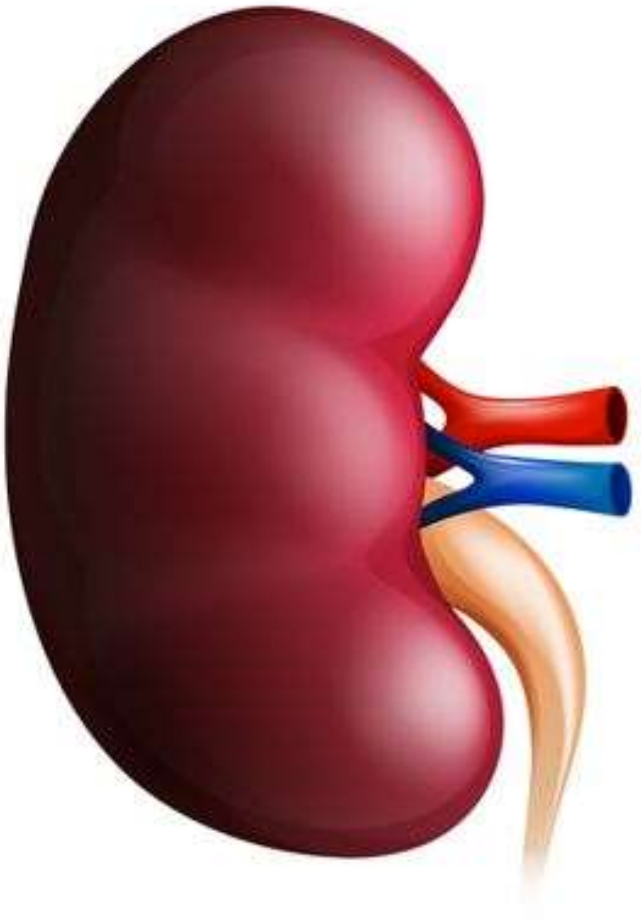
2019 AIOM REVIEW: FROM CHICAGO TO VERONA

Poster Review

Dr Matteo Santoni

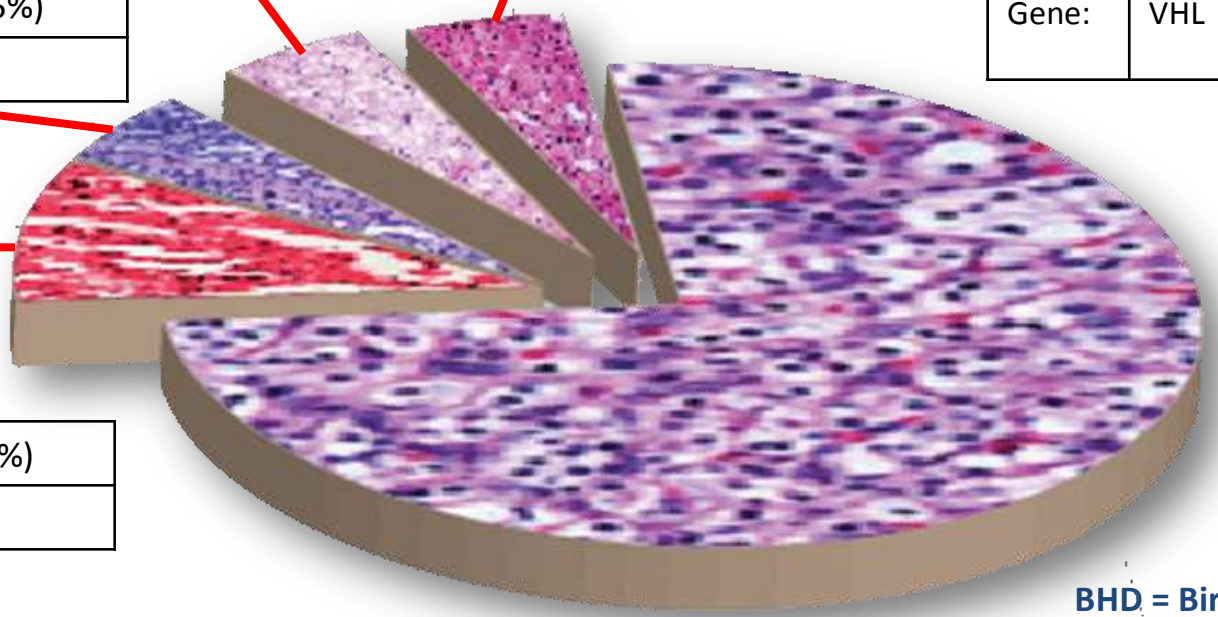
Oncologia Medica - Ospedale di Macerata

Associazione Italiana di Oncologia Medica



KIDNEY CANCER

Gene expression



BHD = Birt-Hogg-Dubé

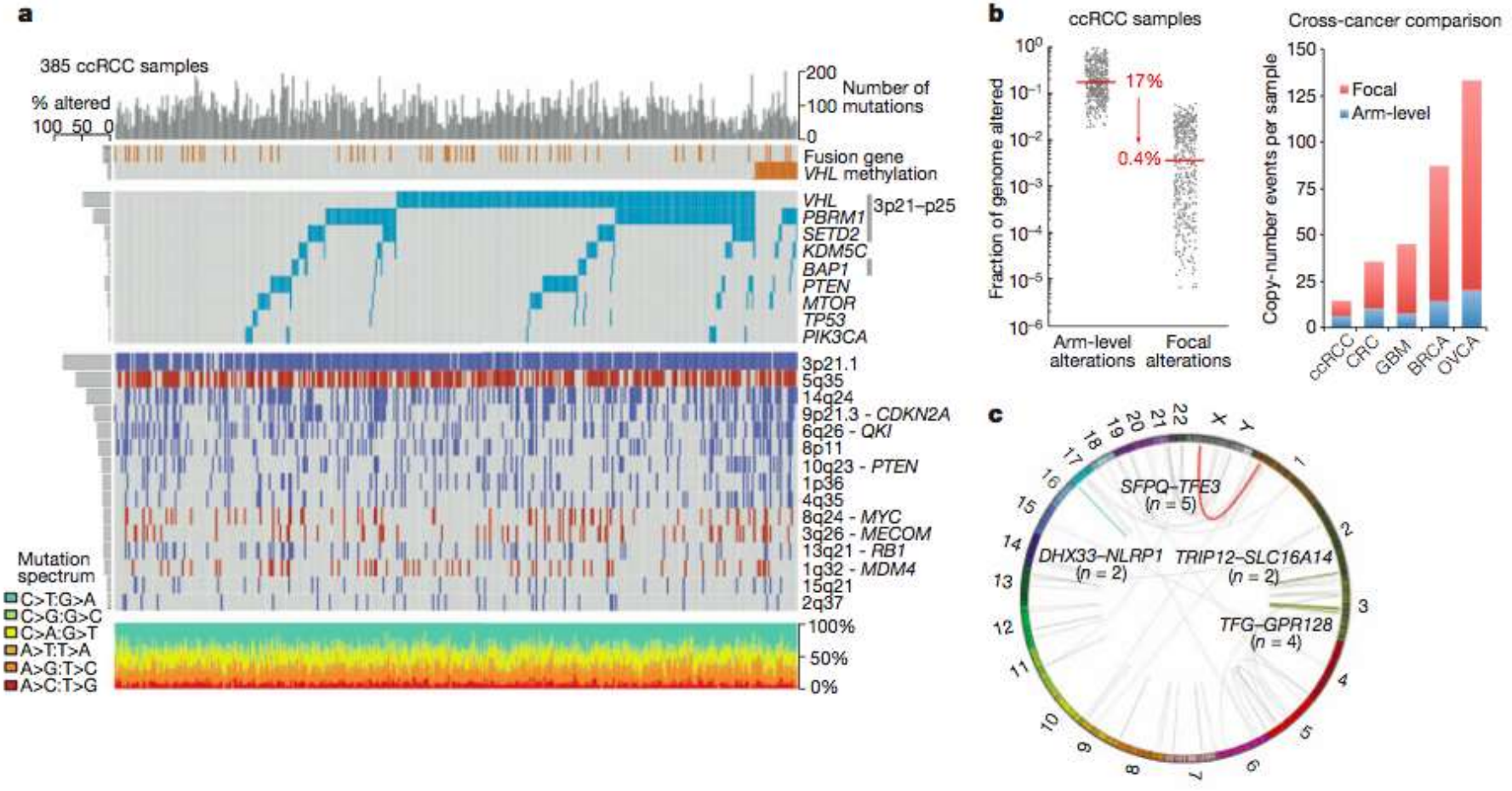
FH = Fumarate hydratase

VHL = von Hippel-Lindau

Linehan WM, et al. In: *Cancer: Principles and Practice of Oncology.* 2006:1139-1140.

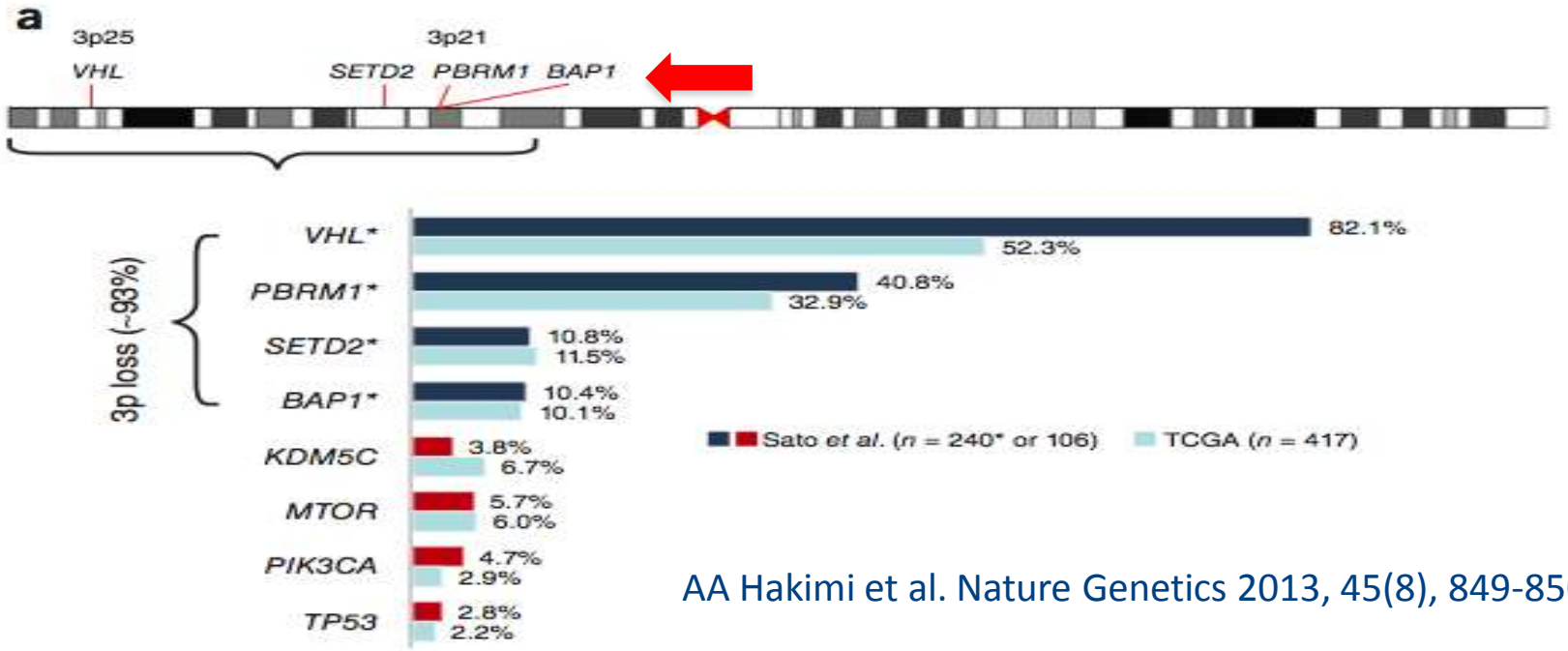
A lot of new genes: SEDT2, PBRM1, BAP1, KMD61, NF2…

Promise: Progress in Genome Sequencingc - RCC

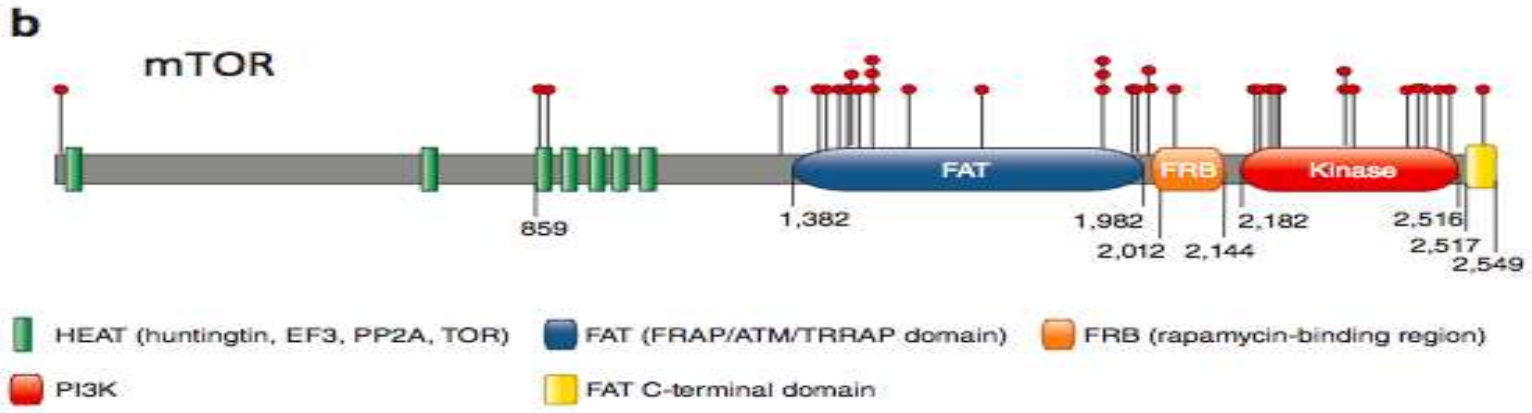


The Cancer Genome Atlas Research Network; Nature 2013, doi:10.1038/nature12222

Promise: Progress in Genome Sequencing - RCC



AA Hakimi et al. Nature Genetics 2013, 45(8), 849-850



Unraveling the molecular profile underpinning pancreatic tropisms in metastatic clear cell renal cell carcinoma.

Author(s): Nirmish Singla, Oreoluwa Onabolu, Layton Woolford, Christina Stevens, Vanina Tcheuyap, Tiffani McKenzie, Qurratulain Yousuf, Yuanqing Ma, Jacob Choi, Ze Zhang, Zhiqun Xie, Tao Wang, Renee McKay, Alana Christie, Ivan Pedrosa, Christopher Przybycin, Payal Kapur, Brian I. Rini, James Brugarolas; University of Texas Southwestern Medical Center, Dallas, TX; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; UT Southwestern Medical Center, Dallas, TX; The University of Texas Southwestern Medical Center, Dallas, TX; Cleveland Clinic Department of Pathology, Cleveland, OH

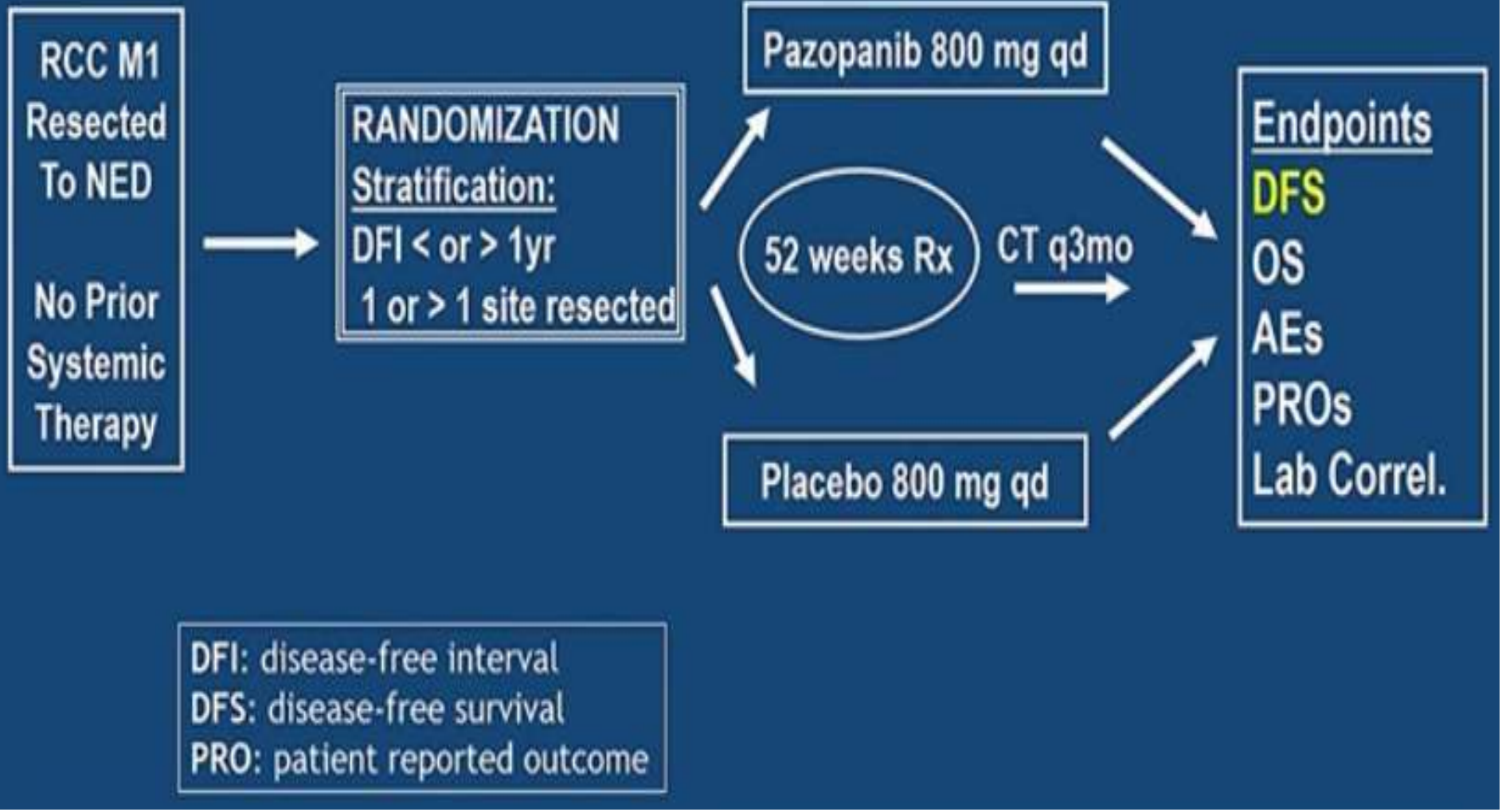
Background: The tropism of cancer metastases is poorly understood yet holds prognostic value. Clear cell renal cell carcinoma (ccRCC) exhibits a broad pattern of metastases, making it an optimal model to study organotropism. Notably, when ccRCC metastasizes to the pancreas (PM) independently of other sites, it is associated with favorable outcomes in patients for unclear reasons. Here, we comprehensively analyzed the clinical and molecular profile of patients with PM. **Methods:** RCC patients with PM from UTSW and Cleveland Clinic were identified. Clinicopathologic data and oncologic outcomes were analyzed. Whole exome sequencing (WES), RNAseq, and histologic assessment of primary and metastatic tumors from PM patients were conducted. **Results:** 31 RCC patients with PM were identified. We observed remarkably favorable outcomes in our PM cohort, with a median overall survival (OS) of 10.7 years from metastatic diagnosis and a long latency between initial diagnosis and development of metastasis (median 69 months in patients who were non-metastatic at diagnosis). OS was independent of both metastatic tumor burden and known IMDC prognostic factors. We discovered that tumors from PM patients were markedly uniform and clustered together by gene expression analysis. WES and DNA copy number analyses revealed a high frequency of *VHL* and *PBRM1* mutations, 3p loss, and 5q amplification, along with a lower frequency of 9p, 14q and 4q losses and *BAP1* mutations, characteristic of indolent ccRCC. Furthermore, the genomic and histologic features of tumors from patients with PM can be recapitulated in patient-derived xenograft models. **Conclusions:** To our knowledge, this is the first report to unravel molecular determinants of organotropism, and we highlight that organotropism can be an independent prognostic factor. Understanding tumor heterogeneity may help refine prognostic models for metastatic RCC and hold implications for improved personalization of therapy.

