Updates in Genitourinary Oncology

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Disclosures

RECENT ADVISORY BOARD MEMBER:

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INVESTIGATOR INITIATED TRIAL RESEARCH FUNDING

Ferring Pharmaceuticals

MILE HIGH VIEW
OF RECENT DATA/ADVANCES IN GU ONCOLOGY

Outline of Topics

BLADDER CANCER (UROTHELIAL)

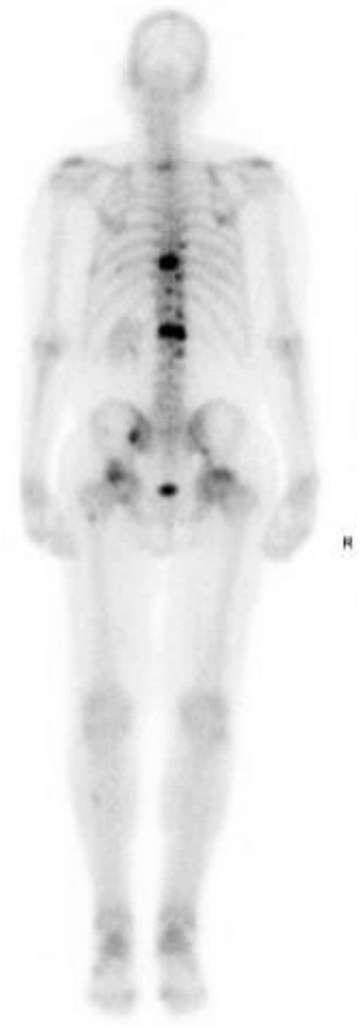
Peri-operative Therapy

- Evaluating the Optimal Chemotherapy Regimen

Metastatic Disease

- Chemotherapy Combinations
- Enfortumab Vedotin/Pembrolizumab

Outline of Topics



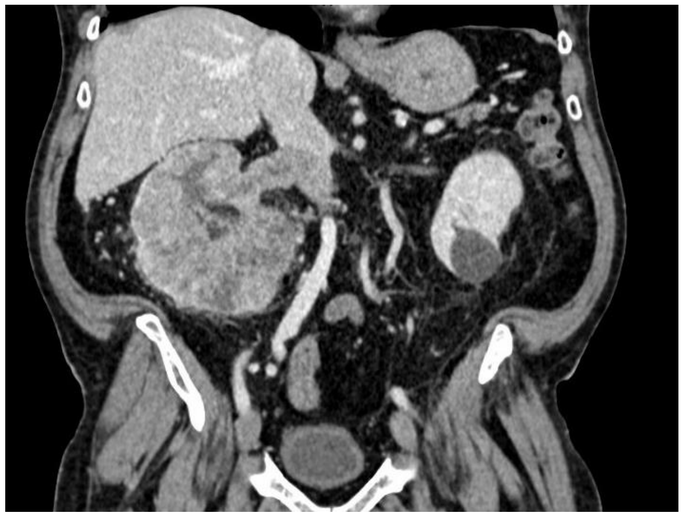
ADVANCED PROSTATE CANCER

- Better Defining Role of PARP
- PSMA – Directed Therapy

Outline of Topics

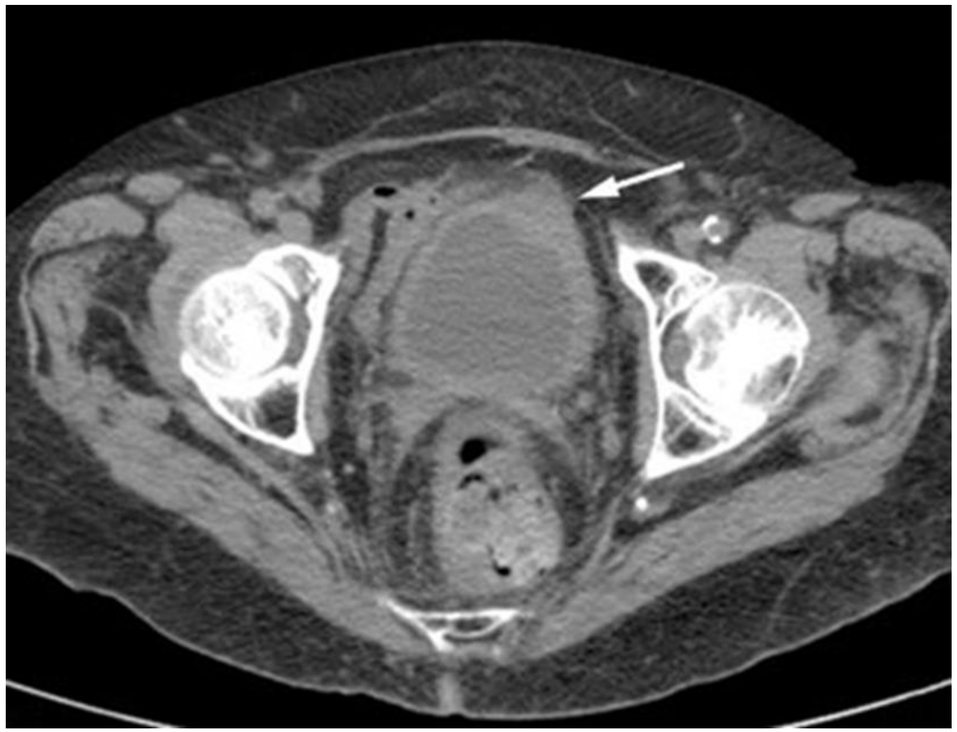
ADVANCED RENAL CELL CARCINOMA (RCC)

- Choosing Second Line Therapy for Metastatic Clear Cell



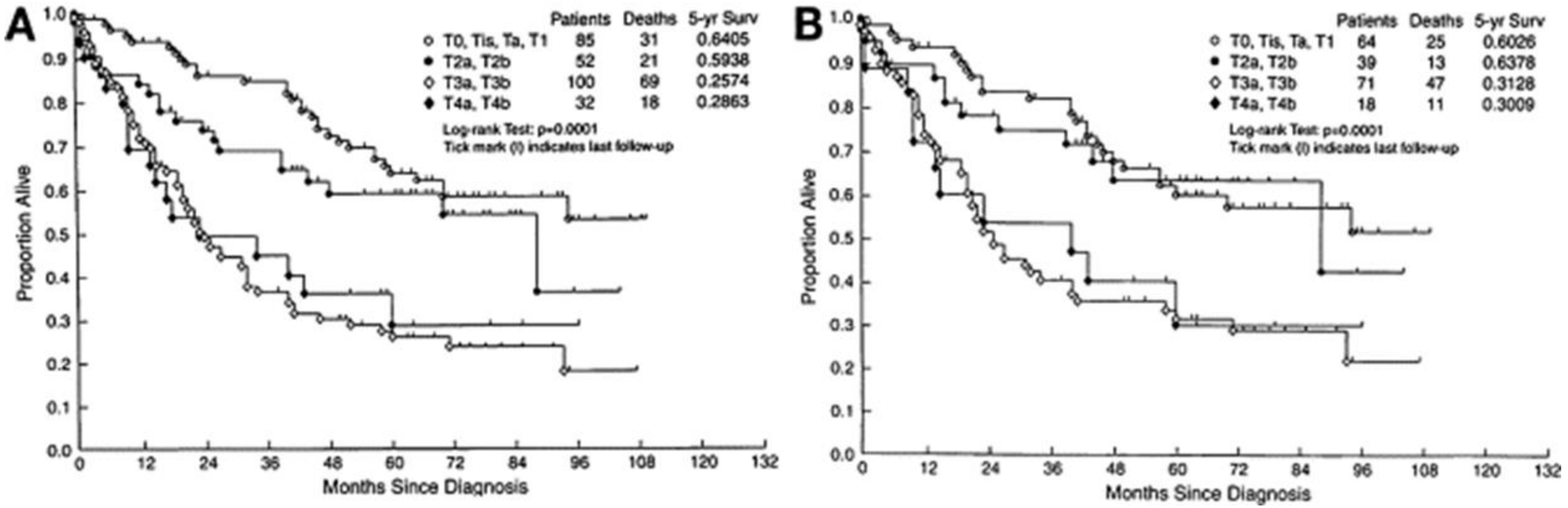
- Non-Clear Cell RCC– *Actual Data!*

MUSCLE INVASIVE BLADDER CANCER



Sandip M. Prasad, G. Joel DeCastro & Gary D. Steinberg. Urothelial carcinoma of the bladder: definition, treatment and future efforts. Nature Reviews Urology 8, 631-642 (November 2011)

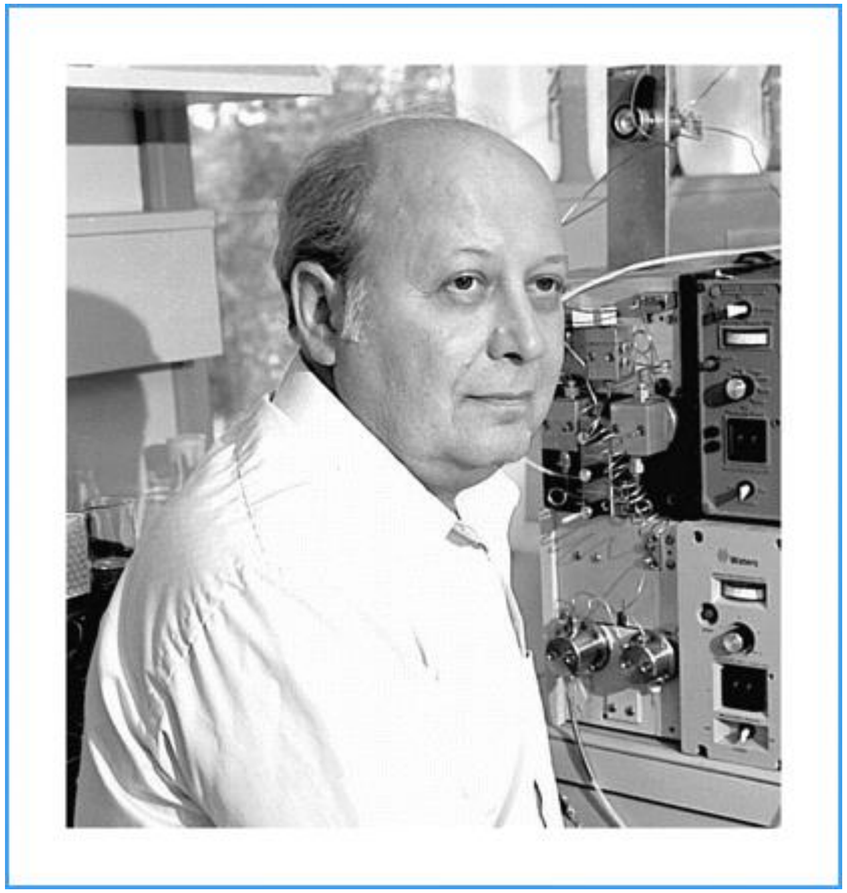
Primary Therapy in Many Instances is Cystectomy



overall survival of 300 patients treated with cystectomy for bladder cancer from 1990-1993 at MSKCC stratified by pathological stage A and those with N0 stratified by pathological stage B from 2001.

