereits routinemäßig beim fortgeschrittenen Urothellarzinom eingesetzt

CLINICAL TRIAL DESIGN



In der Cisplatin-fähigen Kohorte der AURA Studie zeigte die neoadjuvante Avelumab-Therapie in Kombination mit Cisplatin-haltiger Chemotherapie hohe Raten kompletter pathologischer Remission:
- DD-MVAC + A: 64%
- CG + A: 57%

Patienten Charakteristik

BASELINE CHARACTERISTICS AND TREATMENT EXPOSURE

A total of 56 cisplatin-ineligible patients from 8 institutions in Belgium and France were evaluable.

Variable	PG + A N = 28	A N = 28
Median age at diagnosis, years (range)	72 (41-80)	75 (49-89)
Male gender, n (%)	26 (93%)	26 (93%)
Histology, n (%) - Pure UC - UC with mixed histology[1]	 22 (79%) 6 (21%)	 22 (79%) 6 (21%)
ECOG PS, n (%) - 0 - 1	 14 (50%) 14 (50%)	 11 (39%) 17 (61%)
Cisplatin inelegibility[2], n(%) - Renal impairment - Hearing loss - Peripheral neuropathy - Heart failure	 17 (61%) 5 (18%) 1 (4%) 7 (25%)	 22 (79%) 8 (29%) 1 (4%) 4 (14%)
Median BMI, kg/m^2 (range)	26,1 (17,9-36,5)	27,4 (22,3-34,3)
Previous intravesical BCG treatment, n (%)	1 (4%)	1 (4%)
Avelumab cycles received, n(%) - 4 - 3 - 1	 25 (89%) 2 (7%) 1 (4%)	 26 (93%) 1 (4%) 1 (4%)

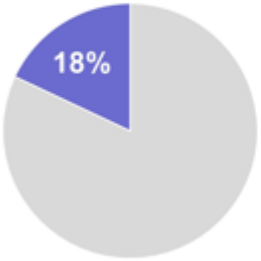
[1]Mixed histology with predominant urothelial component (>50%)
[2] Can have more than one criteria
UC: Urothelial carcinoma; ECOG PS: Eastern Cooperative Oncology Group Performance status; BMI: Body mass index; BCG: Bacillus Calmette-Guérin

Ergebnisse

PATHOLOGICAL RESPONSE BY TREATMENT TYPE

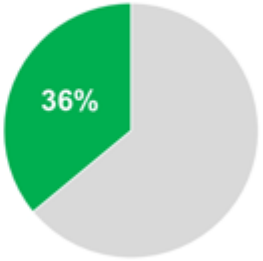
- **pCR** - *pCR rate includes ypT0/Ta/TisN0*

PG + A



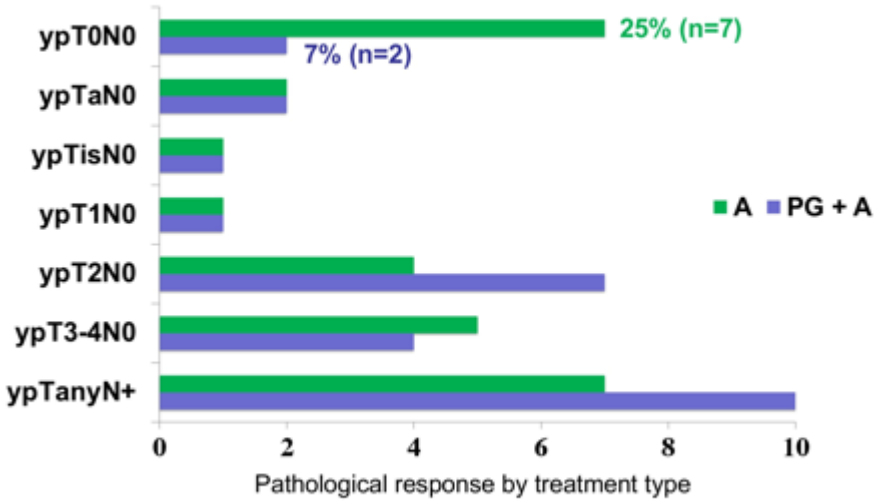
18% (95%CI 6%-37%)

A



36% (95%CI 19%-56%)

- **Pathological response**



**One patient treated with A did not undergo surgery due to progression disease*

Toxizität

SAFETY

- **Immune-related AEs**

Immune-related AEs, n (%)[a]	PG + A (N = 28)		A (N = 28)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Asthenie	7 (25%)	0 (0%)	6 (18%)	0 (0%)
Fatigue	3 (11%)	0 (0%)	5 (18%)	0 (0%)
Rash	3 (11%)	0 (0%)	2 (7%)	0 (0%)
Pruritis	3 (11%)	0 (0%)	2 (7%)	0 (0%)
Colitis	3 (11%)	0 (0%)	3 (11%)	0 (0%)
Arthritis	3 (11%)	0 (0%)	0 (0%)	0 (0%)
Myalgia	2 (7%)	0 (0%)	3 (11%)	0 (0%)
Hyperthyroidism	0 (0%)	0 (0%)	2 (7%)	0 (0%)
Hypothyroidism	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Nausea	2 (7%)	0 (0%)	1 (4%)	0 (0%)
Infusion site reaction	0 (0%)	0 (0%)	2 (7%)	0 (0%)
Hepatitis[b]	2 (7%)	1 (4%)	2 (7%)	0 (0%)
Pneumonitis[c]	1 (4%)	1 (4%)	0 (0%)	0 (0%)

[a] No treatment-related deaths were reported.
[b] One patient treated with **PG + A** developed **grade 3 hepatitis**.
[c] One patient treated with **PG + A** developed **grade 3 pneumonitis** that required systemic steroids and avelumab discontinuation.

- **Feasibility**
  - **No patient failed to undergo surgery due to an adverse event**
  - **No major surgical complications and morbidity were described**
  - Median time from treatment initiation to surgery:
    PG + A : 79 days (49-143)
    A : 64 days (39-81)

FAZIT

- Eine neoadjuvante Avelumab-Therapie führt zu hoher Rate pathologischer Remissionen
- Avelumab + GP führt zu keiner Verbesserung der Rate pathologischer Remissionen
- Avelumab in der Neoadjuvanz ist sicher und führte zu keiner erhöhten chirurgischen Morbidität