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)

Leonard J. Appleman, Maneka Puligandla, Sumanta K. Pal, Wayne Harris, Neeraj Agarwal, Brian A. Costello, Christopher W. Ryan, Michael Pins, Jill Kolesar, Daniel A. Vaena, Rahul A. Parikh, Mehmood Hashmi, Janice P. Dutcher, Robert S. DiPaola, Naomi B. Haas, Michael A. Carducci;

UPMC Hillman Cancer Center, Pittsburgh, PA; Dana Farber Cancer Institute, Boston, MA; City of Hope Comprehensive Cancer Center, Duarte, CA; Emory University School of Medicine, Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Mayo Clinic, Rochester, MN; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; University of Illinois College of Medicine, Chicago, IL; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer Center, Iowa City, IA; University of Kansas Cancer Center, Westwood, KS; University of Kansas, Kansas City, KS; Our Lady of Mercy Cancer Center, New York, NY; University of Kentucky, Lexington, KY; Penn Medicine Abramson Cancer Center, Philadelphia, PA; Sidney Kimmel Cancer Center At Johns Hopkins, Baltimore, MD

E2810 STUDY SCHEMA

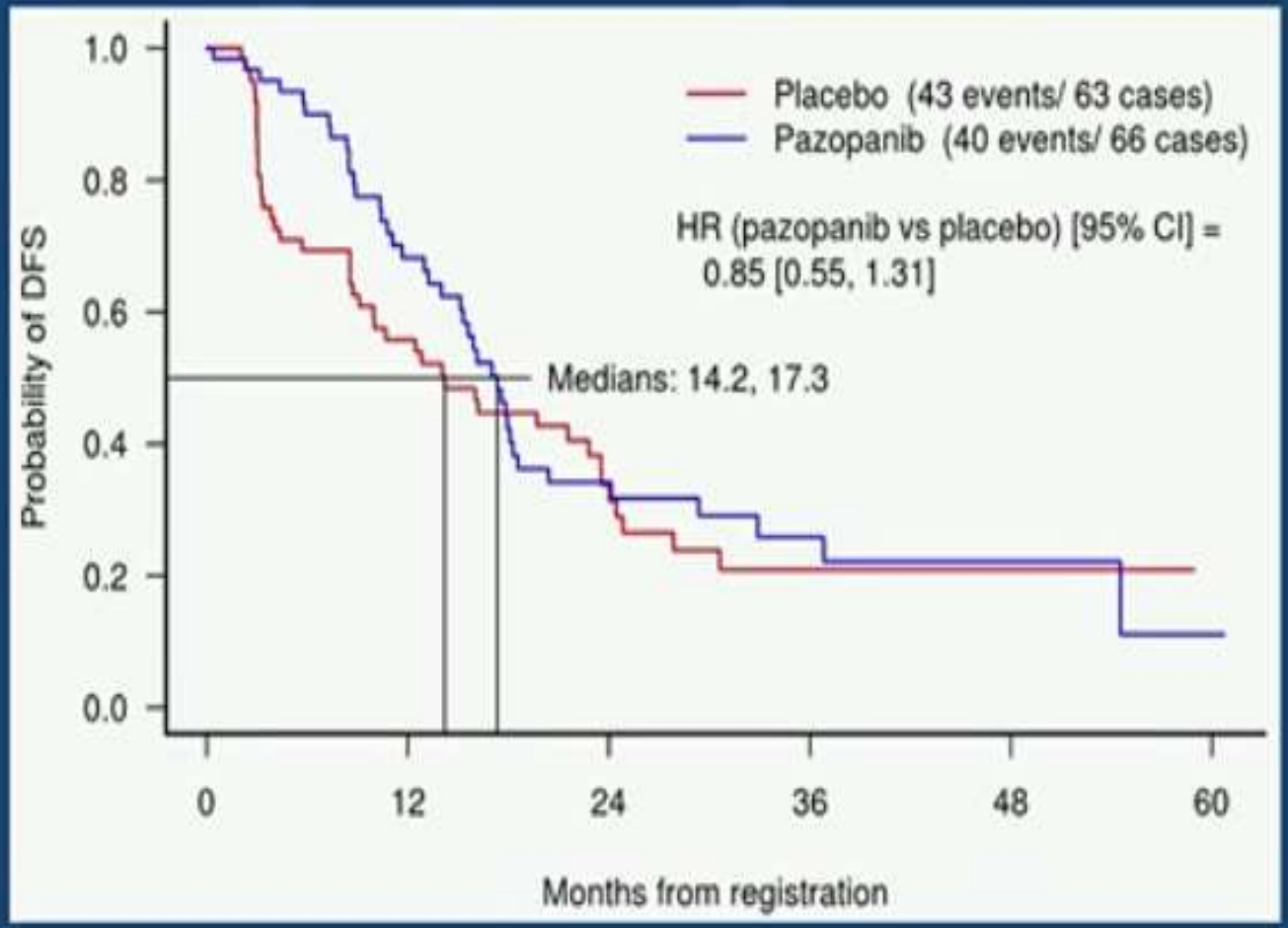


DFI: disease-free interval
DFS: disease-free survival
PRO: patient reported outcome

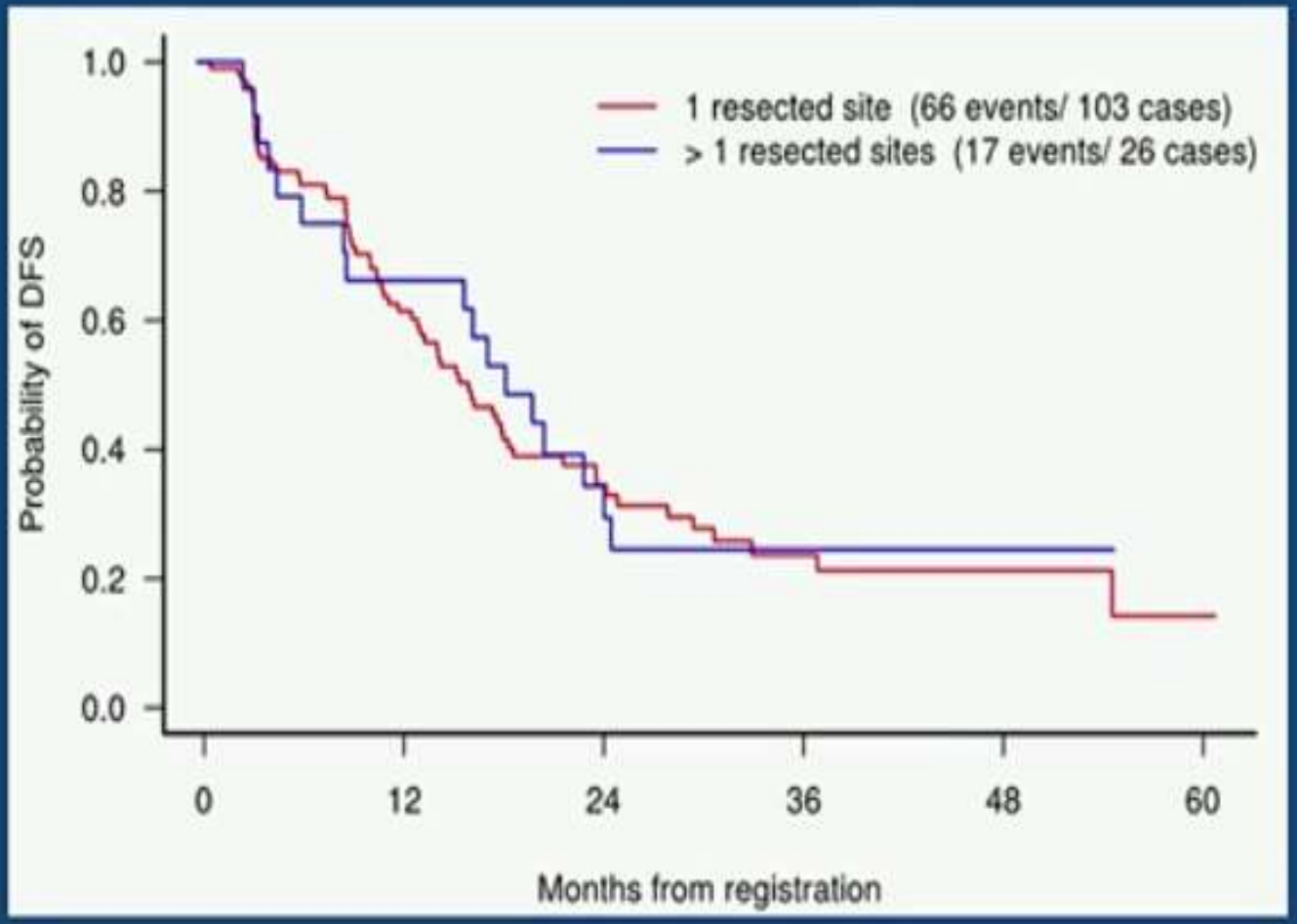
E2810 Key Eligibility

- Synchronous or metachronous primary/metastases allowed
- Any number of resected metastases or past surgeries allowed
- Must have a clear cell component
- No evidence of disease (NED) on baseline staging scans
- ECOG performance status 0-1
- Enrolled within 12 weeks of surgery
- No prior systemic therapy for RCC

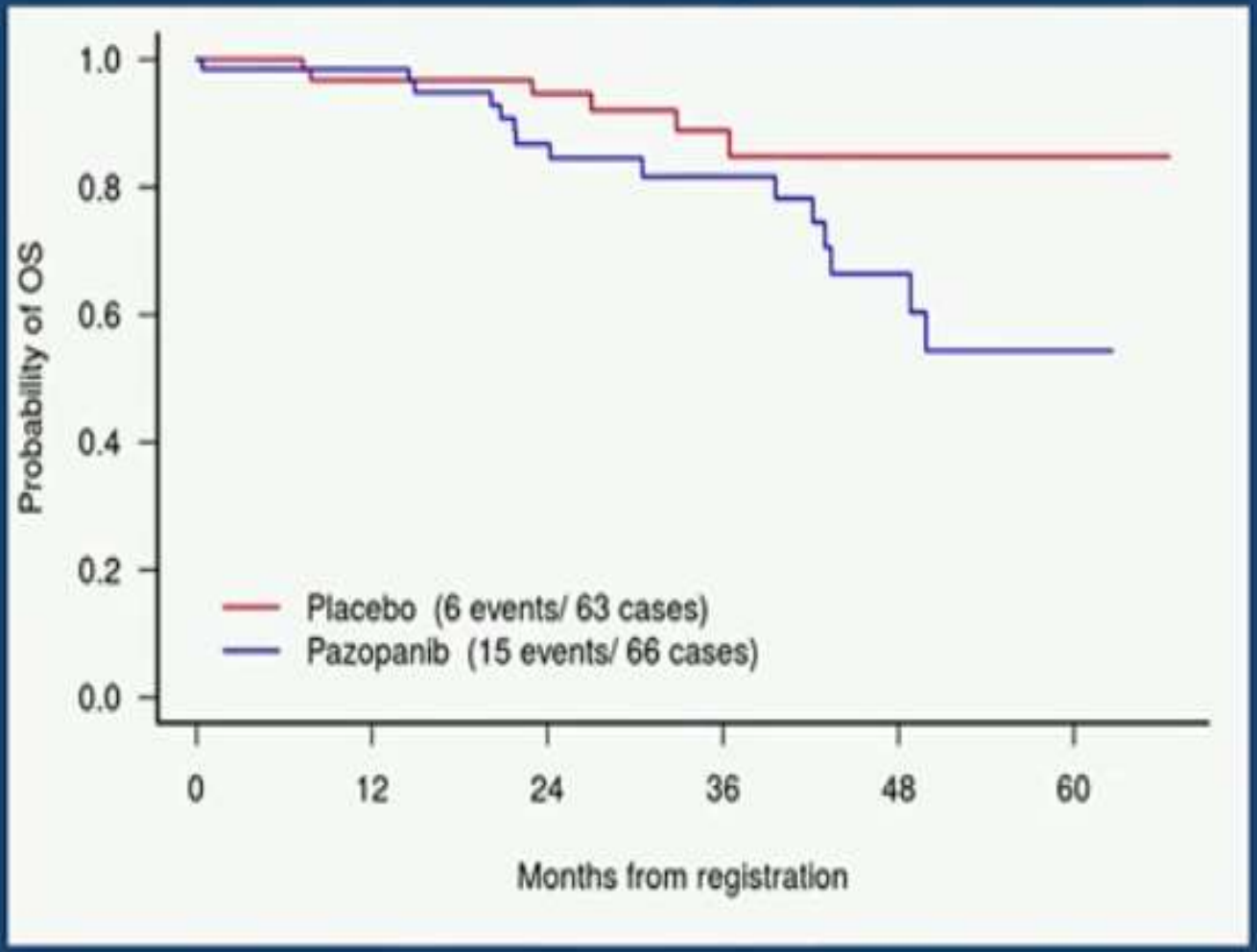
Pazopanib did not improve disease-free survival



DFS by Stratification Factor: Number of Resected Sites



Overall Survival by Blinded Treatment Arm



Hazard Ratio for OS was 2.65 (1.02, 6.9) in favor of placebo (p=0.05)

First-line (1L) immuno-oncology (IO) combination therapies in metastatic renal-cell carcinoma (mRCC): Results from the international mRCC database consortium (IMDC).

Background: In mRCC, ipilimumab and nivolumab (ipi-nivo) is a 1L treatment option. Recent data have also shown efficacy of 1L IO-VEGF (IOVE) inhibitor combinations. Comparative data between these two strategies are limited and the efficacy of subsequent therapies remains unknown. **Methods:** Using the IMDC dataset, patients (pts) treated with any 1L IOVE combination were compared to those treated with ipi-nivo. Multivariable Cox regression analysis was performed to control for imbalances in IMDC risk factors. **Results:** 188 pts received 1L IO combination therapy: 113 treated with IOVE combinations and 75 with ipi-nivo. Baseline characteristics and IMDC risk factors were comparable between groups. When comparing IOVE combinations vs ipi-nivo, 1L response rate (RR) was 33% vs 40% (p=0.39), time to treatment failure (TTF) was 14.3 (95% CI 9.2-16.1) vs 10.2 months (95% CI 6.7-15.1, p=0.23), and median overall survival (OS) was not reached (NR) (95% CI 22.3-NR) vs NR (95% CI 35.1-NR, p=0.17). When adjusted for IMDC risk factors, the hazard ratio (HR) for TTF was 0.71 (95% CI 0.46-1.12, p=0.14) and the HR for death was 1.74 (95% CI 0.82-3.68, p=0.14). Second-line (2L) treatments were varied. In pts receiving subsequent VEGF-based therapy, 2L RR was lower in the IOVE (n=20) versus ipi-nivo (n=20) cohort (15% vs 45%; p=0.04), though 2L TTF was not significantly different (3.7 vs 5.4 months, p=0.40, n=55). The use of IO post IOVE was uncommon and 3/5 pts had PD as best response; 2/5 had PR/SD but their 1L IOVE exposure was short at <3 months. **Conclusions:** There does not appear to be a superior 1L IO combination strategy in mRCC, as IOVE combinations and ipi-nivo have comparable 1L RR, TTF and OS. Most pts received VEGF-based therapy in the 2L. In this group, 2L RR was greater in pts who received ipi-nivo, though there was no difference in 2L TTF.

	IO-VEGF (N=113)	Ipi-Nivo (N=75)
IMDC Risk Groups		
Favourable	29/92 (32%)	17/64 (27%)
Intermediate	49/92 (53%)	33/64 (52%)
Poor	14/92 (15%)	14/64 (22%)
2L Treatments		
Axitinib	5/34	2/30
Cabozantinib	9/34	2/30
Lenvatinib + Everolimus	2/34	0/30
Nivolumab	5/34	0/30
Pazopanib	2/34	9/30
Sunitinib	9/34	15/30
Other	2/34	2/30

	IO + VEGF	Ipi + Nivo
Response Rate	33%	40%
Overall Survival	N.R.	N.R.
RR at second line	15%	45%


RURAL VS. URBAN

Impact of rural/urban residence on relative survival (RS) in patients with kidney cancer: An analysis of 14576 patients from the Austrian National Cancer Registry (ANCR).

Author(s): Martin Marszalek, Henrike E Karim-Kos, Stephan Madersbacher, Michael Rauchenwald, Monika Hackl; Department of Urology, Graz, Medical University, Graz, Austria; Department of Public Health, Erasmus MC University Medical Center, Rotterdam, Netherlands; Sozialmedizinisches Zentrum Sud, Vienna, Austria; Sozialmedizinisches Zentrum Ost - Donauspital, Vienna, Austria; Austrian National Cancer Registry, Statistics Austria, Vienna, Austria

Background: Access to medical diagnostics and treatment might be limited for patients living in rural areas compared to urban residents. To evaluate the potential impact of urban/rural residence, we analyzed trends in RS for patients diagnosed with kidney cancer between 1998 and 2015 in Austria. **Methods:** All patients with kidney cancer aged ≥18 years, diagnosed between 1998 and 2015 were derived from the ANCR (N = 22,041). Patients were categorized into two groups: rural (N = 7,53) and urban (N = 10,552) based on a complex algorithm considering infrastructure, commuter interrelations, accessibility of centers and tourism at the time of diagnosis. Relative survival was calculated based on complete follow-up until December 31st, 2016. Poisson regression modeling was used to evaluate survival differences between the two groups and to calculate the relative excess risk of dying (RER). Analyses were performed for the total patient population and primary metastatic patients (M+, N = 2,490). **Results:** Distribution of age and surgical treatment did not differ between rural and urban patients. Five-year RS was 75% for rural patients compared to 73% for urban patients (RER for rural: 0.85, 95%CI 0.80-0.91). In M+ patients, 5-year RS was 14% for urban patients and 15% for rural patients (p = .02) Multivariate analysis showed that residence remained as an independent predictor for survival in the overall kidney cancer population (RER of rural patients 0.84, 95%CI 0.78-0.89). For M+ patients the RER of rural patients was 0.86 (95%CI 0.79-0.94) compared to urban M+ patients. For patients without surgery, rural patients were even stronger benefited in their survival than urban patients (overall population: RER 0.77, 95% CI 0.71-0.83; M+ patients: RER 0.81, 95%CI 0.72-0.91) whereas in surgical patients RS did not differ between rural and urban patients. **Conclusions:** An advantage in RS was observed for kidney cancer patients living in rural areas. This advantage was evident in metastatic and non-metastatic patients, especially in patients who did not undergo surgery for (metastatic) kidney cancer. These results suggest that access to medical health care for kidney cancer patients in Austria is not limited by rural residence.

Impact of rural/urban residence on relative survival (RS) in patients with kidney cancer: An analysis of 14576 patients from the Austrian National Cancer Registry (ANCR).

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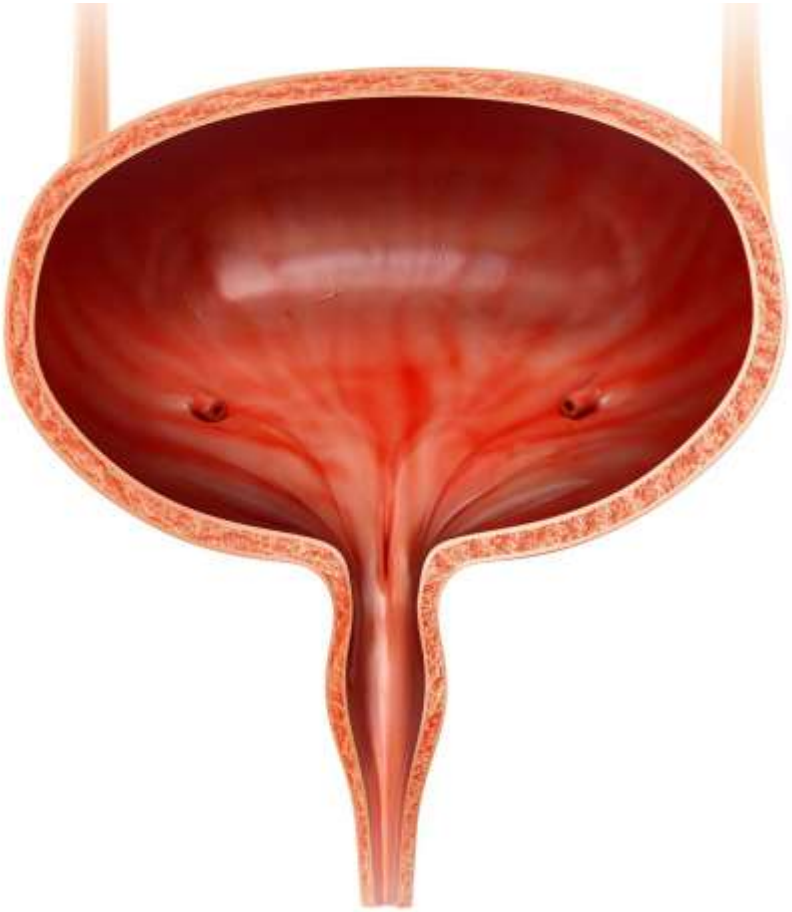


UROTHELIAL CANCER

Abstract n.4581. Comprehensive genomic profiling (CGP) of upper-tract (UTUC) and bladder (BUC) urothelial carcinoma reveals opportunities for therapeutic and biomarker development

Andrea Necchi[1], Sumanta Pal[2], Jeffrey Ross[3,4], Russell Madison[3], Neeraj Agarwal[5], Guru Sonpavde[6], Monika Joshi[7], Yin Ming[8], Vincent A. Miller[3], P Grivas[9], Jon Chung[3], Siraj M Ali[3]

[1]Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, IT, [2]City of Hope Comprehensive Cancer Center, Duarte, CA USA [3]Foundation Medicine, Inc. , Cambridge, MA, USA [4]Upstate Medical University, Syracuse, NY, USA, [5]Huntsman Cancer Institute, Salt Lake City, Utah, USA,[6]Dana Farber Cancer Institute, Boston, MA, USA, [7]Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA, [8]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA, [9]University of Washington, School of Medicine, Seattle, WA, USA

2019 ASCO ANNUAL MEETING

BACKGROUND

UTUC and BUC represent distinct tumor entities that may deserve dedicated therapeutic strategies, in particular with the availability of several clinical studies of targeted therapies or immunotherapy. To understand the genomic landscape and inform the therapeutic development of UC, 2463 cases (479 UTUC and 1984 BUC) were analyzed by CGP for genomic alterations (GAs) and for genome wide signatures.

MATERIALS AND METHODS

- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >600X
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed [1,2]
- Tumor mutational burden (TMB) calculated from 1.14 Mb sequenced DNA [1,2]
- Hybrid capture-based genomic profiling of cell-free DNA (cfDNA) was performed on ≥20 ng of cfDNA and sequencing was performed on up to 70 genes (FoundationOne Liquid) [3] to a mean unique coverage depth of >8,000X.
- For comparison of paired tissue and circulating tumor DNA (ctDNA) samples, concordance was evaluated for baited regions common to both CGP assays.
- Targetable GA and signatures were assessed according to the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) [4]

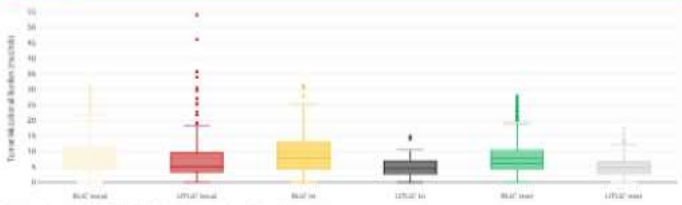
RESULTS

61%/58% primary [PT] and 18%/25% metastatic tumors [MT] from unmatched pts were analyzed. 39% of UC pts overall harbored ≥1 tier 1-2 GA suggesting benefit from approved or investigational targeted therapies (TT). Additionally, 29% had a tier 3 GA that provides a strong rationale for clinical trial consideration. Non-*FGFR3* kinase fusions were observed in 1% of pts (0.6% UTUC v 1.1% BUC), including *BRAF/RAF1* fusions in 0.5%. *BRAF* mut/fusions were observed in 2% (49/2463) of cases and were mutually exclusive with *FGFR3* GA (p=0.002).