GUIDO DALBAGNI, ELIZABETH GENEGA, MIA HASHIBE, et al. CYSTECTOMY FOR BLADDER CANCER: A CONTEMPORARY SERIES. The Journal of Urology Volume 165, Issue 4, April 2001, Pages 1111–1116

Where We've Been…

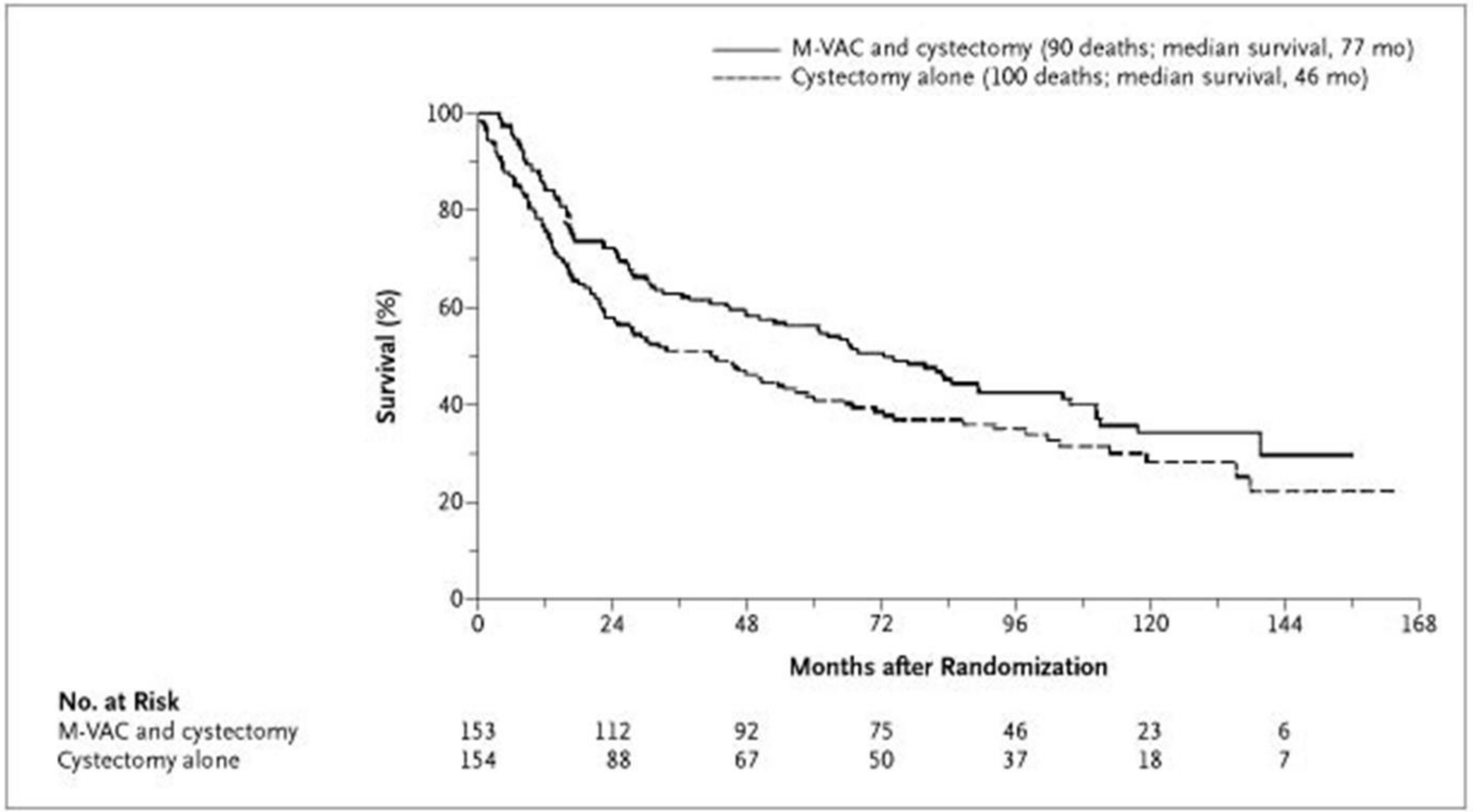


Dr. Barnett Rosenberg - Chabner B A
Cancer Res 2010;70:428-429

Neoadjuvant Chemotherapy (NAC)

SWOG 8710 - 317 patients with clinical T2N0M0 to T4aN0M0 TCC were randomized to radical cystectomy vs. 3 cycles M-VAC q 28 days followed by radical cystectomy.[1]

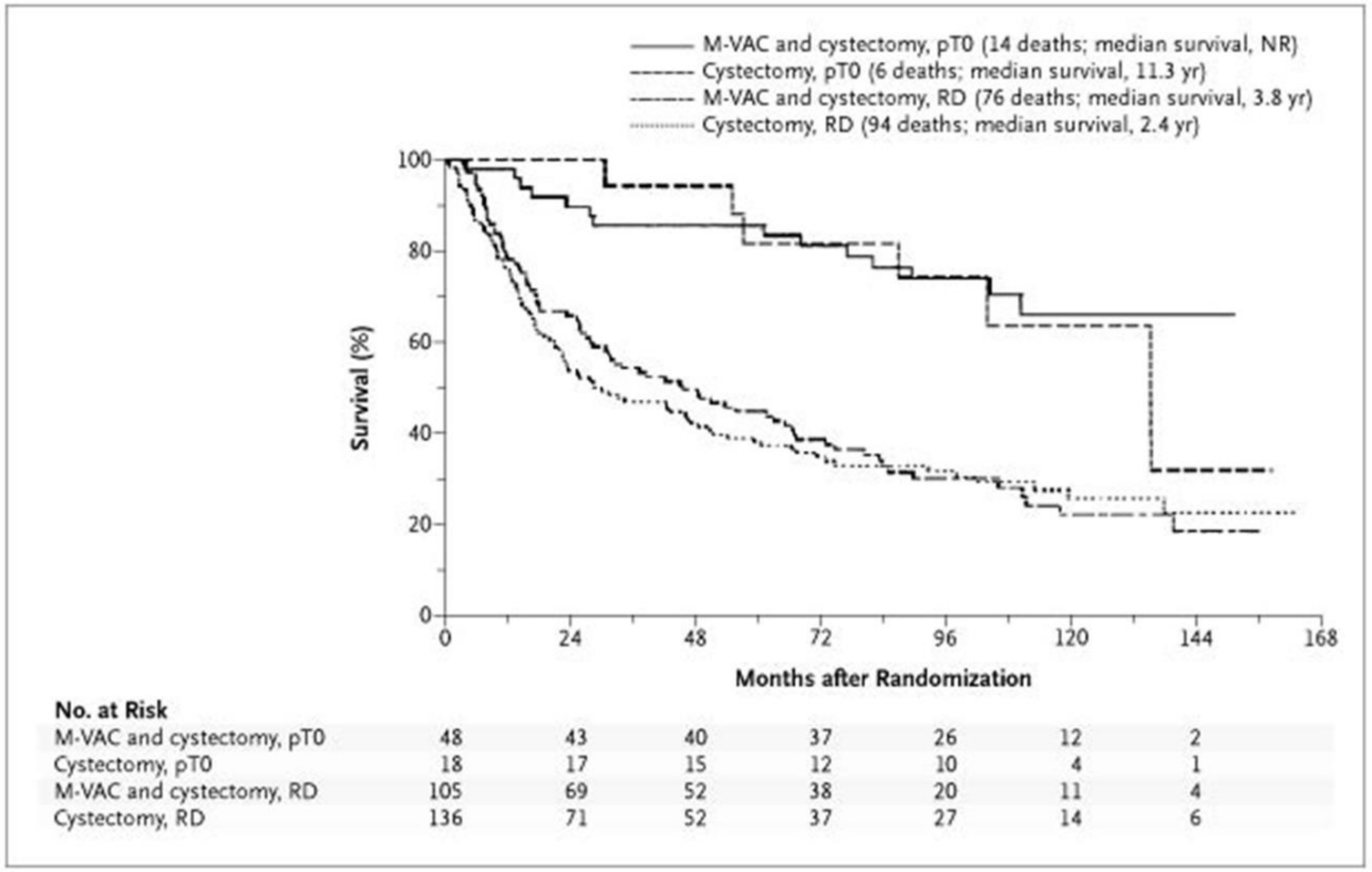
OVERALL SURVIVAL



Intention to Treat Analysis: Median Overall Survival in Neoadjuvant Arm: 77 months vs. 46 months (p=.06)

META-ANALYSES SUGGEST APPROX. 5% OS ADVANTAGE TO NEOADJUVANT CISPLATIN BASED CHEMOTHERAPY[2]

Value of a Complete Response



No. at Risk							
M-VAC and cystectomy, pT0	48	43	40	37	26	12	2
Cystectomy, pT0	18	17	15	12	10	4	1
M-VAC and cystectomy, RD	105	69	52	38	20	11	4
Cystectomy, RD	136	71	52	37	27	14	6

Pathologic Complete Response rate was 38% for the MVAC arm

- Data have suggested improved safety and perhaps better efficacy with Dose-Dense MVAC (ddMVAC) as compared to MVAC.[3]

- Until recently, no randomized trials compared ddMVAC to gemcitabine-cisplatin (GC) in the neoadjuvant setting, but many providers were adopting neoadjuvant GC because of improved safety profile at least as demonstrated in the metastatic setting.[4]

Pendulum may be swinging back to neoadjuvant ddMVAC with results of the GETUG/AFU VOF **VESPER Trial** which compared 6 cycles peri-operative ddMVAC to 4 cycles GC in patients with clinical T2-T4 N0 MIBC.

In the neoadjuvant group (437 patients), organ confined disease (<pT3 pN0) was obtained in 77% of ddMVAC patients and 63% GC patients (p=0.001)

3 year Progression Free survival in the neoadjuvant ddMAC group was **66%** versus **56%** in the GC group; HR = 0.70 [95% CI, 0.51 to 0.96], *P* = .025 [5]

ASCO 2023 UPDATE

At final median follow-up of 5 years and 3 months for 437 patients receiving neoadjuvant chemotherapy:

OS at 5 years was improved in the dd-MVAC arm (64% *vs* 56%, HR=0.77 (95% CI, 0.58-1.03), p=0.078.

Disease Specific survival (DSS) 5-year rate: 72% *vs* 59%, HR=0.63 (95% CI, 0.46-0.86), p=0.004[6]

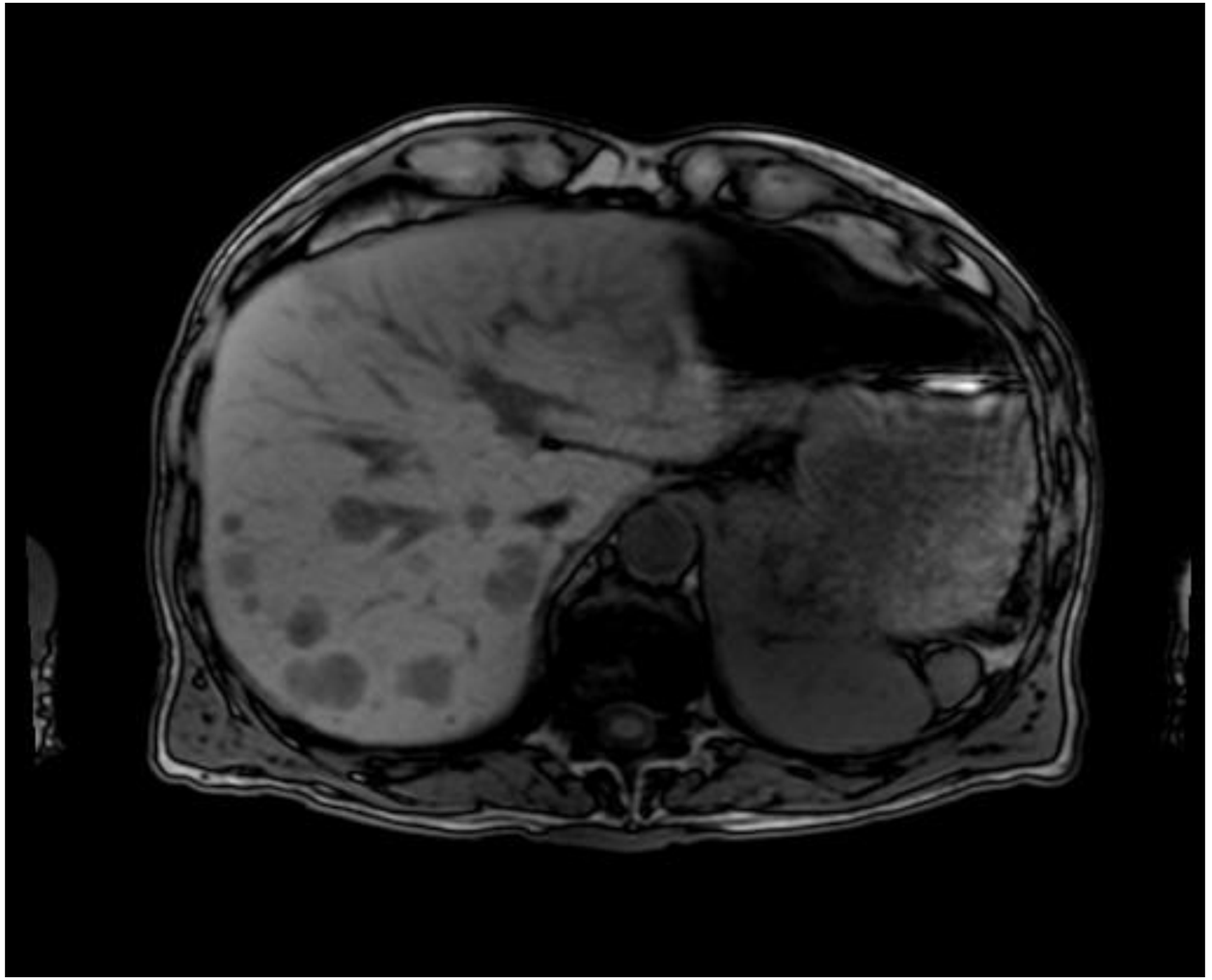
Key Notes

- No one enrolled to trial was greater than 69 years old.
- Only 60% of patients received all 6 cycles ddMVAC.

THINGS TO COME

Wealth of Randomized Trials Ongoing Evaluating Checkpoint Inhibitors and Antibody-Drug Conjugates in the Neoadjuvant Setting

METASTATIC UROTHELIAL CANCER



Recent Treatment Paradigm

Platinum Based Therapy

(Cisplatin/Gemcitabine, ddMVAC) if eligible for cisplatin

If ineligible for cisplatin;

Carboplatin/Gemcitabine if possible

Either platinum regimen followed by consideration of maintenance avelumab

↓

Immunotherapy if not chemo-eligible or given as maintenance

↓

Antibody-drug conjugates versus **Targeted Therapy** versus additional cytotoxic chemotherapy

ORIGINAL ARTICLE

Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

Thomas Powles, M.D., Se Hoon Park, M.D., Ph.D., Eric Voog, M.D., Claudia Caserta, M.D., Begoña P. Valderrama, M.D., Howard Gurney, M.D., Haralabos Kalofonos, M.D., Ph.D., Siniša Radulović, M.D., Ph.D., Wim Demey, M.D., Anders Ullén, M.D., Ph.D., Yohann Loriot, M.D., Ph.D., Srikala S. Sridhar, M.D., Norihiko Tsuchiya, M.D., Evgeny Kopyltsov, M.D., Cora N. Sternberg, M.D., Joaquim Bellmunt, M.D., Ph.D., Jeanny B. Aragon-Ching, M.D., Daniel P. Petrylak, M.D., Robert Laliberte, M.S., Jing Wang, Ph.D., Bo Huang, Ph.D., Craig Davis, Ph.D., Camilla Fowst, M.D., Nuno Costa, M.D., John A. Blake-Haskins, Pharm.D., Alessandra di Pietro, M.D., Ph.D., and Petros Grivas, M.D., Ph.D.

Article Figures/Media Metrics

38 References 580 Citing Articles Letters

September 24, 2020
N Engl J Med 2020; 383:1218-1230
DOI: 10.1056/NEJMoa2002788

Recall, this randomized trial demonstrated survival advantage to maintenance avelumab after upfront response/stable disease to cisplatin/carboplatin and gemcitabine in newly diagnosed metastatic urothelial cancer. Median overall survival 21.4 months with avelumab vs. 14.3 months with best supportive care; (hazard ratio for death, 0.69; 95% confidence interval [CI], 0.56 to 0.86; P=0.001).[7]

Room For Improvement

- Not Everyone Responds to Platinum

- Only a Minority of Metastatic Urothelial Cancer Patients receive a second line therapy

Recent Trials in Treatment-Naive Patients with Metastatic Urothelial Cancer (MUC)

CHECKMATE 901 – Multi-arm trial randomizing cisplatin eligible and ineligible patients with newly diagnosed MUC to:

A)Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg every 3 weeks x 4 followed by Nivolumab 480 mg every 4 weeks

VERSUS

B)Gemcitabine-Cisplatin or Gemcitabine-Carboplatin for up to 6 cycles

Or randomizing cisplatin eligible patients to:

C)Nivolumab 360 mg **PLUS** Gemcitabine-Cisplatin every 3 weeks for up to 6 cycles followed by nivolumab 480 mg every 4 weeks

VERSUS

D)Gemcitabine-Cisplatin for up to 6 cycles[8]

Treatment-Naive Patients with Metastatic Urothelial Cancer (MUC)

CHECKMATE 901 – Multi-arm trial randomizing cisplatin eligible and ineligible patients with newly diagnosed MUC to:

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~~**VERSUS**~~

~~B)Gemcitabine-Cisplatin or Gemcitabine-Carboplatin for up to 6 cycles~~

NEGATIVE FOR PRIMARY ENDPOINTS OF OVERALL SURVIVAL IN PD-L1 POSITIVE AND CISPLATIN INELIGIBLE PATIENTS[9]