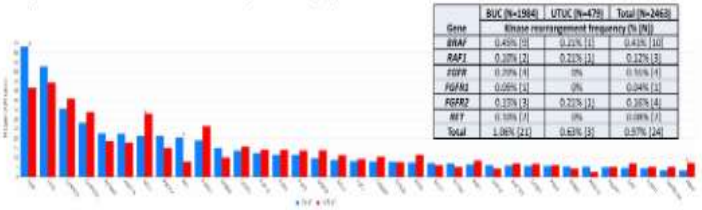
In comparing UC from anatomic sites, there were no differences of TMB-H (≥20 mut/mb)/MSI-H for PT and MT but UTUC was enriched for MSI-H (3.4%) relative to BUC (0.77%, p<0.001, all TMB-H). Excluding MSI-H pts, UTUC has lower median TMB (4.35 mut/mb) than BUC (6.96 mut/mb). *FGFR3* GA (26% v 19%, p <0.05) and specifically short variants (SV) (20% v 13%) were enriched in UTUC vs BUC. *HRAS* SV were also enriched in UTUC vs BC (7.3% v 3.0%), attributed to an enrichment in renal pelvis UC (10.1%) v ureteral UC (1.8%, p <0.05). *RB1* GA were more frequent in BUC vs UTUC (21% v 7.8% p <0.001).

	BUC (n = 1984)	UTUC (n = 479)
M:F	2.82	1.65
Age Median	67	68
TMB Median	6.96 mut/mb	5.23 mut/mb
TMB Mean	9.96 mut/mb	8.29
% MSI-H	0.77%	3.4%
% Local	57.7% (1,146)	61.1% (293)
% Metastatic	25.1% (498)	18.0% (86)
% Lymph Node	9.4% (187)	8.4% (40)
% Unknown	7.7% (53)	12.5% (60)

RESULTS



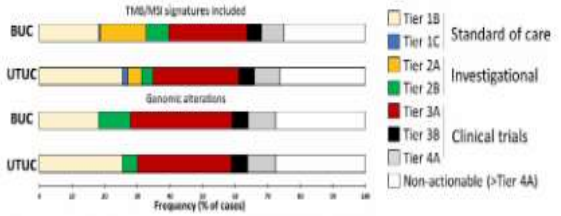
Comparison of TMB in BUC and UTUC by site of biopsy



Gene	BUC (N=1984)	UTUC (N=479)	Total (N=2463)
	Kinase rearrangement frequency (% [N])		
BRAF	0.45% [9]	0.21% [1]	0.41% [10]
RAF1	0.10% [2]	0.21% [1]	0.12% [3]
FGFR	0.20% [4]	0%	0.16% [4]
FGFR3	0.06% [1]	0%	0.04% [1]
FGFR2	0.15% [3]	0.21% [1]	0.16% [4]
RET	0.10% [2]	0%	0.08% [2]
Total	1.06% [21]	0.63% [3]	0.97% [24]

Comparison of genomic alterations in BUC and UTUC

*significant difference between BUC and UTUC; 1% of cases harbored non-*FGFR3* kinase fusions; significant differences between PT and MT were not observed except in *RB1* in BUC (24% v 15%; p = 0.005)

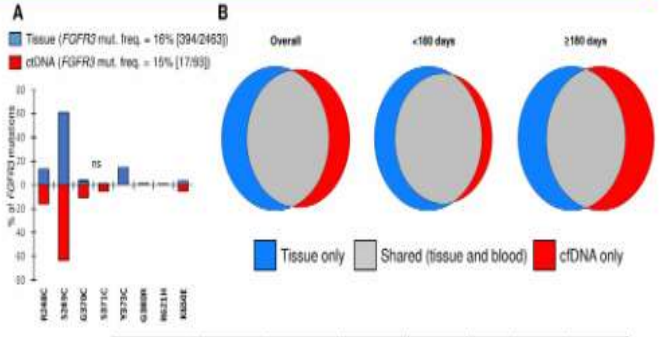


Targetable genomic alterations and signatures identified in BUC and UTUC.

Genomic alterations were ranked using the ESCAT actionability scale. Each case was assigned a tier according to the highest ranked genomic alteration/signature. ESCAT rankings were performed with and without TMB/MSI genomic signatures considered on the actionability scale.

***BRAF* fusions and mutations comprise a potentially targetable genomic subset**

BRAF fusion or mutation was observed in 2% of UC cases and were mutually exclusive with *FGFR3* GAs. Details of *BRAF* fusions and mutations shown.



C

Time interval between tissue/blood collection	Number of cases with matched tissue/blood	Number of tissue only mutations	Number of blood only mutations	Number of shared mutations	Sensitivity (PPA to tissue)	% of all mutations shared	% cases with at least 1 shared mutation
<90 days	7	4	1	13	77%	73%	100% (7/7)
<180 days	10	4	2	16	73%	47%	90% (9/10)
≥180 days	11	7	3	18	67%	50%	100% (9/11)
Overall (median 232 days)	21	11	11	34	68%	57%	71% (15/21)

Comparison of mutations detected by genomic profiling of tissue and blood samples as as function of time.

(A) Unmatched tissue (N=2463) and blood samples with detected ctDNA (N=93) from patients with urothelial cancer were evaluated for *FGFR3* mutation frequency. The distribution of *FGFR3* mutations identified in tissue and blood are shown. ns, not significant.

(B-C) For the 21 patients with matched tissue and blood samples with detected ctDNA, mutations were classified into those found in tissue-only, blood-only, or shared (found in both tissue and blood). Concordance was evaluated as positive-percent agreement (PPA) with tissue as a reference and as % of all detected mutations that were shared.

- Frequency and distribution of targetable *FGFR3* mutations were similar between tissue and ctDNA
- Concordance varied with time interval between tissue and blood collection.
- For samples with a time interval of <180 days between sample collection, there was a 73% PPA to tissue and 90% of cases shared at least 1 mutation.

CONCLUSIONS

- Against a background of 50% actionability in UC with opportunities for immunotherapy, TT, or combinations thereof, the UTUC cohort is enriched for *FGFR3* and *HRAS* SV relative to BUC*HRAS* mutations predominantly in UC of the renal pelvis, that warrants further investigation into the distinct modes of oncogenesis for UC as stratified by anatomic origin.
- Liquid biopsy-based genomic profiling identified targetable *FGFR3* alterations. 73% of mutations present in matched tissue samples were also detected in paired liquid biopsy samples (<180 day time interval).
- These results argue strongly for the routine incorporation of CGP prior to systemic therapy initiation in metastatic UC.

References

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2. Chalmers ZR, Connelly CF, Fabrizio D. Genome Med. 2017;19;9:34
3. Clark, Chung, Hughes , et al. J Mol Diagn. 2018. PMID: 29936259
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Dr. Matteo Santoni – Poster Review

Randomized trial of adjuvant chemotherapy vs. adjuvant radiotherapy for locally advanced bladder cancer after radical cystectomy

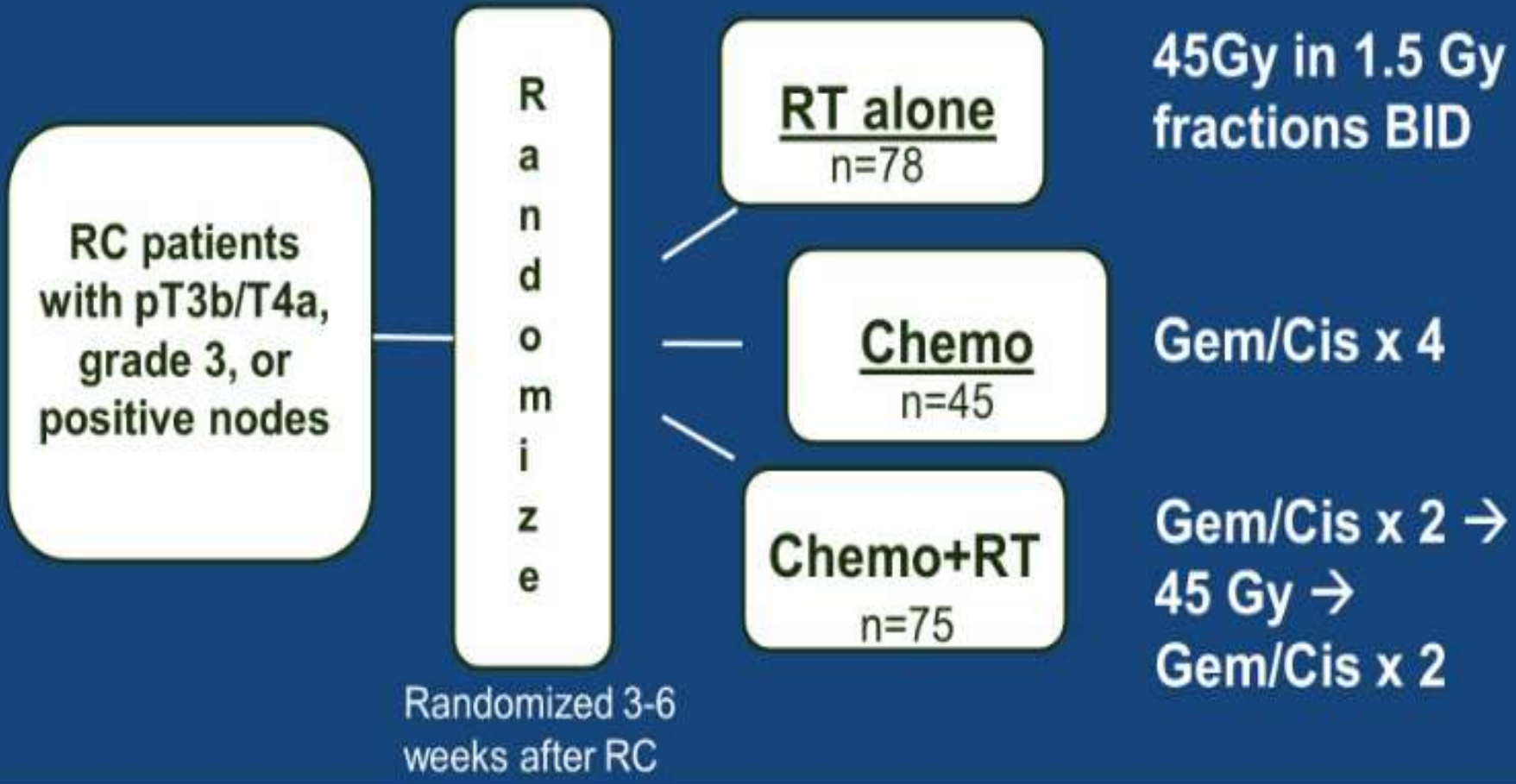
Mohamed Zaghloul, John Christodouleas, Tarek Zaghloul, Andrew Smith, Ahmed Abdallah, Hany William, Wei-Ting Hwang, Brian Baumann

Presenter: Brian C. Baumann, MD
Washington University in St. Louis

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Brian C. Baumann, MD
Washington University in St. Louis

Updated Trial Design w/ 3rd arm added



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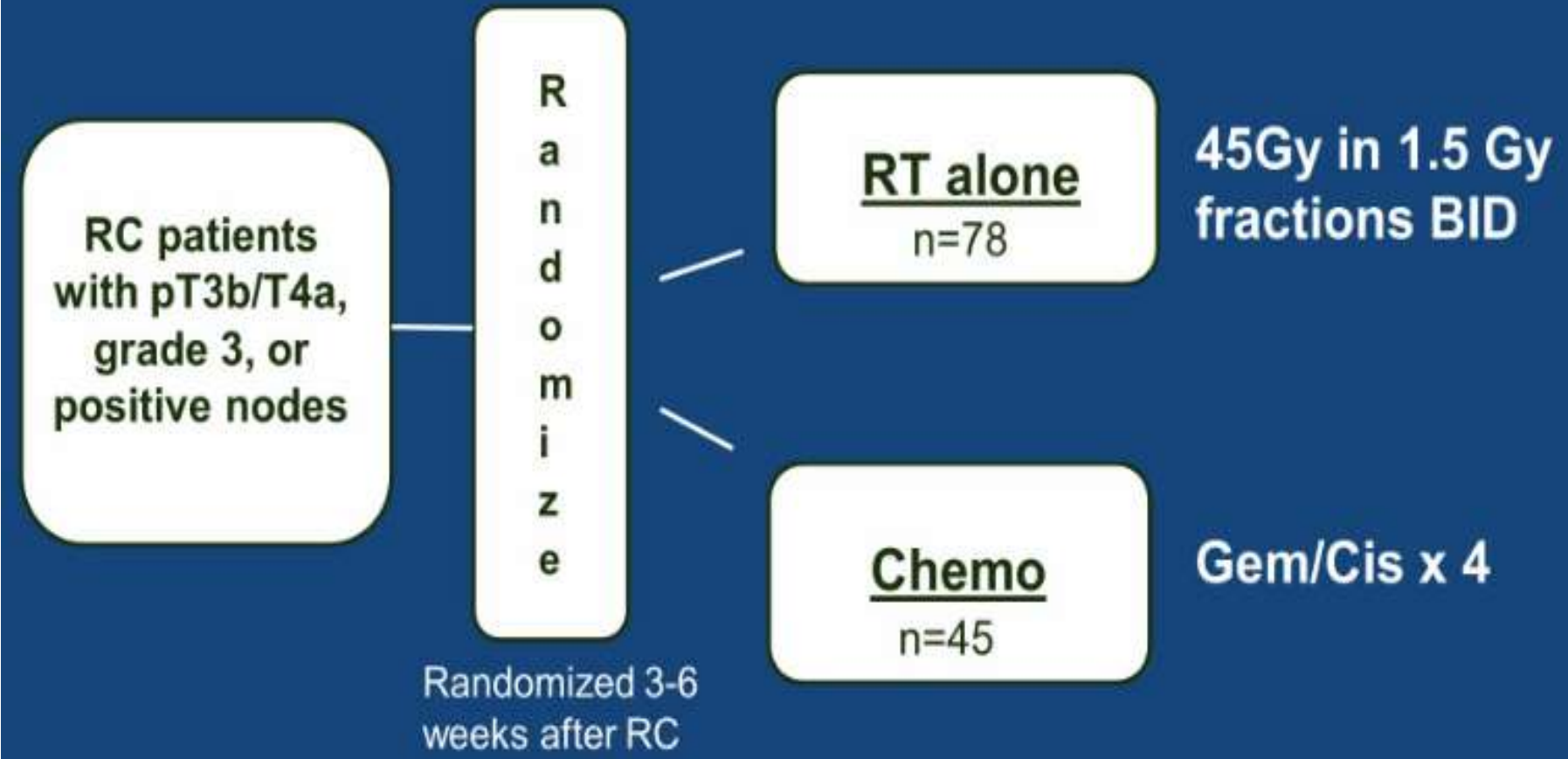
PRESENTED BY: Brian C. Baumann, MD
Washington University in St. Louis

RT vs. Chemo Comparison



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PRESENTED BY: Brian C. Baumann, MD
Washington University in St. Louis

Methods: Radiotherapy Treatment

- 3-D Conformal RT
- Dose: 45Gy in 1.5 Gy fractions twice daily
- Treatment volume: Cystectomy bed plus bilateral pelvic lymph nodes (top of S1)

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Methods: Chemotherapy

- Gemcitabine 1,000 mg/m^2 IV on days 1,8, and 15
- Cisplatin 70 mg/m^2 IV on day 2
- Cycles repeated every 28 days

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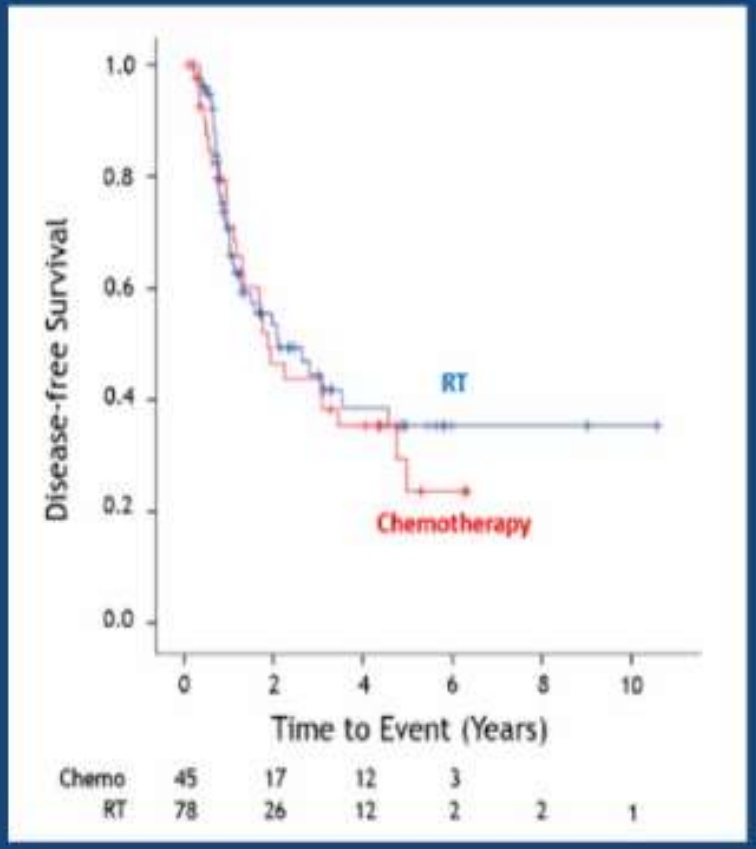
RT vs. chemo: No difference in DFS



Treatment Arm	2-yr DFS	Log-rank *p*-value
RT	**54%** (95%CI 40-65%)	**0.63**
Chemo	**47%** (95%CI 30-61%)	

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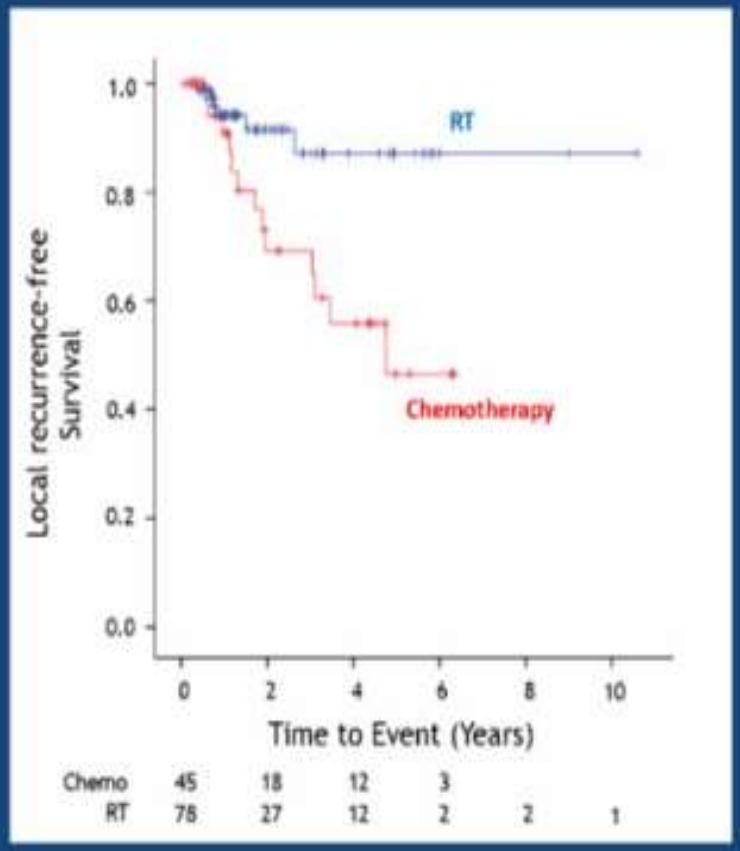
RT significantly improved local control



Treatment Arm	2-yr LRFS	Log-rank *p*-value
RT	**92%** (95%CI 88-95%)	**<0.01**
Chemo	**69%** (95%CI 54-88%)	

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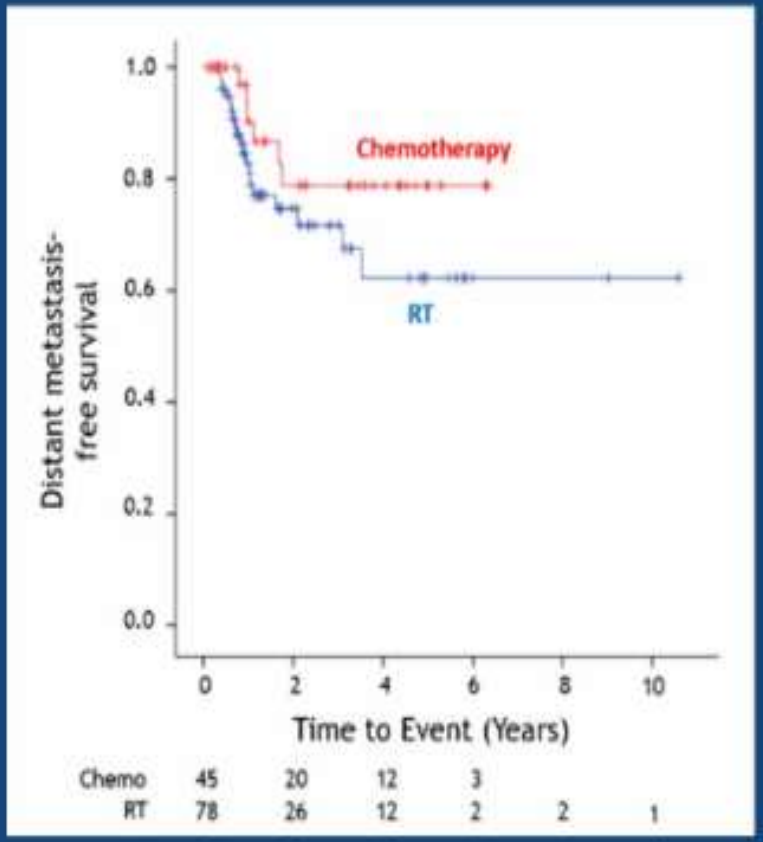
RT vs. chemo: No difference in DMFS



Treatment Arm	2-yr DMFS	Log-rank *p*-value
RT	**75%** (95%CI 69-78%)	**0.16**
Chemo	**79%** (95%CI 65-96%)	

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Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer: HCRN GU14-182

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Icahn School of Medicine at Mount Sinai; City of Hope National Medical Center, Duarte, CA; Ohio State University; University of North Carolina at Chapel Hill School of Medicine; Roswell Park Cancer Institute; Huntsman Cancer Institute-University of Utah Health Care; Virginia Oncology Associates; University of Florida; Fox Chase Cancer Center; Community Cancer Center; John Theurer Cancer Center at Hackensack University Medical Center; University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center; Masonic Cancer Center, University of Minnesota; Vanderbilt University Medical Center; Washington University School of Medicine; Georgetown University Hospital; USC Norris Comprehensive Cancer Center; Johns Hopkins University School of Medicine; University of Wisconsin; Hoosier Cancer Research Network