Treatment-Naive Patients with Metastatic Urothelial Cancer (MUC)

CHECKMATE 901 –

Or randomizing cisplatin eligible patients to:

C)Nivolumab 360 mg **PLUS** Gemcitabine-Cisplatin every 3 weeks for up to 6 cycles followed by nivolumab 480 mg every 4 weeks

VERSUS

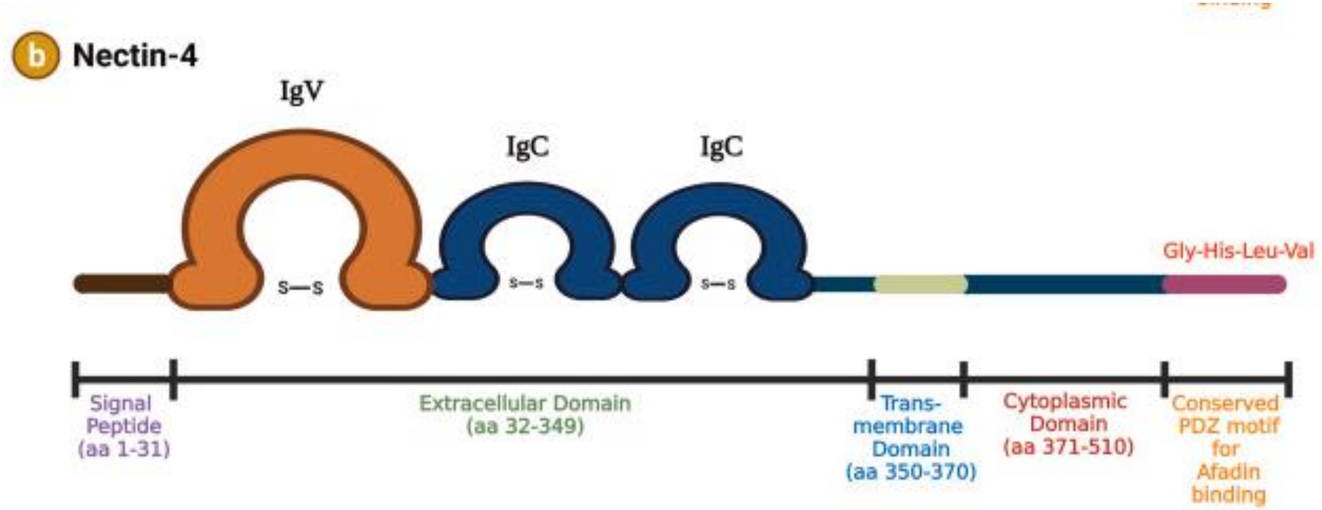
D)Gemcitabine-Cisplatin for up to 6 cycles[9]

POSITIVE

Recent Press Release Notes Improved Overall Survival and Progression Free Survival Favoring Nivolumab/Gem-Cis[10]

Nectin-4

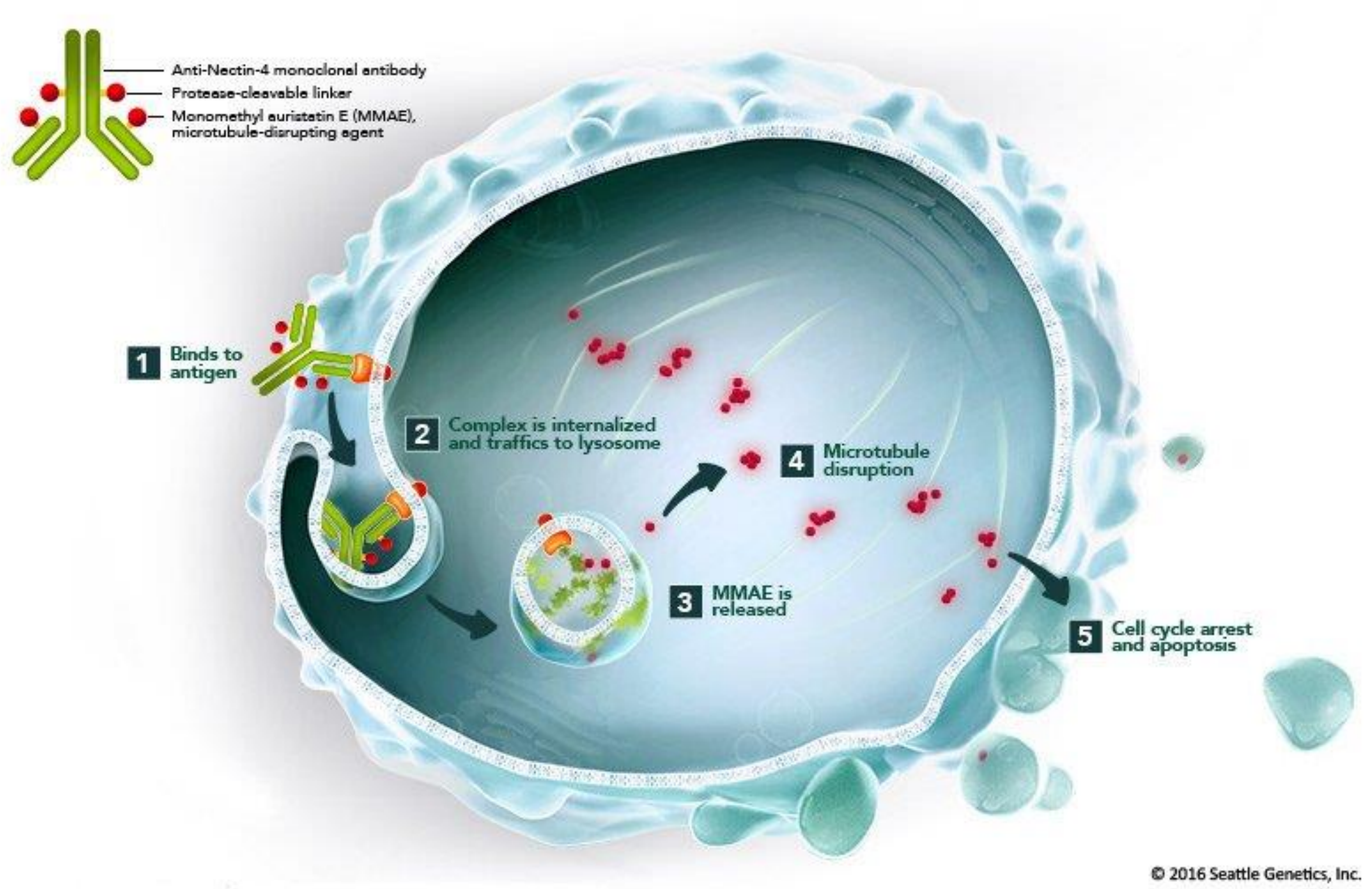
- Transmembrane adhesion molecule that mediates calcium-independent cell-cell adhesion.
- Expressed in skin, bladder, esophagus, breast, and stomach.
- Highly expressed in several solid tumors particularly urothelial cancer.[11]



Chatterjee S, Sinha S, Kundu CN. Nectin cell adhesion molecule-4 (NECTIN-4): A potential target for cancer therapy. Eur J Pharmacol. 2021 Nov 15;911:174516. doi: 10.1016/j.ejphar.2021.174516. Epub 2021 Sep 20. PMID: 34547246.

Enfortumab vedotin (EV)

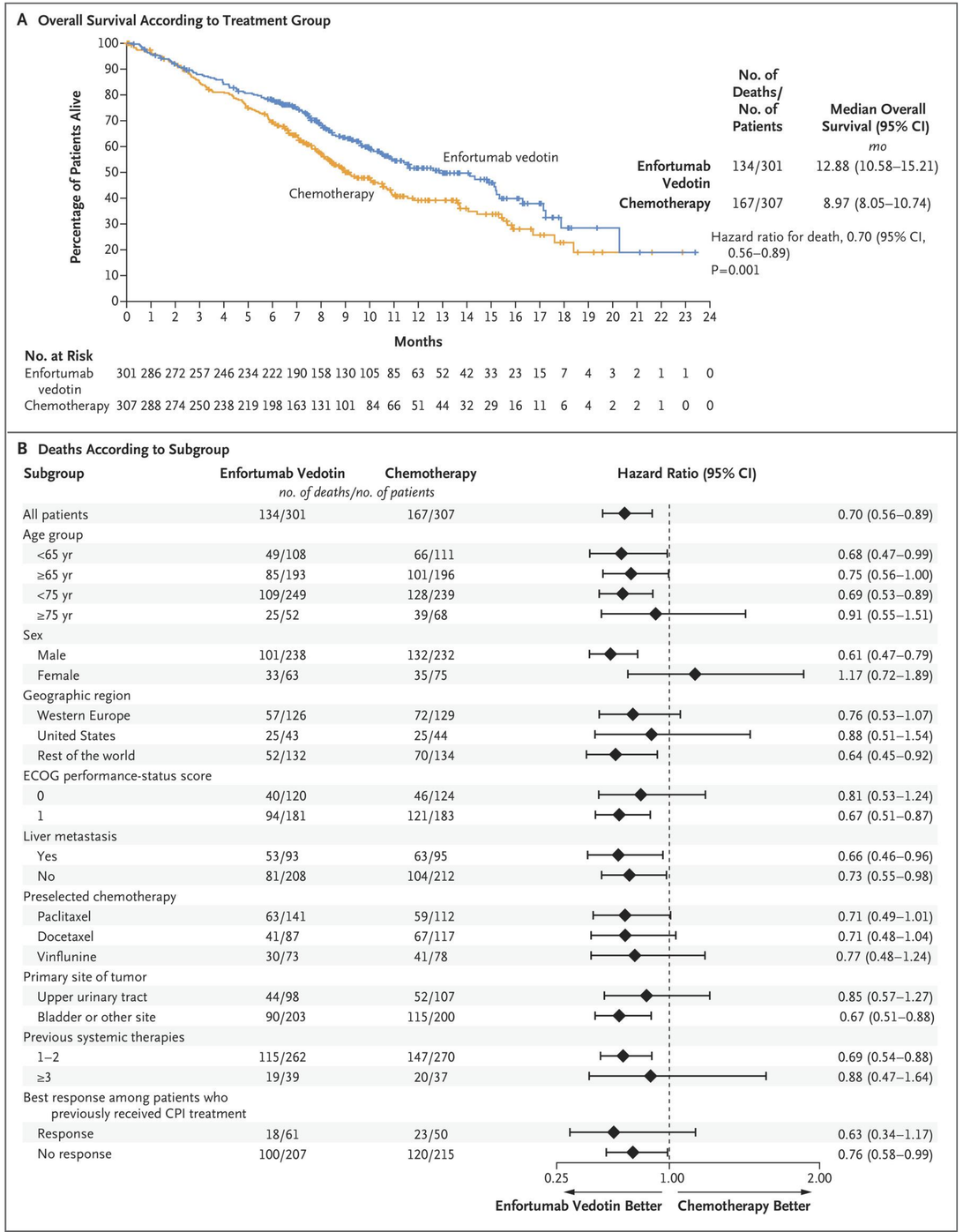
Antibody-Drug Conjugate featuring humanized anti-Nectin-4 antibody linked to MMAE(monomethyl auristatin E), a microtubule disrupting agent.



PREVIOUS EV DATA

Enfortumab Vedotin versus Chemotherapy

- EV-301 randomized 608 patients with <u>metastatic urothelial cancer refractory to platinum chemotherapy and immune checkpoint inhibitor(ICI)</u> to EV 1.25 mg/kg days 1,8,15 versus SOC chemo with docetaxel, paclitaxel, or vinflunine.
- Primary endpoint was OS with secondary endpoints PFS and ORR.[12]



Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N Engl J Med*. 2021;384(12):1125-1135. doi:10.1056/NEJMoa2035807

- Median OS for EV was 12.88 months vs. 8.97 months with SOC chemo. HR = 0.70 (95%CI 0.56-0.89); p=0.001.
- ORR to EV = 40.6% with ORR of 17.9% with chemo.

- FDA approved EV for metastatic UC refractory to platinum chemo and ICI based on these data.

EV-103 Cohort A

- Open Label Multiple Cohort Phase 1b/2 study of EV in advanced urothelial carcinoma.

- A small Dose Escalation cohort and Expansion Cohort A evaluated EV 1.25 mg/kg on days 1,8 and Pembrolizumab 200 mg IV on day 1 of 21 day cycles in 45 cisplatin ineligible patients with first line metastatic urothelial carcinoma.[13]

Overall Objective Response Rates by BICR

- High confirmed ORR (73.3%) with high concordance rate between BICR and INV assessments

	Dose Escalation + Cohort A (N = 45)
Objective Response Rate, n (%)	33 (73.3)
95% CI[a] for ORR	58.1-85.4
Best Overall Response, n (%)	
Complete response	7 (15.6)
Partial response	26 (57.8)
Stable disease	5 (11.1)
Progressive disease	5 (11.1)
No assessment[b]	2 (4.4)
Disease Control Rate, n (%)	38 (84.4)
95% CI[a] for DCR	70.5-93.5
Concordance rate of BOR between BICR and INV[c] assessment	95.3%

BICR = Blinded Independent Central Review
INV = Investigator Assessment
BOR = Best Overall Response

EV-103 Cohort A

- Median Duration of Response (95% CI) 22.1 months (8.38-NE)
- Median Overall Survival (95% CI) 26.1 months (15.51 – NE)

Treatment-Related Adverse Events

- TRAE rates and types are consistent with those previously reported for EV+P

	Dose Escalation + Cohort A (N = 45)
	Any Grade n (%)
Overall	43 (95.6)
Peripheral sensory neuropathy	25 (55.6)
Fatigue	23 (51.1)
Alopecia	22 (48.9)
Diarrhea	21 (46.7)
Decreased appetite	18 (40.0)
Rash maculo-papular	16 (35.6)
Pruritus	15 (33.3)
Dysgeusia	15 (33.3)

	Dose Escalation + Cohort A (N = 45)
	Grade ≥3[a] n (%)
Overall	29 (64.4)
Lipase increased[b]	8 (17.8)
Rash maculo-papular	5 (11.1)
Fatigue	5 (11.1)
Neutropenia	4 (8.9)
Anemia	4 (8.9)
Hyperglycemia	4 (8.9)
Amylase increased	4 (8.9)
Transaminases increased	3 (6.7)

- One patient died from multiple organ dysfunction syndrome with concurrent bullous dermatitis

a = Events occurring in >5% patients b = Not clinically significant

EV-103 Cohort K

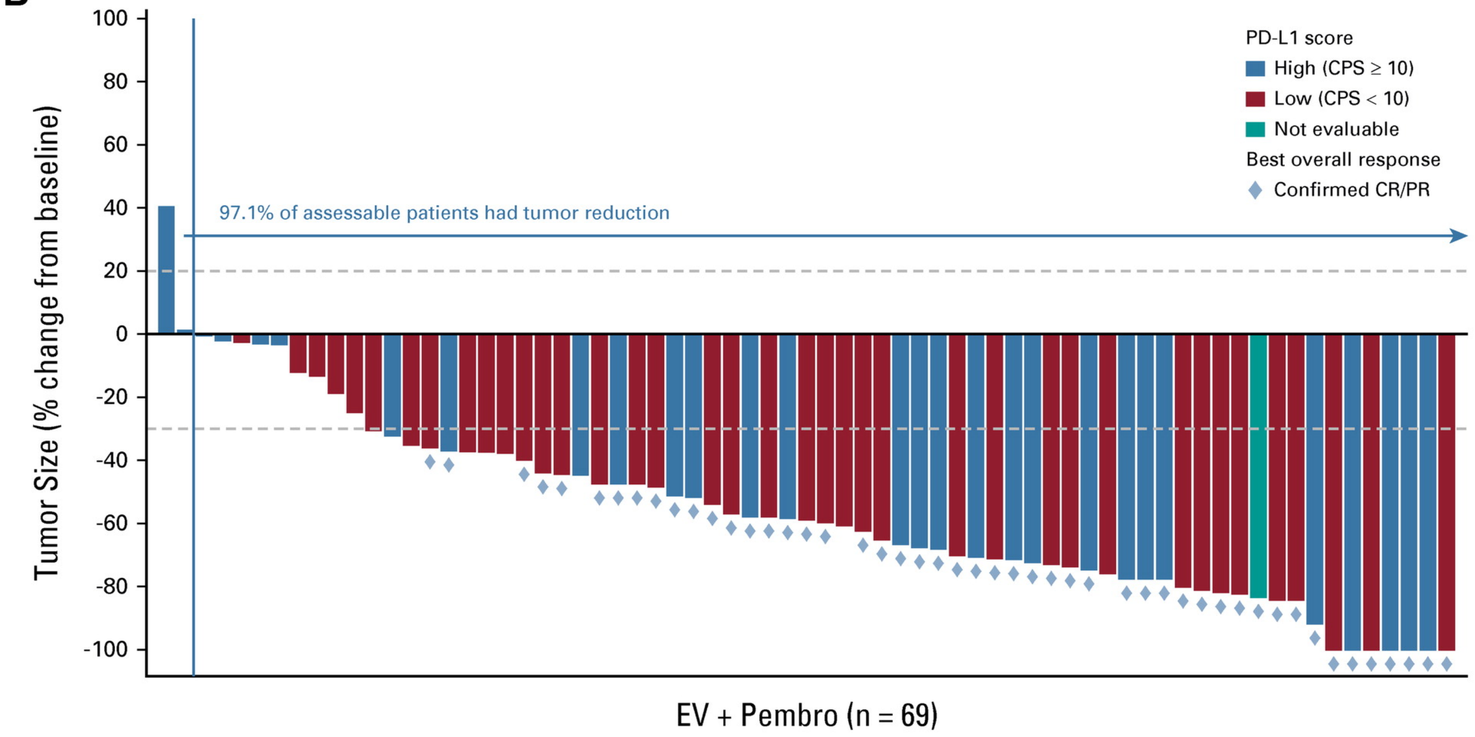
- Randomized 149 patients with cisplatin-ineligible treatment naïve MUC to EV versus EV plus pembrolizumab.[14]

- Primary endpoints were confirmed objective response rate, duration of response, and safety. There were no direct statistical comparisons between arms.