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

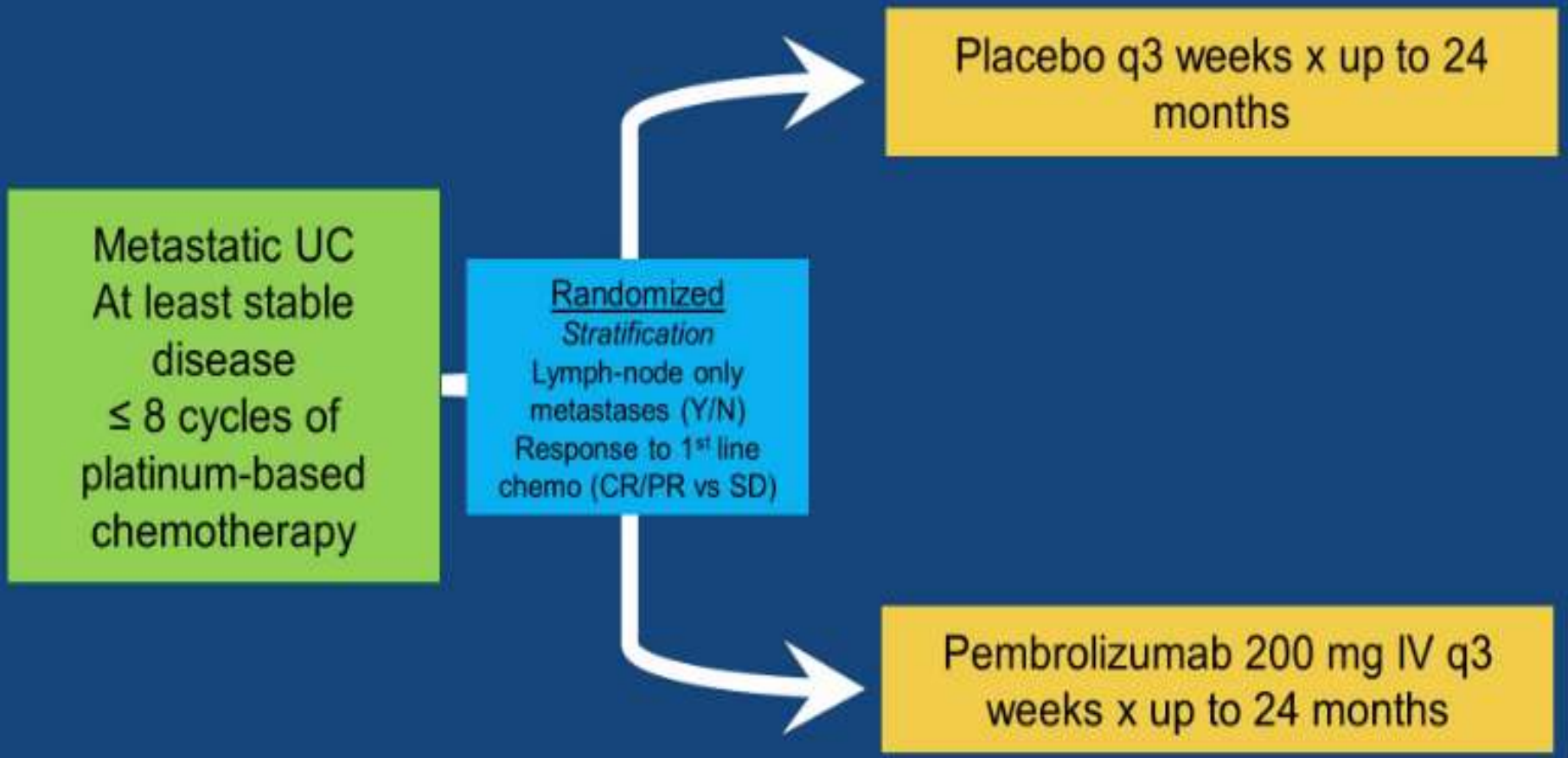
PRESENTED BY: Matthew D. Galsky, MD

Switch maintenance therapy for mUC

Intervention	Eligibility	N	PFS
Sunitinib vs Placebo	At least SD 4-6 cycles 1st line chemo	54	2.9 m vs. 2.7 m
Lapatinib vs Placebo	At least SD 4-6 cycles 1st line chemo HER1/HER2 3+ IHC	446	4.5 m vs 5.4 m
Vinflunine vs BSC*	At least SD Gemcitabine + Cisplatin x 6	88	6.5 m vs 4.2 m

Grivas et al, *Cancer*, 2014; Powles et al, *JCO*, 2017; García-Donas et al, *Lancet Oncology*, 2017
*BSC, best supportive care

HCRN GU14-182



Endpoints

Primary endpoint

- Progression-free survival (PFS) per irRECIST

Secondary endpoints

- Restricted mean PFS
- PFS (PD-L1 ↑)
- PFS (RECIST 1.1)
- Response rate (RECIST 1.1)
- Adverse events (CTCAE v4)
- Overall survival

Baseline Characteristics

Characteristic	Placebo (n=52)	Pembrolizumab (n=55)	*p*
Age, median (range)	65 (44-87)	68 (41-83)	0.2
Male	81%	71%	0.3
Visceral metastases	62%	71%	0.3
1st line chemotherapy			
median # cycles	6	5	0.3
complete/partial response	69%	73%	0.8
cisplatin-based	77%	65%	0.5

Objective Response Rate (RECIST 1.1)

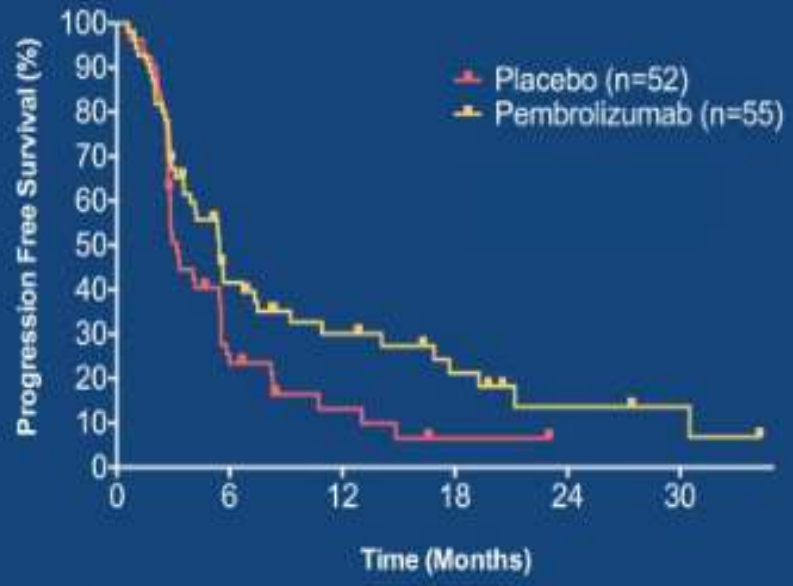
Characteristic	Placebo (n=52)	Pembrolizumab (n=55)
Not evaluable (baseline CR)	10	9
Overall response	12%	22%
Partial response	12%	13%
Complete response	0	9%
Stable disease	29%	35%
Progressive disease	54%	33%
Unknown	5%	10%

Adverse Events (select treatment-emergent in ≥5%)

AE Term	Placebo (n=52)			Pembrolizumab (n=55)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Any adverse event	58%	35%	0%	38%	42%	11%
Fatigue	39%	0%	0%	31%	7%	0%
Anorexia	14%	0%	0%	16%	2%	0%
Dry mouth	0%	0%	0%	11%	0%	0%
ALT increased	2%	0%	0%	11%	4%	2%
AST increased	10%	0%	0%	15%	5%	0%
Diarrhea	19%	0%	0%	35%	0%	0%
Hypothyroidism	4%	0%	0%	9%	0%	0%
Pruritis	13%	0%	0%	22%	2%	0%
Rash	8%	0%	0%	22%	0%	0%
Dyspnea	14%	0%	0%	22%	5%	0%
Renal insufficiency	24%	0%	0%	29%	2%	0%

* One patient randomized to pembrolizumab developed fatal immune-related hepatitis

Progression-free Survival



Median PFS and 95% CI
Placebo: 3.2 (2.8, 5.5)
Pembrolizumab: 5.4 (3.6, 9.2)

Hazard Ratio: 0.64 (0.41, 0.98)

Log rank $p = 0.038$

Number at Risk

Placebo	52	12	4	1	0	0
Pembrolizumab	55	20	12	7	3	2

Conclusions

- Switch-maintenance pembrolizumab significantly delays disease progression in patients with mUC
- Adverse event profile consistent with other treatment settings
- PFS in PD-L1↑ and OS data will be reported in future presentation
- Role of switch-maintenance PD-1 blockade will be refined by ongoing phase 3 studies

Outcomes of patients (pts) with metastatic urothelial cancer (mUC) and poor performance status (PS) receiving anti-PD(L)1 agents

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Background

- Pembrolizumab prolonged overall survival (OS) after platinum-based chemotherapy in mUC[1]
- Four other anti-PD(L)1 agents are FDA-approved for mUC based on durable responses and favorable toxicity profiles (as opposed to chemotherapy) [2-5]
- Little is known about outcomes in pts with poor PS at time of immune checkpoint inhibitor (ICI) initiation as most were excluded from clinical trials
- We hypothesized that outcomes on ICI therapy (response rate (ORR) & OS) would be worse for patients with ECOG PS 2-3 vs ECOG PS <2
- We also hypothesized that pts initiated on ICI within 30 and 90 days of death would have increased odds of dying in the hospital (vs. elsewhere)
- We also estimate ICI cost for pts with ICI initiation within 30 and 90 days of death to inform further discussions about healthcare utilization, cost-effectiveness, outcomes research, and value-based care

Methods

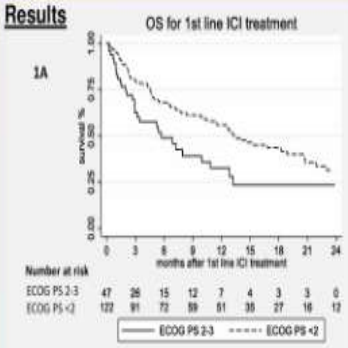
- **Patients/Cohort:** A retrospective multi cohort study including 15 academic institutions identified pts with mUC who received ICI (after IRB approval)
- **Data collected:** Demographic, clinicopathologic, treatment patterns, response, and outcomes data were collected using EMR review at each institution; de-identified data was shared and stored in a secure and compliant database
- **Primary endpoint:** ORR based on ECOG PS
- **Secondary endpoints:**
  - Median (m) OS in pts receiving ICI as 1st line & salvage (2nd line & beyond)
  - Site of death (hospital vs elsewhere) for pts receiving ICI (vs non-ICI therapy or no therapy) within 30 and 90 days of death
  - Estimated drug cost for pts treated with ICI within 30 and 90 days of death based on average wholesale price (AWP)
- **Analysis:**
  - Descriptive statistics used for baseline factors
  - Unadjusted logistic regression used for association between ORR and ECOG PS (2-3 vs <2) and between site of death (hospital vs other) and ICI initiation within 30 and 90 days of death
  - Wald test was used to compare mOS between ECOG PS (2-3 vs <2)
  - ICI cost estimation was calculated as average per patient cost using AWP, also considering ICI therapy duration per patient

Patients Data

Table 1. Patient characteristics for survival analysis cohort stratified by 1st line vs salvage ICI and ECOG PS

	1st Line ICI		Salvage		Total Cohort
ECOG PS	0-1	≥2	0-1	≥2	327
Number of Patients	122	47	118	40	
Age at ICI initiation (mean +/- SD)	70 ± 10	70 ± 13	68 ± 9	68 ± 10	69 +/-10
Sex [number (%)]					
Male	91 (75%)	30 (64%)	91 (77%)	29 (73%)	241 (74%)
Female	31 (25%)	17 (36%)	27 (23%)	11 (28%)	86 (26%)
Smoking History [number (%)]					
Yes/Ever	76 (63%)	29 (62%)	75 (64%)	25 (63%)	205 (63%)
No/Never	45 (37%)	18 (38%)	43 (36%)	15 (38%)	121 (37%)
Race/Ethnicity [number (%)]					
Caucasian/White	96 (79%)	33 (70%)	92 (78%)	28 (70%)	249 (76%)
Hispanic/Latino	3 (2%)	2 (4%)	1 (1%)	2 (5%)	8 (2%)
Black/African-American	12 (10%)	2 (4%)	12 (10%)	4 (10%)	30 (9%)
Asian	2 (2%)	2 (4%)	6 (5%)	0 (0%)	10 (3%)
Native American/Pacific Islander	1 (1%)	0 (0%)	0 (0%)	1 (3%)	2 (1%)
Other	2 (2%)	3 (6%)	1 (1%)	2 (5%)	8 (2%)
Not reported	6 (5%)	5 (11%)	6 (5%)	3 (8%)	20 (6%)
Cystectomy or (Nephro)ureterectomy [number (%)]					
Yes	61 (60%)	23 (53%)	46 (50%)	13 (35%)	143 (52%)
No	40 (40%)	20 (47%)	46 (50%)	24 (65%)	130 (48%)
Hgb<10 [number (%)] at ICI initiation					
Yes	23 (19%)	15 (34%)	28 (24%)	18 (45%)	84 (26%)
No	99 (81%)	29 (66%)	87 (76%)	22 (55%)	237 (74%)
Liver Metastasis at ICI initiation					
Yes	22 (18%)	11 (23%)	17 (14%)	8 (20%)	58 (18%)
No	100 (82%)	36 (77%)	101 (86%)	32 (80%)	269 (82%)

Results



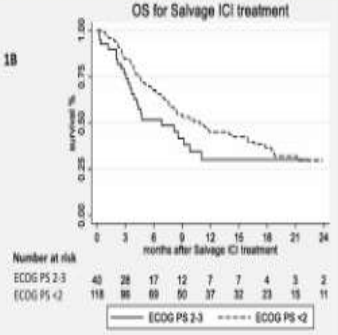


Figure 1A-B. K-M estimate for OS for pts with ECOG PS 2-3 vs ECOG PS <2 receiving 1st line ICI (A) and salvage ICI (B)

Table 2. ORR and mOS results for ECOG PS <2 and ECOG PS 2-3 by line of therapy 1L vs salvage

ECOG PS	1L ORR	1L mOS (mo)	Salvage ORR	Salvage mOS (mo)
<2	28%	14	25%	11
2-3	24%	6	20%	7
p value	0.65	0.0003	0.47	0.22

End of Life Utilization

- Among 369 with vital information, 215 (58%) have died at time of data collection. Among those:
  - 24 (11%) with initiation of ICI vs 4 (2%) with initiation of non-ICI in the last 30 days of life
  - 76 (35%) with initiation of ICI vs 14 (7%) with initiation of non-ICI in the last 90 days of life
- Among 140 pts with known site of death:
  - 14 (10%) with initiation of ICI in the last 30 days of life
  - 48 (34%) with initiation of ICI in the last 90 days of life

Table 3. Odds ratio for ICI initiation within 30 and 90 days among pts with hospital death (vs no hospital death) and estimation of ICI cost per patient for pts with ICI initiation within 30 and 90 days of death

New ICI initiation within days of death	Odds ratio for ICI initiation for hospital death vs no hospital death	ICI cost estimation per patient
30 days	4.27 (CI 1.37, 13.3), p=0.01	$ 1,340.07
90 days	1.36 (CI 0.63, 2.94), p=0.43	$ 2,600.22

Conclusions:

- Pts with ECOG PS 2-3 at ICI initiation had numerically lower, but not statistically significantly different, ORR compared with pts with ECOG PS <2
- Pts with ECOG PS 2-3 had shorter mOS with ICI vs pts with ECOG PS<2, the difference was statistically significant only in 1L setting
- ICI initiation in last 30 days of life was associated with higher odds of hospital death compared to death elsewhere
- ICI might not circumvent the negative prognostic role of poor PS overall
- Given cost & risk of significant morbid death, ICI for pts with poor PS should be reserved for those with best chance of response; additional work on biomarker-based patient selection is critical; data on PD-L1 IHC, TMB, etc. was lacking
- Limitations include lack of adjustment for selection bias and other confounders at the time of ICI initiation, retrospective nature, possible variability in follow up

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Dr. Matteo Santoni – Poster Review

Treatment sequencing of anti-PD-1/PD-L1 and carboplatin (carbo)-based chemotherapy (chemo) in cisplatin-ineligible patients (pts) with metastatic urothelial cancer (mUC)

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Background

- Cisplatin-based chemo is the standard of care for mUC pts who are cisplatin-eligible
- Many mUC pts are unfit for cisplatin due to renal dysfunction, poor performance status, underlying neuropathy, hearing loss, or cardiac dysfunction
- For cisplatin-ineligible pts, 1st-line (1L) treatment options include carbo-based chemo and the anti-PD-1/PD-L1 immune checkpoint inhibitors (ICI) pembrolizumab and atezolizumab
- FDA labels for pembrolizumab and atezolizumab for 1L treatment of mUC were recently revised to limit indications to pts who are cisplatin ineligible and whose tumors express PD-L1, or pts who are ineligible for any platinum-containing chemo regardless of PD-L1 status
- For untreated cisplatin-ineligible mUC pts, the optimal treatment sequence of carbo-based chemo followed by anti-PD-1/PD-L1 versus anti-PD1/PD-L1 followed by carbo-based chemo remains unclear

Objectives

- **Primary:** Association between overall survival (OS) and treatment sequence
- **Secondary:** Objective response rate (ORR) and Time to treatment failure (TTF) by treatment in each sequence

Methods

- We collected data retrospectively from 10 institutions
- Target population: Cisplatin-ineligible mUC pts treated with 1L carbo-based chemo followed by 2nd-line (2L) PD-1/PD-L1 inhibitor, or the reverse order without intervening therapy
- Pts who received cisplatin-based perioperative chemo are allowed if interval between completion of chemo and initiation of 1L therapy for mUC is >1 year
- Demographics, baseline clinical variables, and clinical outcomes, including best radiographic response (investigator-assessed), TTF, interval between 1L and 2L therapies, and OS, were collected
- To assess association between OS and treatment sequence, multivariate analysis was performed from initiation of 2L therapy, adjusted for:
  - Treatment sequence
  - TTF1 + Interval between 1L and 2L therapies
  - Baseline hemoglobin (<10 vs. ≥10 g/dL)
  - ECOG performance status (0-1 vs. 2-3)
  - Site(s) of metastasis (lymph node only vs. non-liver [e.g. lungs, bone] vs. liver)

Results

Patient and Clinical Characteristics at Initiation of 1L Therapy

	PD-1/L1 → Carbo (N = 43)	Carbo → PD-1/L1 (N = 103)	P-value
Male, N (%)	39 (90.7%)	72 (69.9%)	0.01
Age, Median (Q1-Q3)	72 (66-77)	72 (65-77)	0.80
ECOG PS, N (%)			
0 or 1	32 (74.4%)	82 (79.6%)	0.24
2 or 3	10 (23.3%)	15 (14.6%)	
Unknown	1 (2.3%)	6 (5.8%)	
Site(s) of met, N (%)			
LN only	19 (44.2%)	42 (40.8%)	0.88
Non-liver	16 (37.2%)	43 (41.7%)	
Liver	8 (18.6%)	18 (17.5%)	
Peri-op cisplatin, N (%)			
No	40 (93.0%)	97 (94.2%)	0.72
Hb, Median (Q1-Q3)	12.4 (11.3-13.8)	11.4 (10.2-12.9)	0.16
Tumor PD-L1 status			
Positive	1 (2.3%)	0 (0%)	NC
Negative	0 (0%)	4 (3.9%)	
Unknown	42 (97.7%)	99 (96.1%)	

Carbo-based chemo regimens include Carbo/Gemcitabine + Paclitaxel, Carbo/Paclitaxel, and Carbo alone
Abbreviations: Hb, hemoglobin; LN, lymph node; met, metastasis; NC, not calculated due to high proportion of unknown; Peri-op, perioperative; PS, performance status

Objective Response Rate (ORR) by Treatment Sequence

	PD-1/L1 → Carbo (N = 43)		Carbo → PD-1/L1 (N = 103)	
N (%)	1L PD-1/PD-L1	2L Carbo	1L Carbo	2L PD-1/PD-L1
CR	0 (0%)	0 (0%)	4 (3.9%)	3 (2.9%)
PR	4 (9.3%)	19 (44.2%)	43 (41.7%)	19 (18.4%)
SD	11 (25.6%)	8 (18.6%)	21 (20.4%)	13 (12.6%)
PD	28 (65.1%)	8 (18.6%)	32 (31.1%)	53 (51.5%)
Unknown	0 (0%)	8 (18.6%)	3 (2.9%)	15 (14.6%)

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

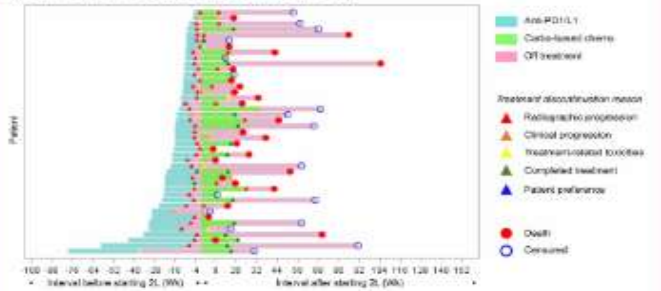
Multivariate Analysis between OS and Treatment Sequence

	HR (95% CI)	P-value
Treatment sequence[1]		
PD-1/L1 → Carbo	1.05 (0.62-1.77)	0.85
Carbo → PD-1/PD-L1 (Ref)	-	
TTF1 + Interval between 1L and 2L		
≤ Median	1.27 (0.77-2.11)	0.35
> Median (Ref)	-	
Hemoglobin		
<10	1.33 (0.74-2.40)	0.34
≥10 (Ref)	-	
ECOG performance status		
0-1 (Ref)	-	0.83
2-3	1.07 (0.60-1.90)	
Site(s) of metastasis		
LN only (Ref)	-	0.002
Non-liver	1.49 (0.84-2.63)	
Liver	3.23 (1.69-6.19)	

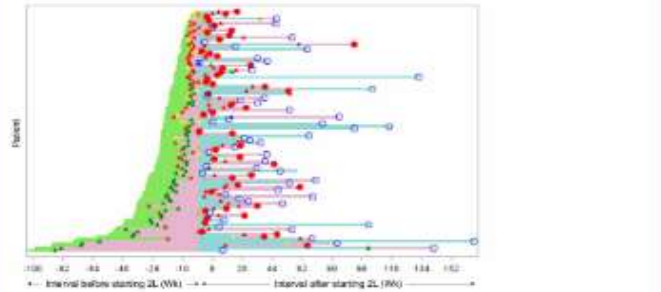
[1]On univariate analysis, treatment sequence was insignificant for OS: HR 1.16 (0.72-1.87), p=0.53

Swimmer's Plot by Treatment Sequence

a) Anti-PD-1/L1 → Carbo-based chemo (N=43)



b) Carbo-based chemo → Anti-PD-1/L1 (N=103)



	TTF1 Median (Q1-Q3)	1L and 2L Interval Median (Q1-Q3)	TTF2 Median (Q1-Q3)	OS[1] Median (95% CI)
PD-1/L1 → Carbo, Wk	15.6 (10.0-22.2)	4.0 (3.0-6.3)	11.0 (3.0-23.9)	37.2 (20.5-70.0)
Carbo → PD-1/L1, Wk	23.0 (14.0-33.7)	7.4 (5.0-15.7)	11.4 (3.1-19.6)	44.8 (27.0-93.1)

[1]Overall survival from start of 2L therapy by treatment sequence

Conclusions

- In this retrospective analysis, treatment sequence of anti-PD-1/L1 and carbo-based chemo conferred comparable OS in cisplatin-ineligible mUC
- Carbo-based chemo resulted in higher ORR, longer TTF1, and longer interval between 1L and 2L therapy compared to anti-PD1/L1, likely at least in part influenced by pt selection
- Most pts were treated before FDA label changes and analysis was independent of PD-L1 status; ongoing phase 3 trials will help to inform optimal treatment sequence

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Dr. Matteo Santoni – Poster Review

Abstract 4509: A Phase II Study of RC48-ADC in Subjects With HER2 Positive Metastatic or Unresectable Urothelial Cancer（NCT03507166 ,RC48-C005)

Xinan Sheng[1], Ai-ping Zhou[2], Xin Yao[3], Yanxia Shi[4], Hong Luo[11], Benkang Shi[5], Jiyan Liu[6], Guohua Yu[7], Zhisong He[9], Changlu Hu[8], Weiqing Han[10], Jianming Fang[12], Jun Guo[1]***

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**Presenting author ** Corresponding author*

BACKGROUND

- RC48-ADC is a novel HER2-targeting antibody drug conjugate (ADC) that selectively delivers anticancer agent MMAE into HER2 positive tumor cells[1].
- Preclinical study demonstrated that RC48-ADC was significantly more effective than lapatinib, trastuzumab and T-DM1[1], in vivo tumor model of human breast cancer resistant to trastuzumab and lapatinib.
- Phase I studies (NCT02881138 and NCT02881190) demonstrated that RC48-ADC was well tolerated in patients with malignant solid tumors.
- Study RC48-C005 is designed to explore the efficacy and safety of RC48-ADC for HER2 positive urothelial cancer.