A

	EV + Pembro (N = 76)	EV Monotherapy (N = 73)
Confirmed ORR, No. (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response		
CR	8 (10.5)	3 (4.1)
PR	41 (53.9)	30 (41.1)
Stable disease	17 (22.4)	25 (34.2)
PD	6 (7.9)	7 (9.6)
Not evaluable	3 (3.9)	5 (6.8)
No assessment	1 (1.3)	3 (4.1)
Time to objective response, months, median (range)	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Treatment cycles, No., months, median (range)	11.0 (1, 29)	8.0 (1, 33)

B

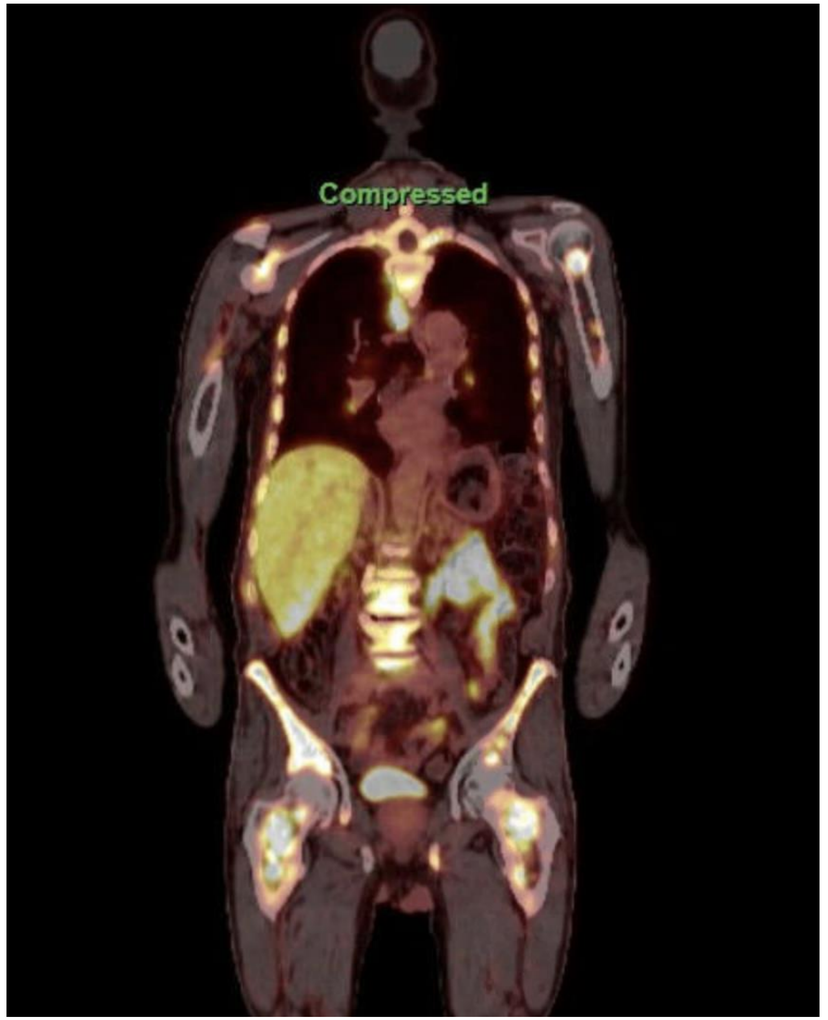


Published in: Peter H. O'Donnell; Matthew I. Milowsky; Daniel P. Petrylak; Christopher J. Hoimes; Thomas W. Flaig; Nataliya Mar; Helen H. Moon; Terence W. Friedlander; Rana R. McKay; Mehmet A. Bilen; Sandy Srinivas; Earle F. Burgess; Chethan Ramamurthy; Saby George; Daniel M. Geynisman; Sergio Bracarda; Delphine Borchiellini; Lionnel Geoffrois; Jose Pablo Maroto Rey; Christiano Ferrario; Anne-Sophie Carret; Yao Yu; Maria Guseva; Blanca Homet Moreno; Jonathan E. Rosenberg; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.22.02887

FDA Approval

- The FDA approved “Enfortumab Vedotin in combination with Pembrolizumab for the treatment of adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.”[15]

ADVANCED PROSTATE CANCER



Homologous Recombination Repair Mutations (HRRm)

- Present in up to 30% of men with metastatic castration resistant prostate cancer (mCRPC) in some series.[16]

- Oral PARP (poly-ADP ribose polymerase) inhibitors have been previously FDA approved for men with mCRPC possessing a select group of homologous recombination repair mutations who have progressed on abiraterone and/or enzalutamide.

- Recent data suggest responses to PARP inhibitors are particularly enriched in men with BRAC1/BRCA2 mutations.[17]

BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RADB1C, RAD51D, RAD54L

Synergism Between PARP inhibition and ADT???

- Pre-clinical data suggest that PARP inhibitors may synergize with hormonal agents through their combined activity in regulating androgen receptor target gene expression.[18]

- Two recent randomized trials, PROPEL and TALAPRO evaluated the combination of PARP inhibition and ARAT (androgen receptor axis targeted therapy) in men with castration sensitive metastatic prostate cancer.

PROPEL

- Randomized double blind phase 3 trial in 796 men with mCRPC (prior treatment was ADT alone or with docetaxel) assigned to abiraterone (abi) 1000 mg daily/prednisone (pred) 5 mg twice daily plus olaparib 300 mg twice daily versus abi/pred plus placebo twice daily.

- Patients were prospectively evaluated for homologous recombination repair mutations (HRRm) using tissue and circulating tumor DNA but were allowed to enroll regardless of results.

- Secondary Endpoint of Overall Survival was examined at The 2023 ASCO Genitourinary Cancers Symposium.[19]

PROPEL OVERALL SURVIVAL

- Entire Intention to Treat (ITT) Population – median OS for abi/olaparib = 42.1 months vs. 34.7 months for abi/placebo = HR 0.81 (0.67-1.00) p = .0544

- HRR mutated patients (28.4% ITT population) - median OS for abi/olaparib = Not Reached vs. 28.5 months for abi/placebo = HR 0.66 (0.45-0.95).

- HRR non-mutated patients (69.3% ITT population) - median OS for abi/olaparib = 42.1 months vs. 38.9 months for abi/placebo = HR 0.89 (0.70-1.14).

- BRCA mutated patients – median OS for abi/olaparib = Not reached vs. 23 months for abi/placebo = HR 0.29 (0.14-0.56).

FDA Approval

- Based on the previous data, the FDA added an indication for olaparib:

"In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC)."[20]

TALAPRO-2

- 402 men with mCRPC, who had progressed after ADT +/- docetaxel (8% had also had abi/pred), were randomized to enzalutamide 160 mg daily plus talazoparib 0.5 mg daily versus enzalutamide plus placebo. Men were treated in a cohort unselected as to HRRm status and a cohort with HRR gene alterations.

- Imaging Based Progression Free Survival (ibPFS) data were presented at the 2023 ASCO annual meeting. Results were stratified by presence of HRRm. Tested genomic anomalies involved *BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, and CDK12*.

- Median ibPFS in the Enza/Talapro arm was not reached vs 21.9 months in the enza/placebo arm; HR 0.63; 95% CI 0.51-0.78; p<0.01. HRR-mutated patients -> HR = 0.46; 95% CI 0.30-0.70; p< 0.011. HRR-non deficient by tumor testing -> HR = 0.66; 95% CI 0.49-0.91; p=.009.[21]

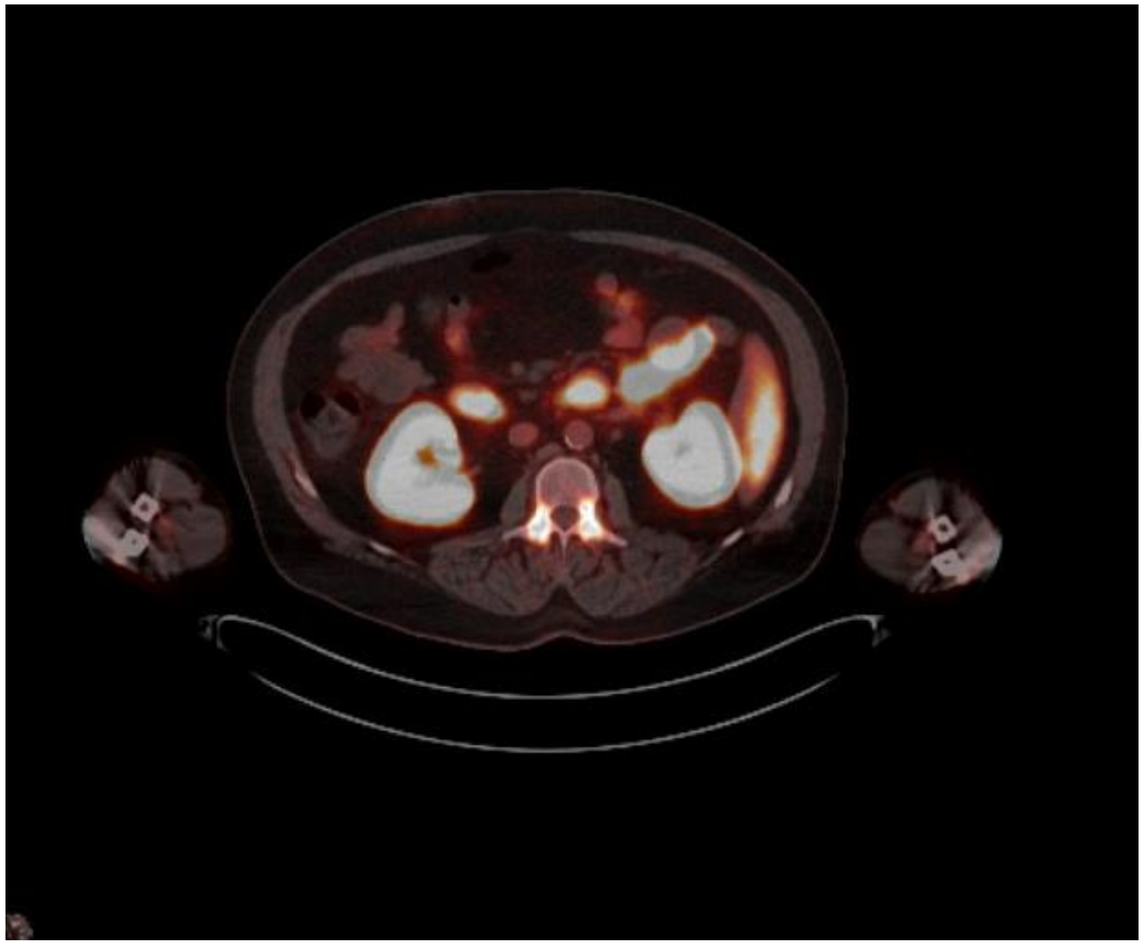
FDA Approval

- Based on the previous data, the FDA added an indication for talazoparib:

"In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC)."[22]

Issues with these 2 approvals include questions about application in an environment where more patients are getting doublet therapies in the first line, financial toxicity, and ongoing trials evaluating whether PARP should actually be targeted in the castration sensitive setting.

RADIO-PHARMACEUTICALS



PSMA F^{18} PET-CT

MOST RECENT UPDATES ON Lutetium Lu 177 vipivotide tetraxetan

- Lutetium^{177}-PSMA-617, a radioligand delivering beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment, has been FDA approved for men with mCRPC progressing after ARAT (androgen receptor axis targeted therapy) and a taxane.

- The phase 3 VISION trial randomized 831 men with PSMA-avid mCRPC who had previously been treated with a taxane and an ARAT to ^{177}Lu-PSMA-617 7.4 GBq every 6 weeks for 4–6 cycles with standard of care therapy (SOC) vs. SOC therapy alone (frequently an alternative ARAT).

- Radiopharmaceutical therapy on this trial improved progression fee survival to median **8.7 months vs. 3.4 months** with SOC therapy [HR 0.40; 99.2% CI 0.29–0.57; *P* < 0.001] and OS to median **15.3 months vs. 11.3 months** (HR 0.62; 95% CI 0.52–0.74; *P* < 0.001).[23]

Lutetium Lu 177 vipivotide tetraxetan

Pluvicto (Lutetium 177 Vipiovide tetraxetan)

External MD referral form

*Please call/email to ensure receipt of documents**

Please return completed form, including boxes checked, via e-mail

CONTACT: Jenny Hill MSN, RN
hilljd@musc.edu
Ph: 843-792-9626

Patient name: _____ Insurance: _____ Ht: _____ Wt: _____
Referring MD: _____ Primary diagnosis code: _____ Secondary diag. code: _____
Direct RN/MA name, number &/or email: _____
Referring MD email: _____ (Requested by Nuclear Medicine MD)

PLUVICTO is a radioligand therapeutic agent indicated for the treatment of adult patients with prostate-specific membran antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androge receptor (AR) pathway inhibition and taxane-based chemotherapy. Given every 6 weeks up to 6 treatments

Requirements for consideration of treatment:

- ☐ PSMA PET-CT images & report (within 6 months) Date: _____
  - Due to the volume of patients, we cannot accept patient info without positive PET PSMA images & report
- ☐ Images must be sent (if not completed at MUSC) via Life Image or

  Mail images to: Dept of Radiology- MUSC
  Attn: Dr. Elojeimy
  96 Jonathan Lucas Street
  Suite 210, MSC 323
  Charleston, SC 29425

  Please indicate how/when images have been requested to be sent to MUSC: _____
- ☐ Baseline CBC with differential & CMP within 1 month of order (must meet parameters as listed below)
- ☐ Sign attached verification. States patient has been treated with androgen receptor (AR) pathway inhibition & taxane-based chemotherapy (to help with pre-approval process)
- ☐ Pathology (related to prostate cancer). Do not send genetics or biomarkers Date: _____
- ☐ Lab work: CBC with differential & CMP 5 weeks after each Pluvicto treatment.
- ☐ **MD/Lab appointment to be completed @ 5 weeks following each Pluvicto treatment.**
  Blood work & adverse reactions to be followed/monitored by referring MD.
- ☐ AAA paperwork: MUST be signed by patient and MD and include primary and secondary diagnosis codes. Return via scan to hilljd@musc.edu
- ☐ Demographics & insurance card
- ☐ Progress note (**1 month only**)

Parameters for treatment:

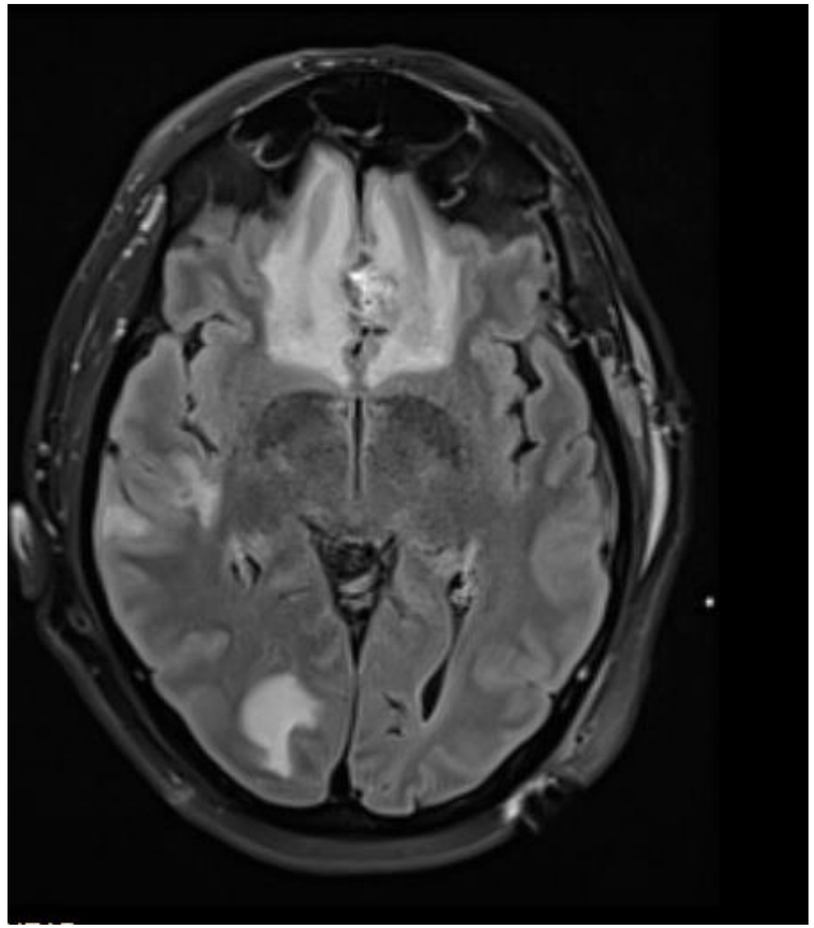
HGB >9
WBC >3
PLT >75
ANC >1.5
Serum creatinine: >1.5-3x baseline or >1.5-3x ULN
Creatinine Clearance > 30 (by Cockcroft-Gault equation)
AST/ALT > 5 times the ULN (upper limit of normal)

Patients Do NOT Need to Give up Their Outside Medical Oncologist

THINGS TO COME IN PROSTATE CANCER

- Data regarding earlier use of PSMA Radio-Pharmaceuticals and Combinations of Agents
- Refining who Needs Triplet Therapy (ADT + ARAT +/- Docetaxel)
- Can PSA/PSMA be Effective CAR-T/Bi-specific antibody targets ?

Advanced Renal Cell Carcinoma



Abundance of Options For Treating Newly Diagnosed Metastatic Clear Cell Renal Cell Carcinoma (ccRCC)

Ipilimumab/Nivolumab
Lenvatinib/Pembrolizumab
Cabozantinib/Nivolumab
Axitinib/Pembrolizumab

Unfortunately, a majority of patients will ultimately progress on their first line regimen. Let's examine some recent data to guide decisions in second line.

CONTACT-03 STUDY

- Randomized Open Label Phase 3 trial of Cabozantinib 60 mg PO daily plus Atezolizumab 1200 mg IV every weeks versus cabozantinib 60 mg alone in patients with metastatic ccRCC progressive after an ICI (immune checkpoint inhibitor) regimen.

- 522 patients randomized. 55% of atezo/cabo and 51% of cabo patients had had their most recent ICI in the first line metastatic setting.[24]

CONTACT-03 EFFICACY

NO ADDED ADVANTAGE TO RECHALLENGE WITH ICI (Atezolizumab)

- Overall Response Rate 41% in both Arms

- No Progression Free Survival (9.8 months vs.10 months) or Overall Survival Advantage (21.5 months vs. Not Reached) to the Combo vs. Cabo Alone

- Adverse Events Leading to Treatment Discontinuation: 16% for combo versus 4% for Cabo alone

THINGS TO COME FOR CLEAR CELL RCC

- Novel First Line Combinations including with HIF inhibitors
- Employing Molecular Subtypes of RCC to select Therapeutics
- Re-examining Value of Cytoreductive Nephrectomy in Combination with ICI-based regimens

NON-CLEAR CELL RCC

Frequency of Renal Cell Carcinoma Subtypes[25]

•Clear Cell	**≥75%**
•Papillary	15%
•Chromophobe	5%
•Translocation	2%
•Collecting Duct	1%
•Medullary	< 1%
•Unclassified/”NOS”	5-10%

HISTORICALLY VERY FEW TRIALS HAVE ENROLLED PATIENTS WITH NON-CLEAR CELL HISTIOLOGIES

TWO PROSPECTIVE TRIALS PRESENTED AT THE 2023 ASCO ANNUAL MEETING EVALUATE TREATMENT OPTIONS IN NON-CLEAR CELL HISTOLOGIES

First-line Lenvatinib plus Pembrolizumab treatment across non-clear cell renal cell carcinomas: Results of the phase 2 KEYNOTE-B61 study.

- 158 patients with locally advanced/metastatic non-clear cell RCC were treated with first line lenvatinib 20 mg PO daily plus pembrolizumab 200 mg IV every 3 weeks for up to 2 years.