METHODS

Primary Outcome Measure:
- Objective Response Rate (ORR)

Secondary Outcome Measures:
- Progression Free Survival (PFS)
- Duration of Objective Response (DOR)
- Overall Survival (OS)
- Adverse events

Key Inclusion Criteria:
- Histologically or cytologically-confirmed diagnosis of urothelial (bladder, renal pelvis, or ureter) cancer which is unresectable, locally advanced or metastatic
- HER2 IHC 2+ or 3+
- Have had progression or intolerance following receipt of at least one systemic chemotherapy for the advanced or metastatic disease
- ECOG performance status 0-1

Study Design

This study was an open-label, multicenter, single-arm, non-randomized phase II study. Eligible patients received RC48-ADC, 2 mg/kg IV infusion, once every two weeks until confirmed disease progression, unacceptable toxicity, withdrawal, or study termination.

Figure 1. Study Design

RESULTS

Patient Characteristics

- As of 30 April 2019, RC48-C005 has completed the enrollment of 43 patients. All patients received at least one dose of study treatment. Thirty-five patients (81.4%) were discontinued from study. Most common cause of discontinuation were progressive disease (41.9%) and AE (32.6%).

Table 1. Demographics and Baseline Characteristics

Characteristics	Total (N=43)
Age (years)	
Median	64
Mean (SD)	62.3 (8.18)
Gender	
Male (n,%)	33 (76.7%)
HER2 status	
IHC3+ (n,%)	11 (25.6%)
IHC2+/FISH+ (n,%)	4 (9.3%)
IHC2+/FISH- (n,%)	24 (55.8%)
IHC2+/FISH unknown (n,%)	3 (7.0%)
Primary Lesion	
Bladder (n,%)	22 (51.2%)
Renal pelvis (n,%)	13 (30.2%)
Ureter (n,%)	11 (25.6%)
Visceral metastases (n,%)	37 (86.0%)
Lung (n,%)	21 (48.8%)
Liver (n,%)	20 (46.5%)
Prior chemotherapy	
1 Line (n,%)	31 (72.1%)
≥2 Lines (n,%)	12 (27.9%)
Prior PD-1/PD-L1 therapy (n,%)	8 (18.6%)

Efficacy

- The confirmed Objective Response Rate (cORR) is 51.2% (22/43). The BOR was PR in 26 patients and SD in 13 patients, bringing to a best Overall Response Rate of 60.5% (26/43) and DCR of 90.7% (39/43).
- Median PFS was 6.9 months (95% CI: 4.2 to 7.8). Six-month PFS rate was 56.9% (95% CI: 39.9% to 70.7%). Six-month OS rate was 85.2% (95% CI: 70.0% to 93.1%) and 12-month OS rate was 59.6% (95% CI, 36.6% to 76.7%).
- Subgroup analysis indicated similar trends in the patients with HER2 overexpression (IHC 2+/FISH+ or IHC3+) (53.3%), with visceral metastasis (56.8%), and previously treated with PD1/PDL1 (62.5%).

Figure 2. Best Overall Response

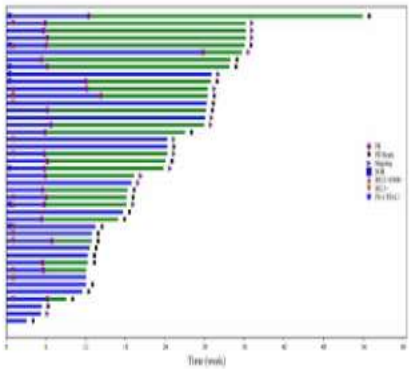
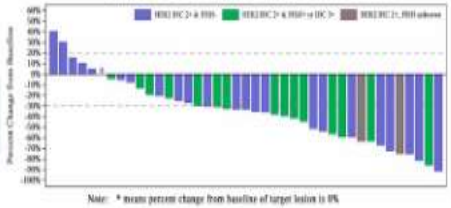


Figure 3. Best Change of Target lesion from Baseline

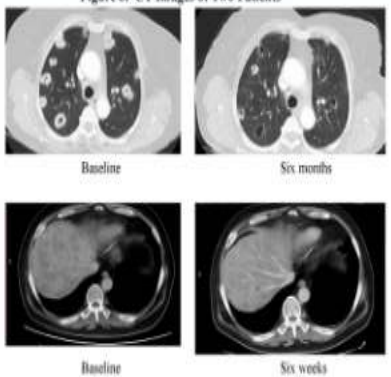


Note: * means percent change from baseline of target lesion is 0%

Table 2. Subgroup Analysis for cORR

Subgroups	cORR (%, 95% CI)
IHC2+/FISH+ or IHC3+ (n=15)	53.3% (26.6%, 78.7%)
IHC2+/FISH- (n=24)	45.8% (25.6%, 67.2%)
Visceral Metastasis (n=37)	56.8% (39.5%, 72.9%)
Metastasis to Liver (n=20)	60.0% (36.1%, 80.9%)
Post to PD1/PDL1 Treatments (n=8)	62.5% (24.5%, 91.5%)
Post to 1 line of Chemotherapy (n=31)	54.8% (36.0%, 72.7%)
Post to ≥2 Lines of Chemotherapy (n=12)	41.7% (15.2%, 72.3%)

Figure 3. CT Images of Two Patients



Safety

- The most commonly reported treatment related adverse events (TRAEs) were hypoesthesia (55.8%), alopecia (55.8%), white blood cell count decreased (55.8%) and neutrophil count decreased (41.9%).
- The most commonly reported grade 3/4 TRAEs were hypoesthesia in 7 patients (16.3%) and neutrophil count decreased in 6 patients (14.0%).
- Serious Adverse Event (SAE) was reported in 14 patients (32.6%). Most commonly reported SAEs were intestinal obstruction (4.7%) and incomplete intestinal obstruction (4.7%).

CONCLUSION

- RC48-ADC has demonstrated a clinically meaningful cORR of 51.2%, and mPFS of 6.9 months in HER-2 positive mUC patients, especially in those with visceral metastasis, previously treated with I-O agents.
- The commonly reported adverse events were hypoesthesia, alopecia and hematotoxicity. The adverse events were manageble. RC48-ADC was well tolerated.
- The study demonstrated a favourable benefit-risk profile of RC48-ADC. A pivotal study (NCT03809013) is initiated to further confirm the RC48-ADC as the satisfaction of unmet medical needs in HER2 positive mUC.

Reference:

1.Xuejing et al.Breast cancer research and treatment 153.1(2015):123-133

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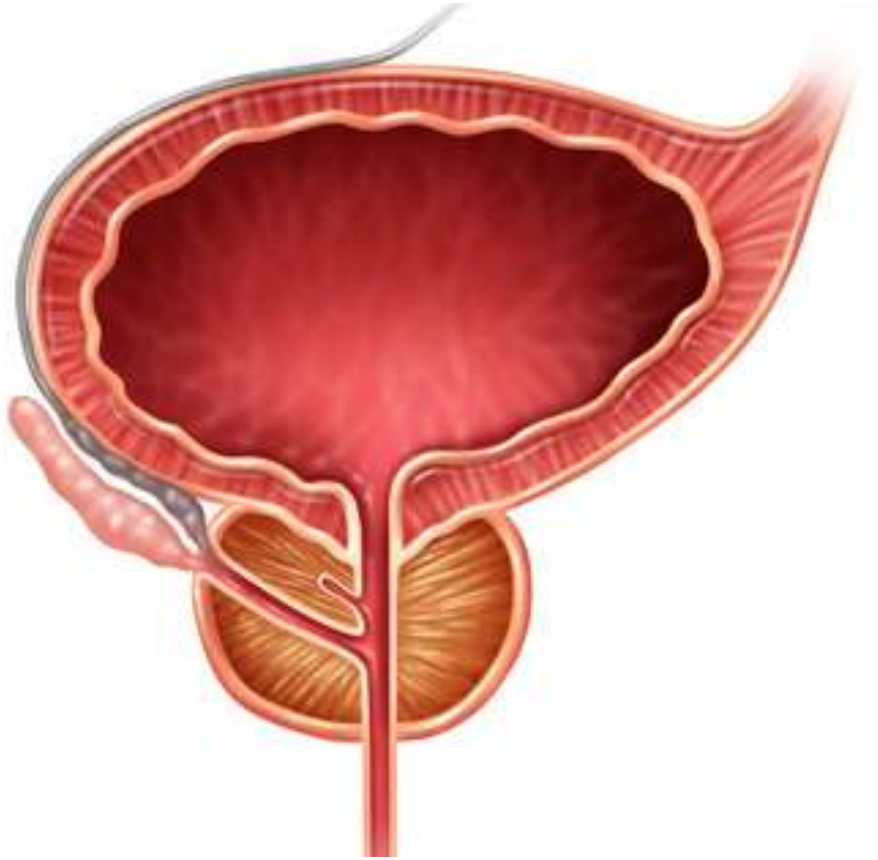
Associazione Italiana di Oncologia Medica



PROSTATE CANCER

Impact of darolutamide on pain and quality of life in patients with nonmetastatic castrate-resistant prostate cancer

Karim Fizazi,[1] Neal Shore,[2] Teuvo L. Tammela,[3] Iris Kuss,[4] Marie A. Le Berre,[4] Ateesha F. Mohamed,[5] Dawn Odom,[6] Jennifer Bartsch,[6] Amir Snapir,[7] Toni Sarapohja,[7] Matthew R. Smith[8]

[1]Institut Gustave Roussy, University of Paris-Sud, Villejuif, France; [2]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [3]Tampere University Hospital and University of Tampere, Tampere, Finland; [4]Bayer HealthCare, Loos, France; [5]Bayer HealthCare, Whippany, NJ, USA; [6]Research Triangle Institute, Durham, NC, USA; [7]Orion Corporation Orion Pharma, Espoo, Finland; [8]Massachusetts General Hospital Cancer Center, Boston, MA, USA

ARAMIS (NCT02200614) was sponsored by Orion Corporation Orion Pharma and Bayer AG

Dr. Matteo Santoni – Poster Review

ARAMIS trial design: Patient-relevant endpoints

Primary endpoint (significance level 0.05)

- MFS

Secondary endpoints (hierarchical testing; interim a=0.0005)

- OS
- Time to pain progression
- Time to first cytotoxic chemotherapy
- Time to first SSE
- Safety

Exploratory endpoints (significance testing does not apply)

- PFS
- Time to PSA progression
- PSA response rate
- Time to first prostate cancer-related invasive procedure
- Time to initiation of subsequent antineoplastic therapy
- Time to ECOG performance status deterioration
- Quality of life

Primary results from ARAMIS have been published (Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246).
ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; SSE, symptomatic skeletal event.

Baseline characteristics

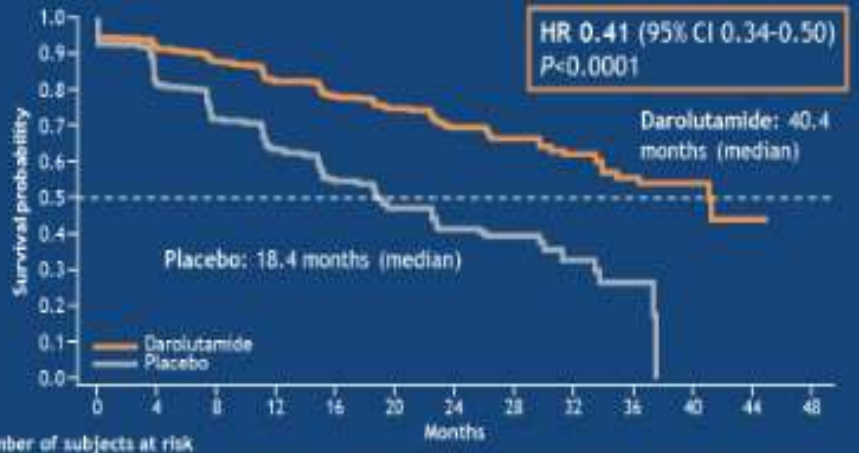
Characteristic	Darolutamide (N=955)	Placebo (N=554)
Median age, years (range)	74 (48-95)	74 (50-92)
Median serum PSA (range), ng/mL	9.0 (0.3-858.3)	9.7 (1.5-885.2)
Median PSADT (range), months	4.4 (0.7-11.0)	4.7 (0.7-13.2)
≤6 months, n (%)	667 (70)	371 (67)
>6 months, n (%)	288 (30)	183 (33)
Use of bone-sparing agent, n (%)		
Yes	31 (3)	32 (6)
No	924 (97)	522 (94)
ECOG performance status, n (%)		
0	650 (68)	391 (71)
1	305 (32)	163 (29)
Prior hormonal therapy, n (%)		
1	177 (19)	103 (19)
≥2	727 (76)	420 (76)
Orchiectomy	51 (5)	31 (6)
Baseline lymph nodes by central imaging review, n (%)		
Yes	163 (17)	158 (29)
No	792 (83)	396 (71)

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

Metastasis-free and overall survival

Primary endpoint: Metastasis-free survival

59% risk reduction of distant metastases or death

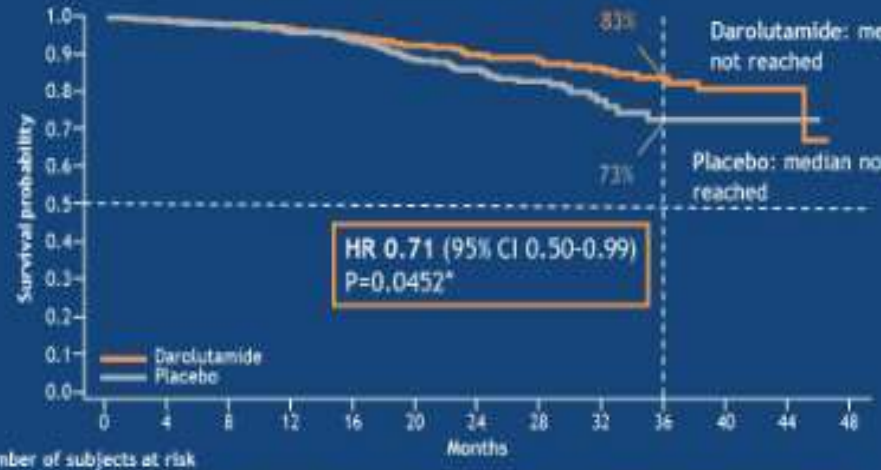


Number of subjects at risk

Darolutamide	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0

Secondary endpoint: Overall survival

29% risk reduction of death



Number of subjects at risk

Darolutamide	955	932	880	737	586	428	302	218	123	64	35	8	0
Placebo	554	529	467	394	307	214	154	110	56	34	14	2	0

Median follow-up time at primary analysis was 17.9 months

*P value calculation was for descriptive purposes only.
CI, confidence interval; HR, hazard ratio.

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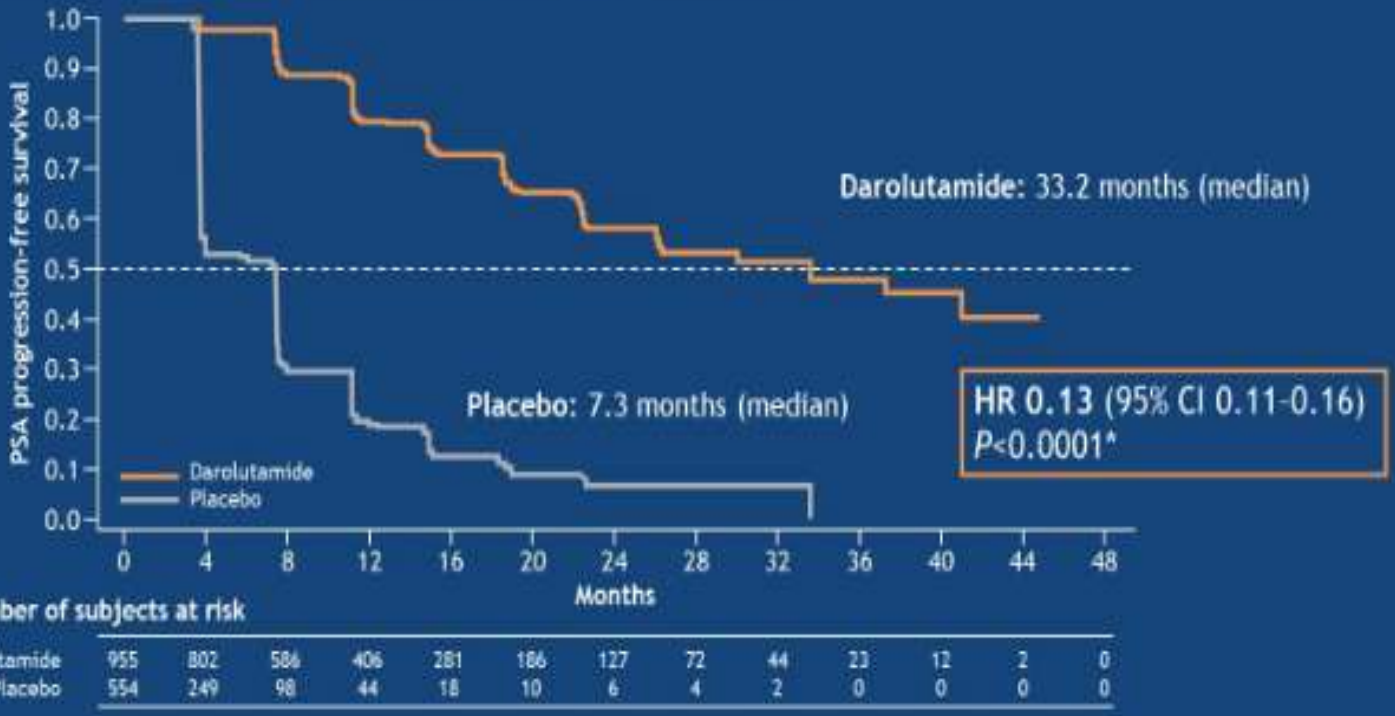
Exploratory endpoint: Time to PSA progression

Darolutamide delayed time to PSA progression



*Time to PSA progression was an exploratory endpoint. *P* value calculation was for descriptive purposes only.
CI, confidence interval; HR, hazard ratio.; PSA, prostate-specific antigen.

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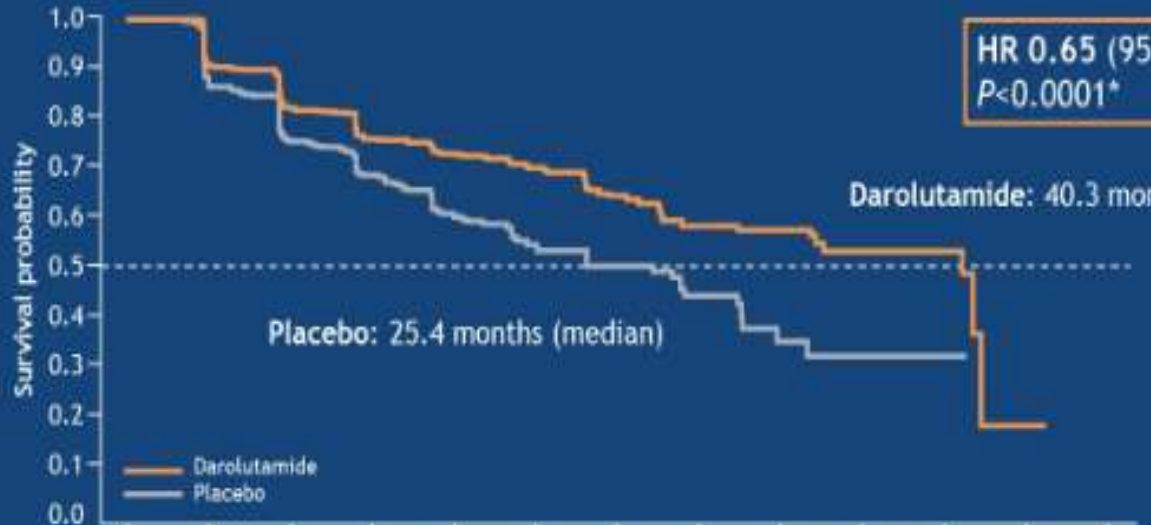
Secondary endpoint: Time to pain progression

35% risk reduction in progression of pain



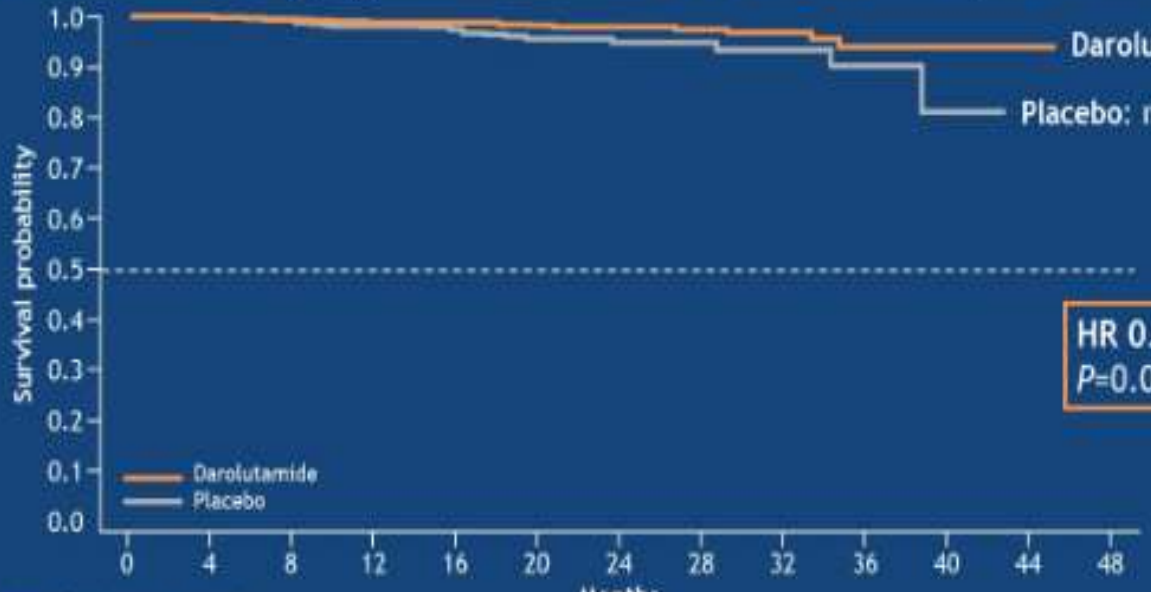
Number of subjects at risk

Darolutamide	955	749	585	444	337	238	170	99	59	29	14	1	0
Placebo	554	387	285	198	125	83	54	30	14	6	1	0	0

*P value calculation was for descriptive purposes only.
CI, confidence interval; HR, hazard ratio.

Secondary endpoint: Time to first SSE

57% risk reduction of symptomatic skeletal event development



Darolutamide: median not reached

Placebo: median not reached

HR 0.43 (95% CI 0.22-0.84)
P=0.011*

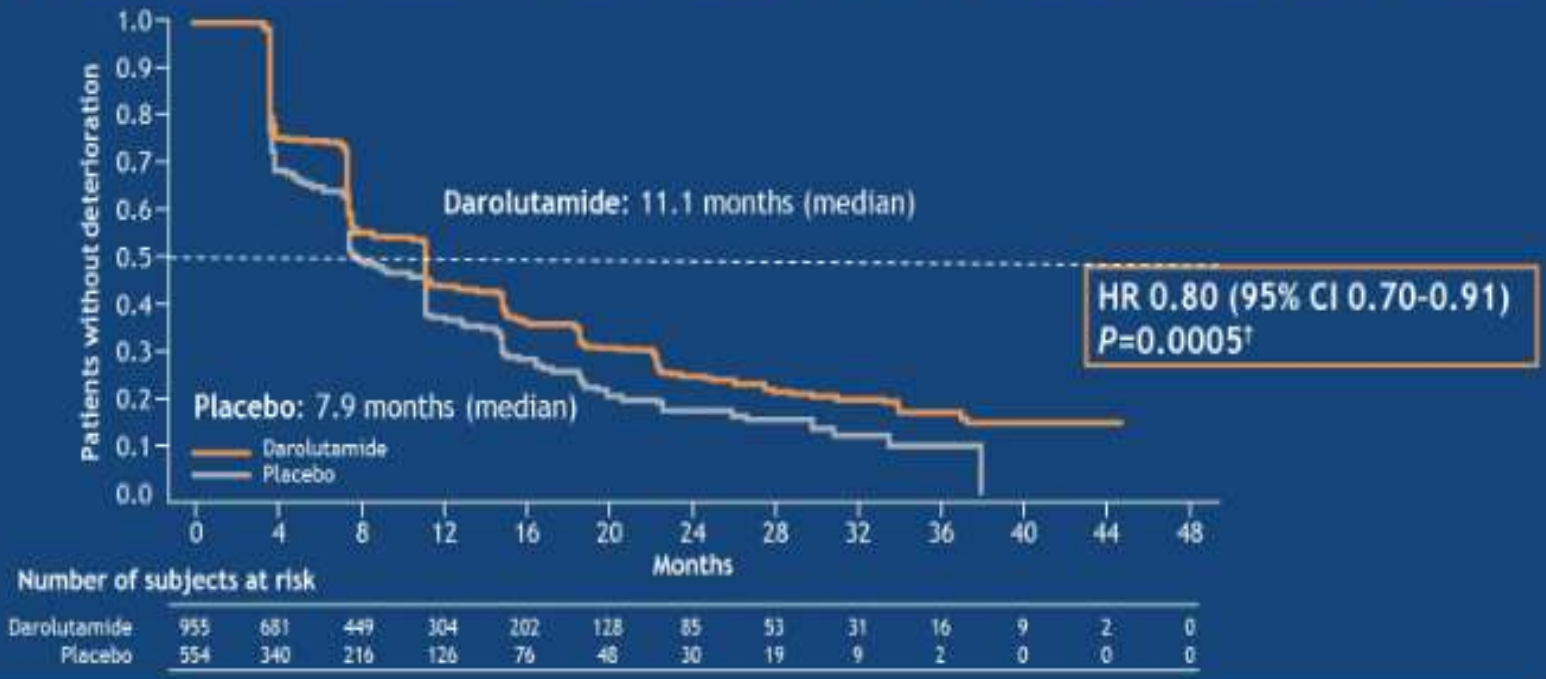
Number of subjects at risk

Darolutamide	955	896	780	623	471	340	260	161	93	51	24	3	0
Placebo	554	492	424	325	236	163	123	80	40	19	6	0	0

*P value calculation was for descriptive purposes only.
CI, confidence interval; HR, hazard ratio; SSE, symptomatic skeletal event.

Exploratory endpoint: Time to deterioration of FACT-P PCS

Time to deterioration (unconfirmed)* was longer for darolutamide than placebo



- Least-squares mean difference in scores over the study period favored darolutamide[1]

*Time to deterioration was defined as time from randomization to date of ≥3 point decline in FACT-P PCS score from baseline. †P value calculation was for descriptive purposes only.

1. Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246. CI, confidence interval; FACT-P PCS, Functional Assessment of Cancer Therapy-Prostate, prostate cancer subscale; HR, hazard ratio.

Updated results from a randomized phase II study of cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic CRPC

Kim N. Chi, Sinja Taavitsainen, Nayyer Iqbal, Cristiano Ferrario, Michael Ong, Deepa Wadhwa, Sebastien J. Hotte, Gregory Lo, Ben Tran, Arun Azad, Lori Wood, Joel R. Gingerich, Scott A. North, Carmel J. Pezaro, J. Dean Ruether, Srikala S. Sridhar, Jack Bacon, Gillian Vandekerkhove, Matti Annala, Alexander W. Wyatt

BC Cancer - Vancouver Centre, Urologic Sciences - University of British Columbia, Saskatoon Cancer Centre, Jewish General Hospital , Ottawa Hospital Cancer Centre, BC Cancer - Kelowna Centre, Juravinski Cancer Centre, Durham Regional Cancer Centre, Peter MacCallum Cancer Centre, Monash Health, QEII Health Sciences Centre, CancerCare Manitoba, Cross Cancer Institute, Eastern Health, Tom Baker Cancer Centre, Princess Margaret Hospital

Dr. Matteo Santoni – Poster Review

Study Schema

- mCRPC with poor prognosis
- Liver metastases
- CRPC within 12 months of ADT for metastatic disease
- Presence of ≥4 of:
  - LDH > ULN
  - ECOG PS 2
  - Visceral metastases
  - Albumin < 4 g/dl
  - ALK PHOS > ULN
  - <36 months from ADT

November 2014 - December 2017

Randomize 1:1

Stratification: Centre, Prior Docetaxel

ARM A: Cabazitaxel 20-25 mg/m² (cfDNA, cfDNA)

ARM B: Abiraterone 1000 mg + Prednisone 10 mg OR Enzalutamide 160 mg (cfDNA, cfDNA)

Progression 1

ARM A: Abiraterone 1000 mg + Prednisone 10 mg OR Enzalutamide 160 mg (cfDNA)

ARM B: Cabazitaxel 20-25 mg/m² (cfDNA)

Progression 2

Primary Objective
- Clinical Benefit Rate
  - PSA decline ≥ 50%
  - Measurable disease response
  - Stable disease > 12 weeks

Other Objectives
- Time to progression
- Progression free survival
- Overall survival
- Response and survival after second-line therapy
- cfDNA correlatives with outcomes

ClinicalTrials.gov: NCT02254785

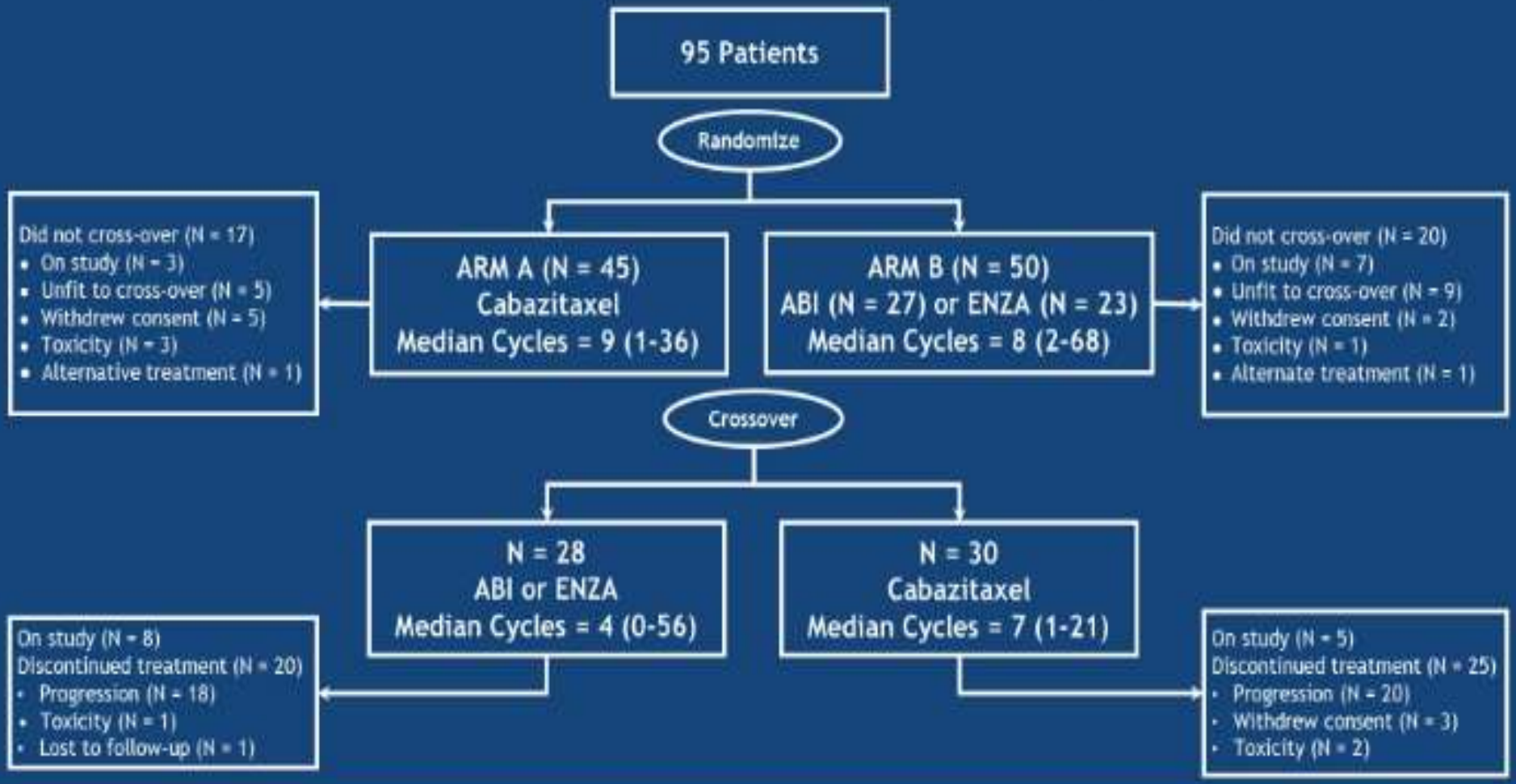
- A planned accrual of 120 patients (60 per arm) to detect a an absolute difference of 20% in CBR
- Due to slow accrual and changes in treatment standards, the trial was closed after 95 patients had been accrued

Results: Baseline Characteristics

Characteristic	Cabazitaxel N = 45	Abiraterone or Enzalutamide N = 50
Median Age, years (range)	67 (45 - 81)	67 (47 - 85)
Poor Prognosis Criteria		
Liver Metastases	5 / 45 (11%)	12 / 50 (24%)
CRPC within 12 months	41 / 45 (91%)	42 / 50 (84%)
≥4 Prognostic Criteria	9 / 45 (20%)	13 / 50 (26%)
ECOG Performance Status		
0-1	41 / 45 (91%)	48 / 50 (96%)
2	4 / 45 (9%)	2 / 50 (4%)
Median PSA, µg/L (range)	18.7 (1.9 - 315)	39.4 (2.7 - 4765)
Median Hemoglobin, g/L (range)	128 (92 - 149)	131 (91 - 156)
Alkaline Phosphatase > ULN	23 / 44 (52%)	26 / 50 (52%)
LDH > ULN	16 / 44 (36%)	25 / 50 (50%)
Site of Metastases		
Lymph Node	23 / 45 (51%)	35 / 50 (70%)
Bone	36 / 45 (80%)	44 / 50 (88%)
Visceral	13 / 45 (29%)	19 / 50 (38%)
Prior Docetaxel		
No	21 (47%)	23 (46%)
Yes For CSPC	13 (29%)	12 (24%)
Yes For CRPC	11 (24%)	15 (30%)

PRESENTED BY: [redacted]

Treatment Delivered and Patient Disposition



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Related Adverse Events on 1st-line Treatment (Grade ≥3)

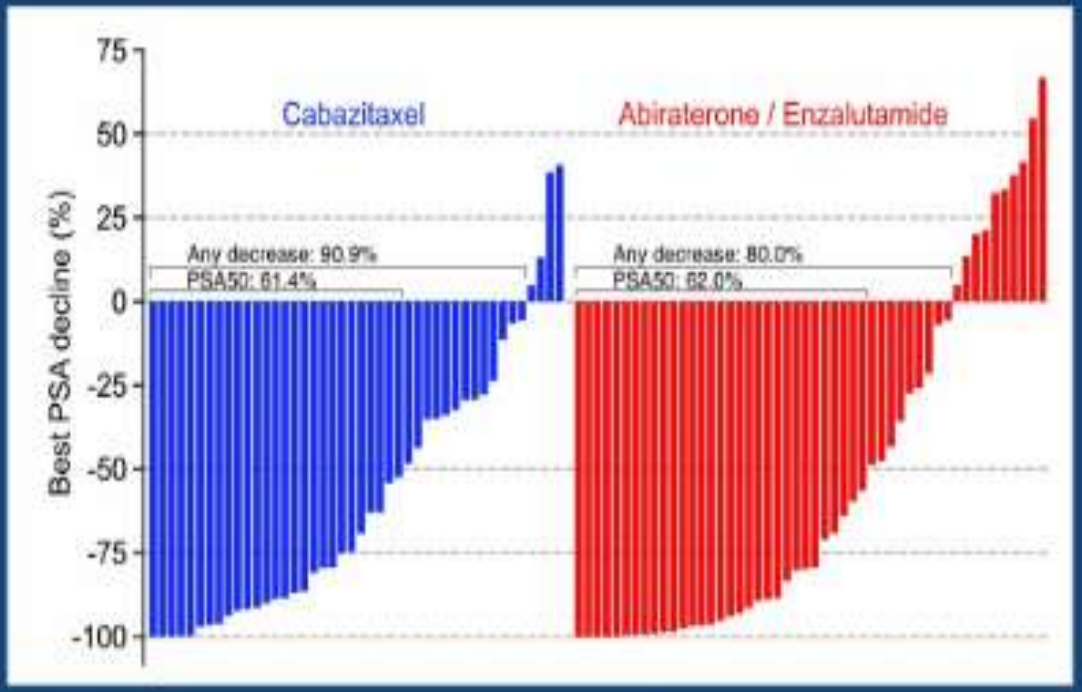
	Arm A (1st-line CAB) N = 44	Arm B (1st-line ABI/ENZ) N = 50
Any grade ≥3 adverse event	***21 (48%)***	***3 (6%)***
Neutropenia	14 (32%)	0 (0%)
Diarrhea	4 (9%)	0 (0%)
Infection	3 (7%)	0 (0%)
Fatigue	3 (7%)	1 (2%)
Hematuria	2 (5%)	0 (0%)
Dehydration	2 (5%)	0 (0%)
Sepsis	1 (2%)	0 (0%)
Anemia	1 (2%)	0 (0%)
Anorexia	1 (2%)	0 (0%)
Cataract	1 (2%)	0 (0%)
Myalgia	0 (0%)	1 (2%)
Infusion related reaction	1 (2%)	0 (0%)
Syncope	1 (2%)	0 (0%)
Enterocolitis	1 (2%)	0 (0%)
Duodenal ulcer and hemorrhage	1 (2%)	0 (0%)
Other	1 (2%)	1 (2%)

Primary Endpoint: Clinical Benefit Rate

	Arm A 1st-line Cabazitaxel	Arm B 1st-line ABI/ENZ	P-value
Clinical Benefit Rate	**38 / 43 (88.4%)**	**35 / 50 (70.0%)**	**0.043**
PSA Decline ≥ 50%	27 / 44 (61.4%)	31 / 50 (62.0%)	1.000
Measurable disease response (PR, CR)	5 / 22 (22.7%)	4 / 23 (17.4%)	0.722
Stable disease >12 weeks*	11 / 43 (25.6%)	4 / 50 (8.0%)	0.026

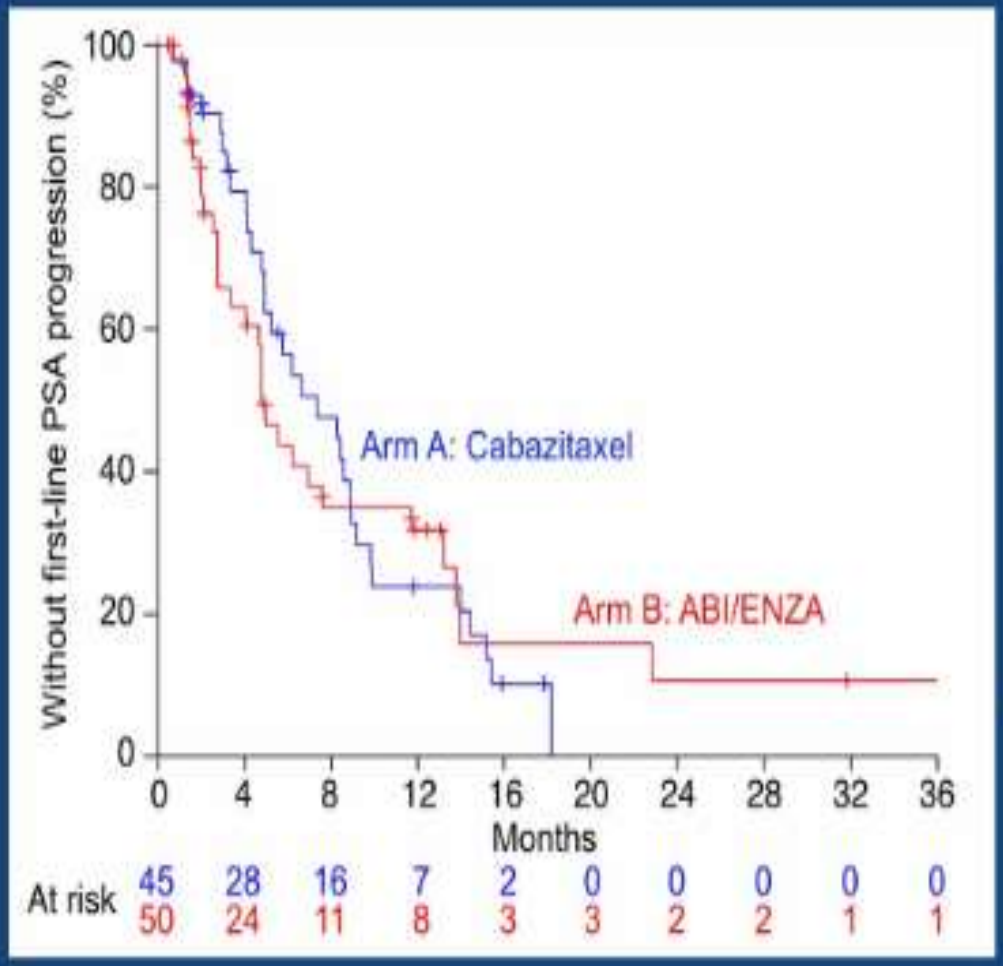
*No PSA, objective or clinical progression for >12 weeks as best response
Clinical Benefit Rate: PSA decline ≥ 50%, CR/PR, or stable disease > 12 weeks

PSA response to first-line treatment



	Arm A 1st-line Cabazitaxel	Arm B 1st-line ABI/ENZ	P-value
PSA Decline ≥ 30%	33 / 44 (75.0%)	35 / 50 (70.0%)	0.649
PSA Decline ≥ 50%	27 / 44 (61.4%)	31 / 50 (62.0%)	1.000
No PSA Decline	4 / 44 (9.1%)	10 / 50 (20.0%)	0.159