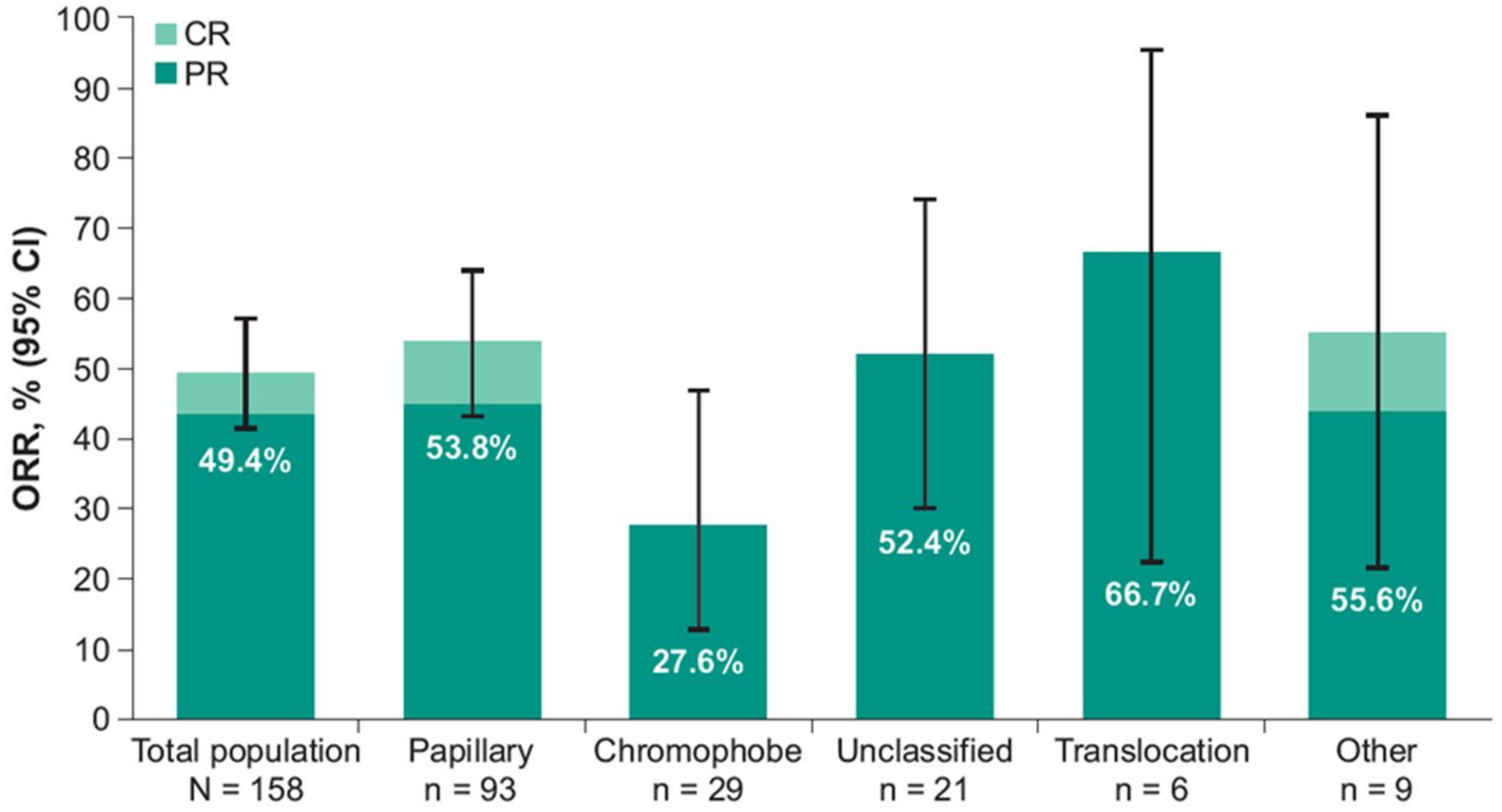
- Efficacy Data Presented at 14.9 months Median Follow-up[26]

DEMOGRAPHICS

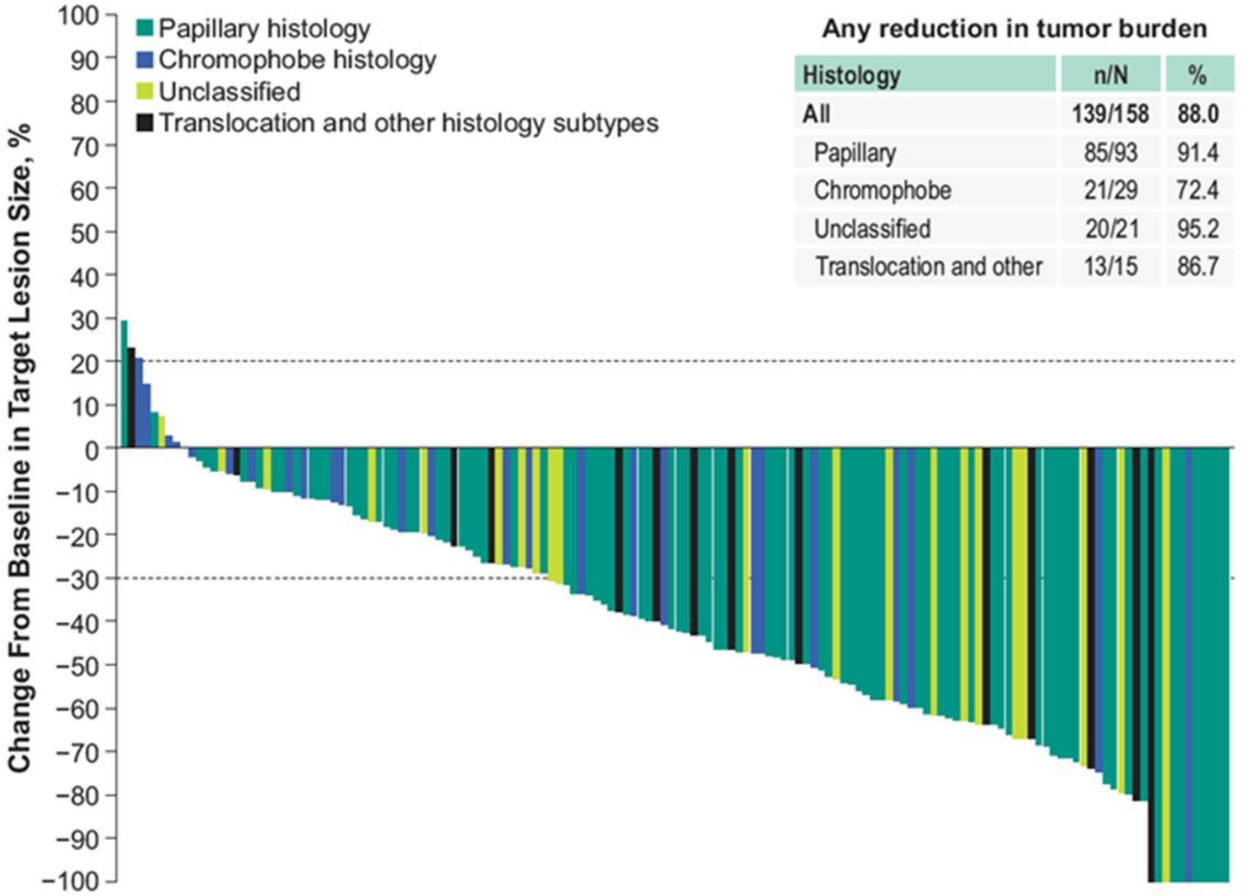
	Pembrolizumab + lenvatinib N = 158
Age, median (range)	60 (24-87)
Histology	
Papillary	93 (58.8)
Chromophobe	29 (18.4)
Unclassified	21 (13.3)
Translocation	6 (3.8)
Other	9 (5.7)
Presence of sarcomatoid features[a]	
Yes	19 (12.0)
No	96 (60.8)
Unknown	43 (27.2)

Lee CH, Gurney H, Atduev V, Suárez C, Climent Duran MA, et al. First-line lenvatinib + pembrolizumab treatment across non-clear cell renal cell carcinomas: Results of the phase 2 KEYNOTE-B61 study. 2023 ASCO Annual Meeting. J Clin Oncol 41, 2023 (suppl 16; abstr 4518).

Objective Response Rates



BEST PERCENT CHANGE IN TARGET LESIONS BY HISTOLOGY



Any reduction in tumor burden

Histology	n/N	%
All	139/158	88.0
Papillary	85/93	91.4
Chromophobe	21/29	72.4
Unclassified	20/21	95.2
Translocation and other	13/15	86.7

Phase II study of cabozantinib (Cabo) with nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma with variant histologies (RCCvh).

- Patients with advanced non-clear cell RCC were treated with Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg IV Q3 weeks for 4 cycles followed by Nivolumab 480 mg IV Q 4 weeks . Cabozantinib was given concurrently at dose of 40 mg PO daily

- 89% of patients were treatment naïve.

- At time of recent analysis, 38 patients had received study drug.[27]

EFFICACY

- Overall Response Rate = 21% (Papillary 32%, Chromophobe 9%)
- Stable Disease = 50%

SO WHAT'S THE BOTTOM LINE???

BLADDER CANCER

-Neoadjuvant Cisplatin Based Chemotherapy Remains the Standard in Muscle Invasive Bladder Cancer … for now

-Consider ddMVAC in fit patients

-Treatment for metastatic urothelial carcinoma is rapidly changing:

Cisplatin-eligible patients → We will follow up soon-to-be presented data for chemoimmunotherapy combinations

Cisplatin Ineligible → Enfortumab vedotin/pembrolizumab

PROSTATE CANCER

- PARP inhibitor/ARAT combinations may be of use in a subset of patients. More important will be to follow-up data in the metastatic castration **sensitive** setting.

- Radiopharmaceuticals will likely have an expanding role in treatment combinations for mCRPC and possibly earlier in the disease course.

KIDNEY CANCER

- A Recent Randomized Trial Suggests that Continuing Immune Checkpoint Inhibitors Past Progression with new TKIs does NOT Improve Outcomes.

- Novel Biomarkers are needed to Refine Treatment Selection for Patients With Metastatic Clear Cell and NON-Clear Cell Renal Cell Carcinomas.

THANK YOU ALL FOR YOUR ATTENTION!!!!

Feel Free to Reach Out With Questions/Concerns:

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