Time to first-line PSA Progression



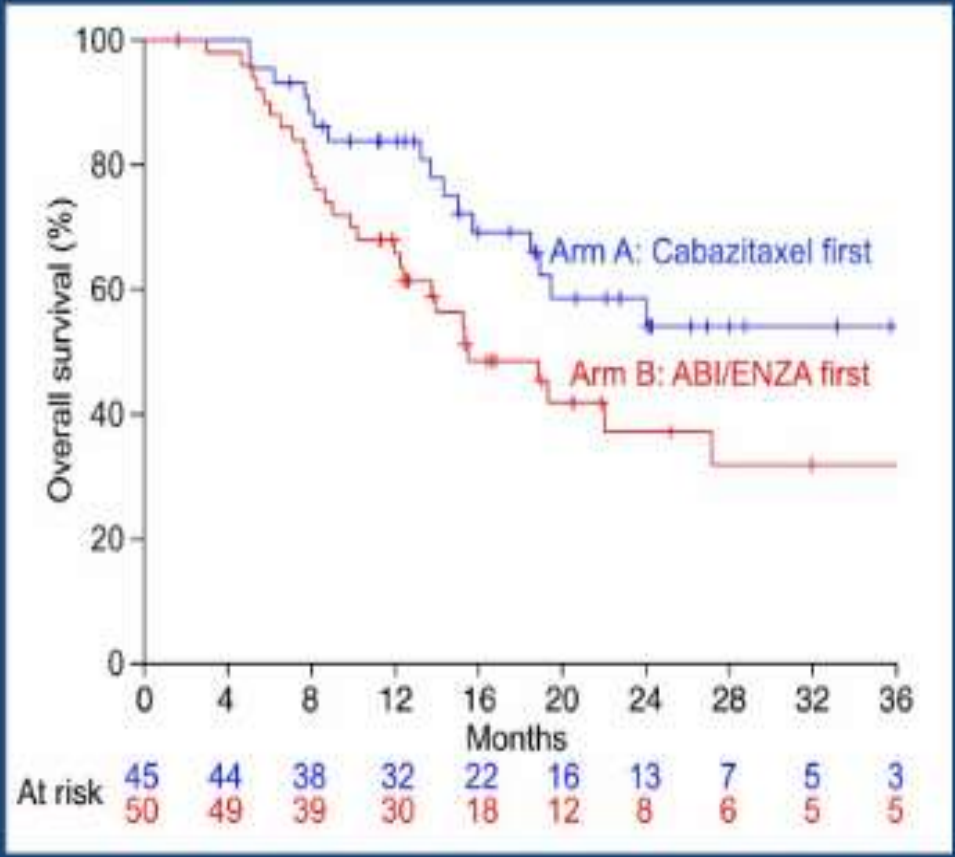
	Median (95% CI) *Months*	HR (95% CI)
Arm A (1st-line CABA)	7.4 (4.9 - 9.1)	0.94 (0.57 - 1.56) p = 0.821
Arm B (1st-line ABI/ENZA)	4.7 (3.4 - 13.2)	

Clinical Benefit Rate: 2nd Line Therapy

	Arm A 2nd Line ABI/ENZA	Arm B 2nd Line Cabazitaxel	P-value
Clinical Benefit Rate	**17 / 23 (73.9%)**	**17 / 27 (63.0%)**	**0.546**
PSA Decline ≥ 50%	12 / 25 (48.0%)	12 / 29 (41.4%)	0.784
Measurable disease response (PR, CR)	0 / 9 (0.0%)	2 / 10 (20.0%)	0.474
Stable disease >12 weeks*	5 / 23 (21.7%)	5 / 27 (18.5%)	1.000

*No PSA, objective or clinical progression for >12 weeks as best response
Clinical Benefit Rate: PSA decline ≥ 50%, CR/PR, or stable disease > 12 weeks

Overall Survival



	Median (95% CI) *Months*	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Arm A (CABA first)	37.0 (18.9 - NR)	0.57 (0.31 - 1.03) p = 0.06	0.77 (0.41 - 1.44) p = 0.410
Arm B (ABI/ENZA first)	15.5 (12.4 - NR)		

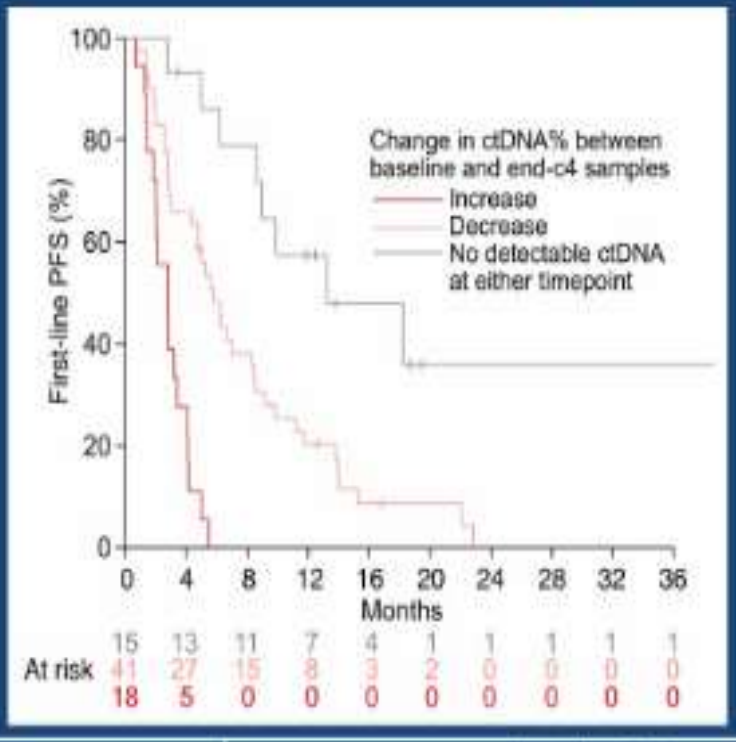
*Hazard ratio adjusted using a multivariate model including LDH, ALP, ECOG performance status, and presence of visceral metastases as variables.

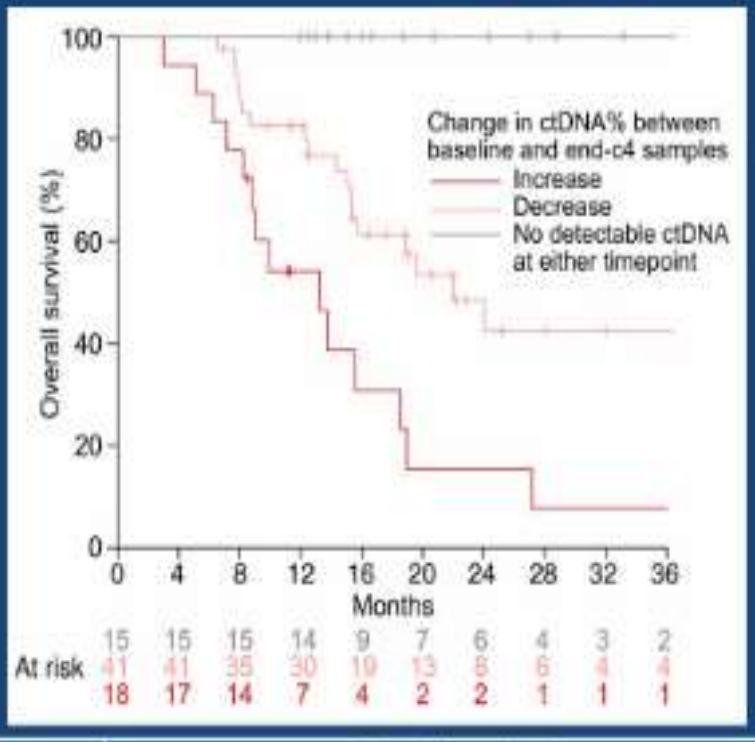
cell-free DNA

- Targeted sequencing
  - Plasma cfDNA and germline (matched leukocyte DNA)
  - 73 CRPC-related genes (all exons) including [1,2]
    - Prostate cancer drivers (e.g. AR, SPOP, NKX3.1, FOXA1)
    - Cell cycle (e.g. TP53, RB1, CDKN1B, CDKN2A)
    - DNA repair (e.g. BRCA1/2, FANC family genes, ATM, MSH2/6)
    - PI3K pathway (e.g. PIK3CA, PTEN, AKT1)
- AR gene sequencing (exons, introns, flanking regions) to detect AR gene rearrangements
- ctDNA fractions (ctDNA/cfDNA) were estimated based on the allele fractions of autosomal somatic mutations

[1]AW Wyatt, et al. J Natl Cancer Inst, 110(1): 78–86, 2018; [2]M Annala, et al. Cancer Discov, 8:1–14, 2018

On-treatment change in ctDNA fraction is prognostic





	First-line PFS		Overall survival	
	Median (months)	Hazard ratio (95% CI)	Median (months)	Hazard ratio (95% CI)
ctDNA% increase	2.8	3.99 (2.03 - 7.84) p < 0.001	13.2	2.72 (1.34 - 5.50) p = 0.006
ctDNA% decrease	5.8		22.0	
No detectable ctDNA	13.2	-	Not reached	-

TAXOMET : A French prospective multicentric randomized controlled phase II study comparing docetaxel plus metformin versus docetaxel plus placebo in mCRPC

Marc Pujalte-Martin[1], Delphine Borchiellini[1], Julien Viotti[1], Aline Guillot[2], Jean-Baptiste Paoli[3], Dominique Besson[4], Werner Hilgers[5], Claude El Kouri[6], Gerard Cavaglione[1], Frank Priou[7], Tifenn Lharidon[7], Remy Largillier[8], Jean-Laurent Deville[9], Benjamin Hoch[8], Renaud Schiappa[1], Jean-François Tanti[10], Frédéric Bost[10], Jean-Marc Ferrero[1]

[1]Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; [2]Institut de Cancérologie de la Loire, Priest en Jarez, France; [3]Hôpital de Clairval, Marseille, France; [4]Centre CARIO-HPCA, Plérin sur Mer, France; [5]Institut Sainte Catherine, Avignon, France; [6]Centre Catherine de Sienne, Nantes, France; [7]CHD Vendée, La Roche sur Yon, France; [8]Centre Azuréen de cancérologie, Mougins, France; [9]APHM - CHU Timone, Marseille, France; [10]Inserm U1065 C3M, Nice, France

ClinicalTrials.gov Identifier: NCT01796028

TAXOMET Study Design

Whenever docetaxel was definitevly interrupted, Metformin or Placebo had to be discontinued

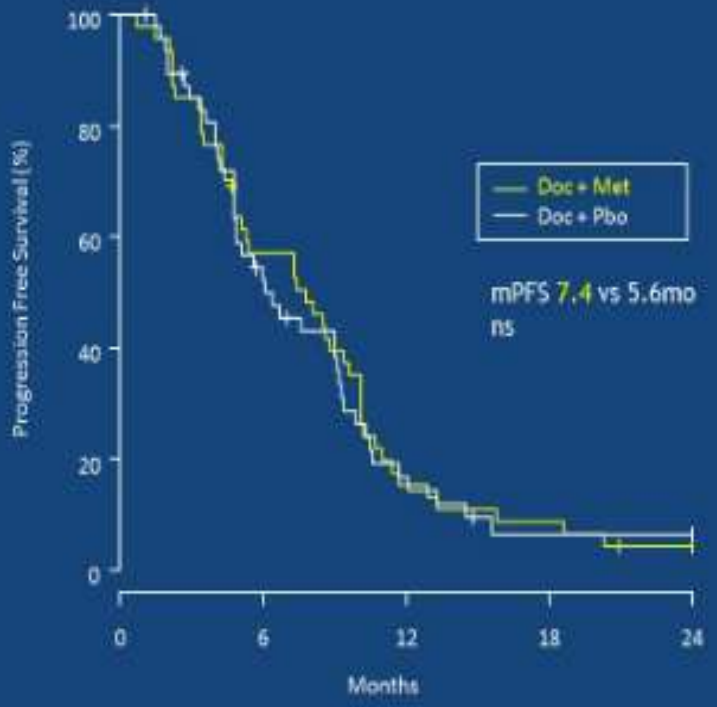
Follow-up after treatment
- Every 3mo the first year
- Every 6mo the next 2 years

[1]Kordes S and al. Lancet oncol 2015

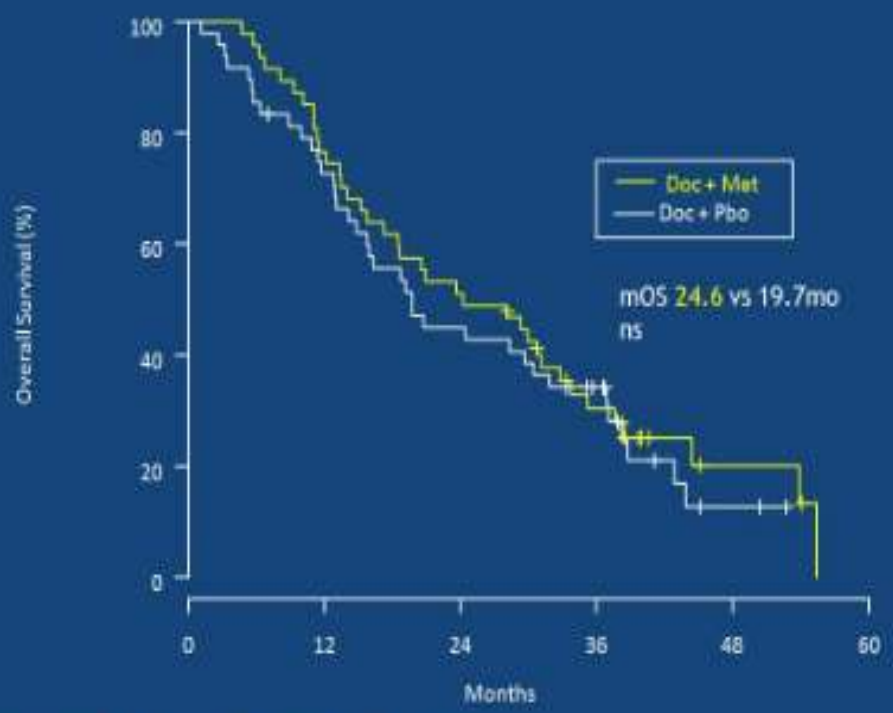
Survival (ITT)

Secondary end-points

- Progression free-survival



- Overall survival



Median (range) follow-up : 41.1mo (38.5-54.1)

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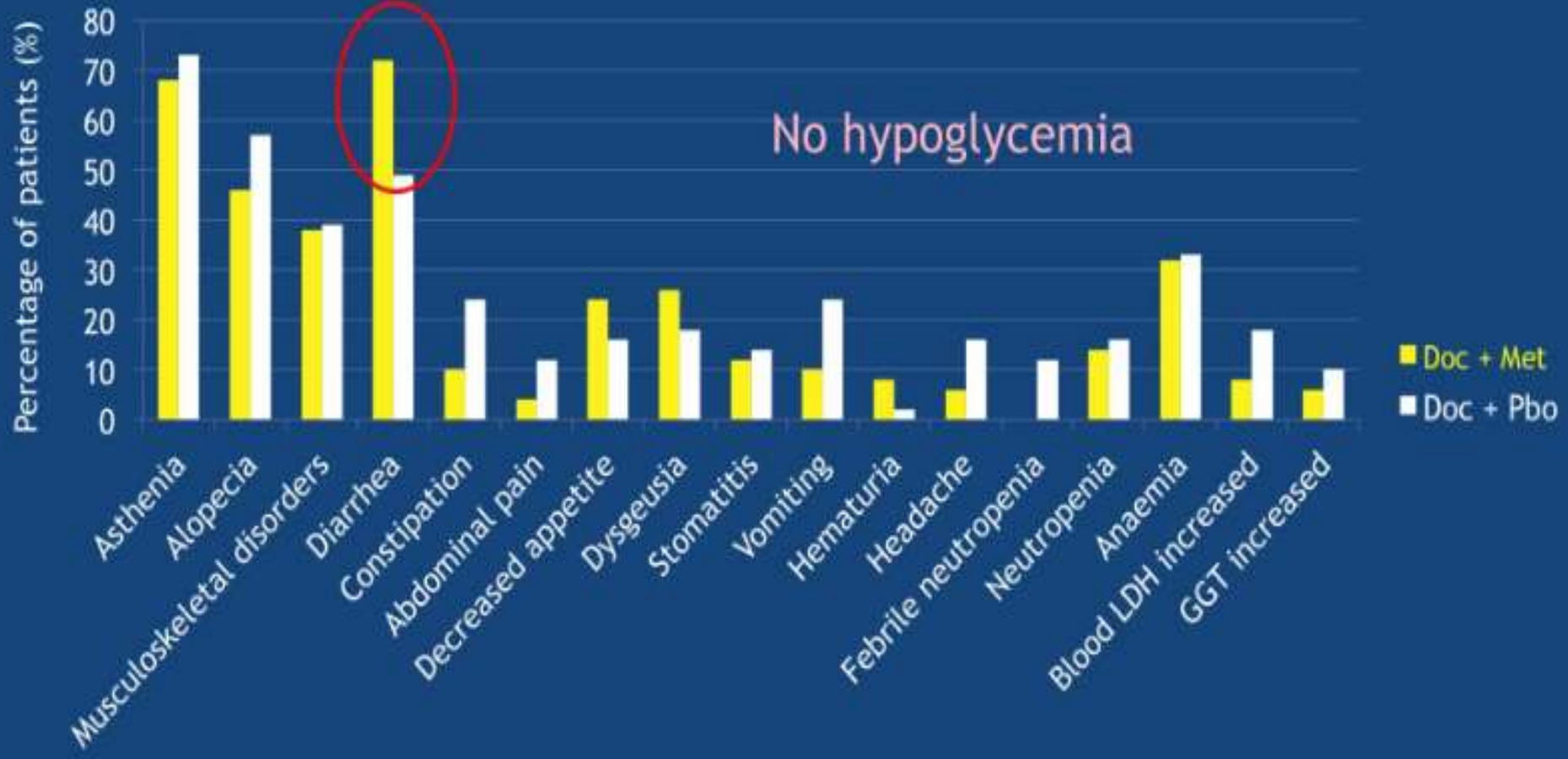
Adverse Events (all grades), incidence ≥ 5%



Dr. Matteo Santoni – Poster Review

A multicentric phase II randomized trial of docetaxel plus enzalutamide versus docetaxel as first line chemotherapy for patients with metastatic castration-resistant prostate cancer – CHEIRON study.

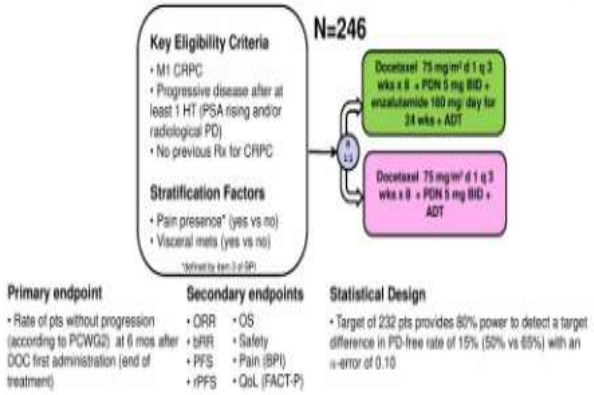
Orazio Caffo[1], Erica Palesandro[2], Franco Nolé[3], Donatello Gasparro[4], Claudia Mucciarini[5], Michele Aieta[6], Vittorina Zagonel[7], Roberto Iacovelli[8], Ugo De Giorgi[9], Sabrina Rossetti[10], Lucia Fratino[11], Cosimo Sacco[12], Maurizio Nicodemo[13], Monica Giordano[14], Donata Sartori[15], Daniela Scapoli[16], Elena Verri[3], Stefania Kinspergher[1], Giovanni L. Pappagallo[15],and Massimo Aglietta[2]

[1]Santa Chiara Hospital, Trento; [2]Institute for Cancer Research and Treatment, Candiolo; [3]European Institute of Oncology, Milan; [4]AOU, Parma; [5]Ramazzini Hospital, Carpi; [6]CRO, Rionero in Vulture; [7]Veneto Institute of Oncology, IOV, Padua; [8]AOU, Verona; [9]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola; [10]Istituto Nazionale Tumori Fondazione G. Pascale, Naples; [11]National Cancer Center CRO, Aviano; [12]AOU S. M. della Misericordia, Udine; [13]Sacro Cuore - Don Calabria Hospital, Negrar; [14]Santa Anna Hospital, Como; [15]Azienda ULSS 13, Mirano; [16]S.Anna Hospital, Ferrara (Italy)

BACKGROUND

Today docetaxel (DOC) and enzalutamide (ENZ) represent two standard treatments for first line management of patients with metastatic castration-resistant prostate cancer (mCRPC). They exert their anticancer activity by different mechanisms: ENZ impairs androgen receptor machinery at three different levels (it binds androgen receptors, prevents their nuclear translocation and inhibits coactivator recruitment of the ligand–receptor complex); DOC, producing a microtubule-stabilization, is able to alter signaling from the androgen receptor by inhibiting its nuclear accumulation downstream of microtubule stabilization, providing a clear connection between the microtubule-dependent trafficking of the androgen receptor and the clinical efficacy of DOC. On these bases, It could be postulated that the administration of enzalutamide during a DOC-based chemotherapy could improve disease control.

STUDY DESIGN



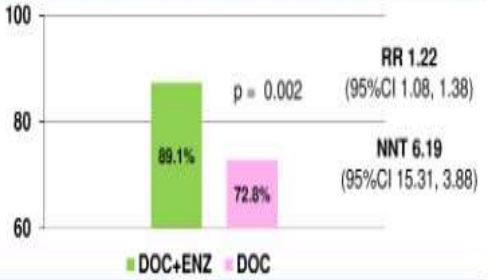
PATIENTS CHARACTERISTICS

Characteristic	DOC + ENZ + ADT (n= 120)	DOC + ADT (n = 126)
Median age (range), y	70 (52-88)	72 (44-84)
ECOG PS, no. (%)		
0-1	116 (97%)	122 (97%)
2	4 (3%)	4 (3%)
Baseline pain presence, no (%)		
No	93 (78%)	99 (79%)
Yes	27 (22%)	27 (21%)
Baseline visceral metastases presence, no (%)		
No	94 (78%)	93 (74%)
Yes	26 (22%)	33 (26%)
Median serum PSA (range), ng/ml	25.9 (0.3-1,360)	30.5 (0.2-5,000)

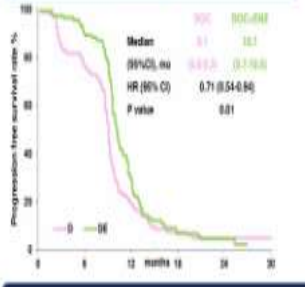
GRADE ≥ 3 AE OCCURRING IN ≥ 5% OF PATIENTS

Event, No. (%)	DOC + ENZ + ADT	DOC + ADT
Neutropenia	19 (15.8%)	15 (11.9%)
Fatigue	15 (12.5%)	7 (5.6%)
Leukopenia	10 (8.3%)	15 (11.9%)
Febrile neutropenia	10 (8.3%)	7 (5.6%)
Other skin toxicities	7 (5.8%)	2 (1.6%)
Skin rash	6 (5.0%)	2 (1.6%)

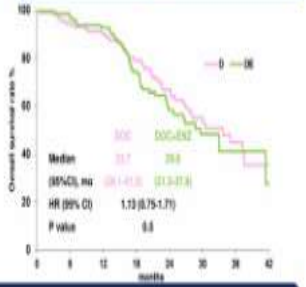
PD-FREE PATIENTS RATE AT 6 MOS AFTER D START



PFS



OS



CONCLUSIONS

This is the first randomized phase II trial testing the combination of docetaxel with an ARTA
Although control arm DCR was higher than expected, the trial met its primary endpoint
Our results showed that the combination: 1)is feasible and safe (although slightly higher than docetaxel alone); 2) provides a better disease control compared to docetaxel alone; 3) does not improve OS (immature data)

For further information please email to orazio.caffo@apss.tn.it

Dr. Matteo Santoni – Poster Review

18F-Fluciclovine and 68Ga-PSMA-11 PET/CT in patients with biochemical recurrence after prostatectomy at PSA levels of ≤ 2.0ng/ml: a prospective, single-arm, comparative imaging trial

Jeremie Calais[1,2], Francesco Ceci[1,3], Matthias Eiber[1,4], Thomas A. Hope[5], Michael S. Hofman[6], Christoph Rischpler[7], Tore Bach-Gansmo[8], Cristina Nanni[9], Bital Savir-Baruch[10], David Elashoff[11], Tristan Grogan[11], Roger Slavik[1], Magnus Dahlbom[1], Jeannine Gartmann[1], Kathleen Nguyen[1], Vincent Lok[1] Hossein Jadvar[12], Amar U Kishan[2,13], Matthew B Rettig[2,14], Robert E Reiter[2,14], Wolfgang P. Fendler[1,7], Johannes Czernin[1,2]

[1] Ahmanson Translational Theranostics Division, Department of Medical and Molecular Pharmacology, [2] Institute of Urologic Oncology, [11] Department of Medicine Statistics Core, [13] Department of Radiation Oncology, [14] Department of Urology, University of California Los Angeles, USA; [3] University of Turin, Italy; [4] Technical University of Munich, Germany; [5] University of California San Francisco, USA; [6] Peter MacCallum Cancer Centre Melbourne, Australia; [7] University Hospital Essen, Germany; [8] Oslo University Hospital, Oslo, Norway; [9] S.Orsola-Malpighi University Hospital, Bologna, Italy; [10] Loyola University Medical Center, Maywood, Illinois, USA; [12] University of Southern California, Los Angeles, USA

PSMA vs FACBC - NCT03515577

Study Design and Methods

- **Background:**
Two PET/CT imaging tests for detection and localization of prostate cancer (PCa) tumor site(s) in patients with biochemical recurrence (BCR) have been introduced recently: 18F-Fluciclovine PET/CT (FACBC, targeting the **upregulated amino acid transporter activity (LAT1)**) and PSMA PET/CT (targeting the **overexpression of the transmembrane Prostate Specific Membrane Antigen** via its extra-cellular part). It is unknown which test performs better, especially in patients with BCR at low PSA levels (≤2.0 ng/ml). The aim of this study was to compare these 2 tests head-to-head and prospectively.
- **Study design:**
Prospective, single-center, open-label, single-arm comparative imaging trial using **external, anonymized, blinded and independent interpretations** of consecutive **paired FACBC and PSMA PET/CT studies** (IND#130649, clinicaltrial.gov identifier NCT02940262, UCLA IRB#17-001885).
- **Primary Endpoint:**
  - **Detection rates** (+positivity rates) on per-patient and per-region based analysis
- **Secondary Endpoints:**
  - Detection rates stratified by PSA.
  - Sensitivity and positive predictive value verified by histopathology, clinical and imaging follow-up.
  - Inter-reader agreement
- **Population:**
Patients with PCa BCR and **PSA levels ranging from 0.2 to 2.0 ng/mL** without any prior salvage therapy (ex: salvage radiotherapy and/or salvage lymph node (LN) dissection) were eligible irrespective of prior conventional imaging findings and underwent FACBC and PSMA scans **within ≤15 days**.
- **Hypothesis – Statistical Power analysis:**
Based on literature data we **hypothesized a detection rate difference of 22% in favor of PSMA** in this population. A sample size of **50 patients** (one-sided McNemar exact conditional test) provides >86% power assuming a one-sided alpha of 0.05.
- **Outcomes:**
FACBC PET/CT scans were each interpreted by 3 independent experts:
  - ***Cristina Nanni BOLOGNA (ITA), Bital Savir-Baruch CHICAGO (USA), Tore Bach-Gansmo OSLO (NOR)***

PSMA PET/CT scans were each interpreted by 3 independent experts:
  - ***Tom Hope UCSF (USA), Christoph Rischpler ESSEN (GER), Michael Hofman MELBOURNE (AUS)***

The readers were not involved in study design and data acquisition. Each reader was blinded for the interpretations of the 5 other readers. In cases of reader disagreement, **consensus majority rule (2:1)** was applied. All patients were followed for subsequent biopsies, imaging studies, PSA measurements and disease management. Treatment decisions were not standardized and made at the discretion of the referring physician based on all available clinical information, including the non-blinded local reports of both PET scans and any other imaging findings.

PET/CT characteristics

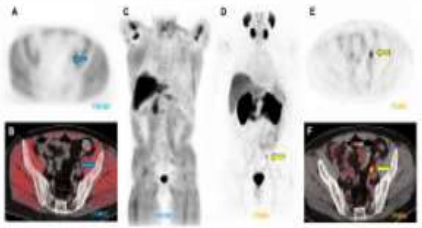
Time interval (median)	**6 days IQR 2-8**
FACBC before PSMA	28 (58%)
FACBC with IV CT contrast	35 (70%)
FACBC injected activity (median)	381 MBq IQR 359-407
FACBC uptake time (median)	2 min. IQR 1-3
PSMA before FACBC	21 (42%)
PSMA with IV CT contrast	48 (96%)
PSMA injected activity (median)	200 MBq IQR 192-204
PSMA uptake time (median)	61 min. IQR 57-66

Patients Characteristics

Age (median)	68 y-o IQR 64-74
NCCN Risk group	
Intermediate	17 (34%)
High	14 (28%)
Very High	5 (10%)
N1	11 (22%)
NA	3 (6%)
Pelvic LN Dissection	40 (80%)
Margin R1	13 (26%)
Adjuvant RT	6 (12%)
Adjuvant ADT	10 (20%)
PSA persistence	12 (24%)
PSA recurrence	38 (76%)
On-going ADT	7 (14%)
Time RP to PET (median)	3 years IQR 1-8
Last PSA before PET (median)	**0.48 ng/mL IQR 0.38-0.83**
PSA doubling time (median)	4 months IQR 3-16
PSA velocity (median)	0.3 ng/mL/yr IQR 0.1-1.2

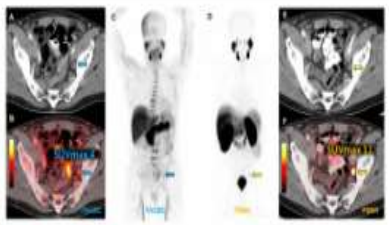
PSMA vs FACBC - NCT03515577

Results



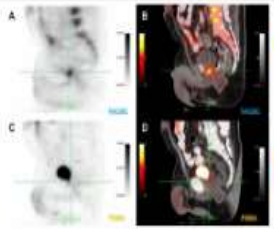
DISCORDANT CASE: T0 N1 M0 - FACBC False Negative / PSMA True Positive

75 y-o man with a PSA of **0.37 ng/mL**. High PSMA uptake in a single 9mm left external iliac LN (SUVmax 6, Panel D,E,F, yellow arrows) without visible increased FACBC uptake (Panel A,B,C, blue arrows). Patient underwent lymph node dissection and **histopathology confirmed metastatic prostatic adenocarcinoma**. PSMA was read as positive (3/3 readers positive) whereas FACBC was read as negative (1/3 readers). *Note the high muscle background FACBC signal (Panel C).*



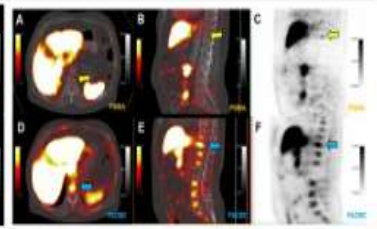
CONCORDANT CASE: T0 N1 M0 - FACBC Positive / PSMA Positive

68 y-o man with a PSA of **0.38 ng/mL**. High PSMA-expression in a single 5 mm left obturator iliac LN (SUVmax 10.8, Panel D,E,F, yellow arrow) with increased FACBC uptake (SUVmax 4.1, Panel A,B,C, blue arrow). Patient was treated with ADT, SRT to the prostate bed and the whole pelvis with a dose boost to the PET-positive LN. PSA became undetectable. Both scans were read as positive by the readers (3/3 PSMA readers, 2/3 FACBC readers).



DISCORDANT CASE: TxN0 M0 - FACBC Positive / PSMA negative

62 y-o man with PSA of **0.39 ng/mL**. Focal increased FACBC uptake (SUVmax 5.8, Panel A,B, green cross) suspicious of local recurrence without visible PSMA uptake (Panel C,D). Patient underwent salvage RT with ADT. PSA became undetectable. FACBC was read as positive (2/3 readers), PSMA was read as negative (1/3 readers).



DISCORDANT CASE: T0 N0 M1b - FACBC false negative / PSMA True Positive

73 y-o man with a PSA of **0.62 ng/mL**. Focal PSMA uptake in a T11 lesion without CT correlate (SUVmax 3.3, panel A,B,C,) with low FACBC uptake (Panel D,E,F). **MRI confirmed the T11 bone lesion.** Patient remained under active surveillance. PSMA was read as positive (2/3 readers positive) whereas FACBC was read as negative (1/3 readers positive). *Note the high FACBC bone marrow background activity (Panel E,F).*

Paired PET/CT findings

	FACBC	PSMA	n (%)	Cancer Confirmed
Equal false negative (n=18)	T0 N0 M0	T0 N0 M0	18 (36%)	3
Equal positive detection per-patient (n=9)	T+ N0 M0	T+ N0 M0	3 (6%)	3
	T0 N1 M0	T0 N1 M0	3 (6%)	0
	T0 N0 M1b	T0 N0 M1b	3 (6%)	0
FACBC superior detection per-patient (n=4)	T+ N0 M0	T0 N0 M0	3 (6%)	2
	T0 N1 M0	T0 N0 M0	1 (2%)	0
PSMA superior detection per-patient (n=33)	T0 N0 M0	T+ N0 M0	3 (6%)	0
	T0 N0 M0	T0 N1 M0	8 (16%)	8
	T0 N0 M0	T0 N1 M1a	1 (2%)	0
	T0 N0 M0	T0 N0 M1a	1 (2%)	0
	T0 N0 M0	T0 N0 M1b	4 (8%)	1
	T0 N0 M0	T0 N0 M1c	1 (2%)	1
	T0 N0 M0	T0 N0 M1a M1c	1 (2%)	1

Semi-quantitative Analysis in Patients with Concordant lesions (n=7)

Concordant Lesion	n	Lesion SUVmax	L/B Liver	L/B Aorta	L/B muscle	Lesion SUVmax	L/B Liver	L/B Aorta	L/B muscle
		FACBC				PSMA			
Pelvic LN (N)	3	3.13	0.50	2.18	3.65	5.60	0.94	4.35	13.03
Prostate fossa (T)	4	4.17	0.55	2.71	5.73	10.18	2.24	8.69	54.67
All concordant lesions	7	3.73	0.52	2.44	3.69	8.21	1.68	6.83	25.39

x 7 (p<0.003)

Treatment Management after PET (median follow-up 8 months IQR 7-9)

Metastasis Surgery	3 (6%)
Metastasis SBRT	2 (4%)
Prostate Fossa SRT	4 (8%)
Prostate Fossa SRT + Whole-Pelvic LN RT	1 (2%)
Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT	1 (2%)
ADT	7 (14%)
ADT + Abi/Enza	2 (4%)
ADT + Prostate Fossa SRT	10 (20%)
ADT + Prostate Fossa SRT + Metastasis SBRT	1 (2%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT	2 (4%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT	1 (6%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT + Abi/Enza	2 (4%)
ADT + Metastasis SBRT	3 (6%)
Surveillance	9 (18%)

Contingency Tables

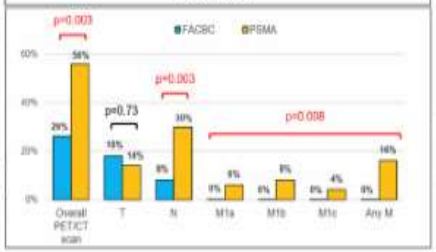
Per-region

	T		N		M1a		M1b		M1c		Any M	
	FACBC neg.	FACBC pos.	FACBC neg.	FACBC pos.	FACBC neg.	FACBC pos.	FACBC neg.	FACBC pos.	FACBC neg.	FACBC pos.	FACBC neg.	FACBC pos.
PSMA neg.	38	5	34	1	47	0	46	0	48	0	42	0
PSMA pos.	3	4	12	3	3	0	4	0	2	0	8	0
	p=0.73		p=0.0034		p=0.25		p=0.13		p=0.50		p=0.0078	

Per-patient

	Full Analysis Pop. (n=50)		Lesion Validation Pop. (n=15)	
	FACBC neg.	FACBC pos.	FACBC neg.	FACBC pos.
PSMA neg.	18	4	3	2
PSMA pos.	19	9	7	3
	p=0.0026		p=0.18	

Detection Rates



- To assess potential bias, a post-hoc analysis was performed and confirmed the differences among the 35 patients in whom both studies were performed with contrast-enhanced CT (**11/35 (31% [$CI_{95\%}$:17%-49%]) vs 20/35 (57% [$CI_{95\%}$:40%-74%]); OR 4.0 [$CI_{95\%}$:1.08-22.1), p=0.035**). Additionally, there was no significant difference between the detection rates of FACBC PET/CT performed with or without IV CT-contrast (11/35 (31% [$CI_{95\%}$:17%-49%]) vs 2/15 (13% [$CI_{95\%}$:2%-40%]); difference 18% [$CI_{95\%}$:10%-37%], p=0.29). A post-hoc analysis was performed by conducting multivariable mixed effects logistic regression models. The following variables were tested with the outcome of a positive PET scan: PET tracer (PSMA vs FACBC), on-going ADT, history of adjuvant ADT, history of adjuvant radiation treatment, NCCN risk group, PSA doubling time (higher vs lower than median), PSA velocity, FACBC uptake time (<3 vs >3 min) and FACBC with contrast-enhanced CT. The only significant predictor for test positivity was the PET tracer used (FACBC vs. PSMA; ORs 3.56-3.88; p<0.05). **Neither FACBC uptake time (<3min vs >3 min), nor the administration of IV contrast for CT imaging were confounding factors.**
- In patients with PSA levels from 0.2 to 0.5 ng/mL, 0.5 to 1.0 ng/mL and 1.0 to 2.0 ng/mL detection rates were 7/26 (27% [$CI_{95\%}$:12%-48%]), 5/18 (28% [$CI_{95\%}$:10%-53%]), and 1/6 (17% [$CI_{95\%}$:2%-64%]) with FACBC and 12/26 (46% [$CI_{95\%}$:27%-67%]), 12/18 (67% [$CI_{95\%}$:41%-87%]) and 4/6 (67% [$CI_{95\%}$:22%-96%]) with PSMA, respectively. There was no statistically significant difference between these sub-groups.
- **PET findings were validated in 15/50 (30%) patients** (5/13 with FACBC-positive (38%) and 10/28 with PSMA-positive (36%) findings). Reference standard included histopathology (n=4), follow-up imaging (n=7), and PSA decreases after PET-directed focal therapy without ADT (n=4). No false positive findings occurred with either tracer in the 15 patients in whom lesions were verified (PPV of 100% for both FACBC and PSMA findings). **Per-patient sensitivity was 33% [$CI_{95\%}$:15%-58%] (5 true positive/10 false negative) and 66% [$CI_{95\%}$:42%-85%] (10 true positive/5 false negative) for FACBC and for PSMA PET/CT, respectively (OR 3.5 [$CI_{95\%}$:0.67-34.5], p=0.18).**

Inter-reader agreement - Multi-rater Kappa (95% CI)

Region	PSMA	FACBC	p
T	0.65 (0.49, 0.81)	0.43 (0.27, 0.59)	0.046
N	0.76 (0.60, 0.92)	0.05 (-0.11, 0.21)	<0.0001
M1a	0.60 (0.44, 0.76)	-0.02 (-0.18, 0.14)	0.0025
M1b	0.46 (0.30, 0.62)	-0.03 (-0.19, 0.13)	0.0051
M1c	0.65 (0.49, 0.81)	-0.01 (-0.17, 0.15)	0.034
Any M	0.60 (0.44, 0.76)	-0.07 (-0.23, 0.09)	<0.0001
PET/CT scan	**0.47 (0.31, 0.63)**	**0.20 (0.04, 0.36)**	**0.0020**

PSMA vs FACBC - NCT03515577

Conclusion

- **Due to higher lesion-to-background ratio, PSMA PET/CT demonstrates superior detection rates and reader agreement than FACBC PET/CT.**
- **Primary and secondary endpoints were met:** PSMA PET/CT detection rates per-patient, for pelvic LN regions (N) and for extra-pelvic metastasis (M) were more than twice as high than those for FACBC PET/CT.
- PSMA should be the PET agent of choice when PET/CT imaging is considered for subsequent treatment management decisions in patients with PCa and post-RP BCR at low PSA levels (≤2.0 ng/ml) and should become the standard of care in these patients.
- Whether early detection of BCR sites by PET/CT imaging affects patient outcome is the subject of ongoing randomized phase 3 clinical trials (NCT03582774 and NCT03762759).

Dr. Matteo Santoni – Poster Review

RESIST-PC phase 2 trial: 177Lu-PSMA-617 radionuclide therapy for metastatic castrate-resistant prostate cancer.

Authors:
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Methods:

Patients with progressive mCRPC (biochemical, radiographic or clinical) after ≥1 novel androgen axis drug (NAAD), either chemotherapy (CTX) naïve or post-CTX, with sufficient bone marrow reserve and normal kidney function were eligible. All patients underwent a screening PSMA PET/CT to confirm target expression. Patients received up to 4 cycles of ^{177}Lu-PSMA-617 every 8±1 weeks and were randomized into 2 treatment activities groups (6.0 or 7.4 GBq). Kidney dosimetry was performed for the first cycle. Efficacy was defined as serum PSA decline of ≥50% from baseline at 12 weeks and served as primary endpoint.

Results:

64 patients (median PSA 75 ng/ml; range 0.5-2425) were included in the study. 20% were CTX naïve while 80% were post-CTX (1.9 CTX regimens on average, range 1-4). 45% completed 4 cycles of ^{177}Lu-PSMA-617. Androgen deprivation therapy was given concomitantly in 83%, NAAD in 23% and immunotherapy in 6%. PSA decline of ≥50% was observed in 23% of patients at 12 weeks and in 38% of patients at any time (best PSA response). The median time to best PSA response was 22 weeks (range 6-49 weeks). 16% had a PSA decline of ≥90% and 59% had any PSA decline (> 0%). Mild and transient (CTCAE grade 1-2) side effects included xerostomia (72%), nausea/vomiting (69%) and bowel movement disorders (45%). CTCAE grade 3 toxicity included nausea/vomiting (6%), anemia (8%), leukopenia (5%), kidney failure (3%), thrombocytopenia (3%), and neutropenia (3%). The mean kidney dose was 2.7 Gy for the first cycle (range 0.9-5.9) i.e. 0.4 Gy/GBq (range 0.15-0.9). There was no difference between the efficacy and toxicity for the 6.0 GBq (n = 23) and 7.4 GBq (n = 41) treatment arms.

Phase 1 study of pasotuxizumab (BAY 2010112), a PSMA-targeting Bispecific T cell Engager (BiTE) immunotherapy for metastatic castration-resistant prostate cancer (mCRPC).

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Methods:
NCT01723475 was a first-in-human, multicenter, dose-escalation study in patients (pts) with mCRPC refractory to standard therapy. Pts received pasotuxizumab as a continuous intravenous infusion in cohorts of 3–4 pts. Dose-escalation followed a continuous reassessment methodology design. The primary objective was to determine safety and maximum tolerated dose (MTD); secondary objectives included pharmacokinetics, biomarkers, and tumor response.

Results:
16 pts were enrolled into 5 dosing cohorts (5 µg/d, n = 3; 10 µg/d, n = 4; 20 µg/d, n = 3; 40 µg/d, n = 4; 80 µg/d, n = 2). All pts had ≥1 AE of any grade; most common were fever (94%), chills (69%), and fatigue (50%). 13 pts (81%) had ≥1 AE of grade ≥3; most common were decreased lymphocytes and infections (both 44%). No grade 5 AE occurred. A serious AE related to study drug was reported for 1 pt (fatigue, 20 µg/d). No anti-drug antibodies were observed. Recruitment was stopped before MTD was reached to facilitate initiation of a new study sponsored by Amgen. Antitumor activity as indicated by PSA serum level decline was dose dependent, with a mean best PSA change per dosing cohort versus baseline of +0.74% (5 µg/d), –17.9% (10 µg/d), –37.4% (20 µg/d), –42.5% (40 µg/d) and –54.9% (80 µg/d). PSA decreases of ≥50% occurred in 3 pts (n = 1 each in 20 µg/d, 40 µg/d, and 80 µg/d cohorts). One long-term PSA responder was treated for 14 months (40 µg/d) and one for 19.4 months (80 µg/d). The latter pt showed a complete regression of soft-tissue metastases and marked regression of bone metastases as assessed by PSMA-PET/CT, > 90% reduction in PSA and alkaline phosphatase, and a significant and durable improvement in disease related symptoms.

Grazie per l'attenzione