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COMPREHENSIVE
CANCER CENTER


# State of the Art in Genitourinary Cancers

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# Presentation Outline

- KIDNEY CANCER
  - Current Status Front-Line Metastatic RCC : Doublets and Triplet
  - Recent updates and upcoming trials
  - The state of perioperative therapies in RCC
  - Treatment decisions (?biomarkers or lack- thereof)
- BLADDER CANCER
- PROSTATE CANCER

# Kidney Cancer: Change in Landscape

1990-2000's
IFN-a ; IL-2

2005, 2006
Sorafenib, Sunitinib
Anti-VEGF TKI's

2007, 2009
mTOR inhibitors
Everolimus, Temsirolimus

October 2009
Pazopanib
Anti-VEGF TKI's

July 2009
Bevacizumab
VEGF Inhibitor

2012
Axitinib
VEGF Inhibitor

CHECKPOINT INHIBITORS

2015
Nivolumab

2016
Cabozantinib
Lenvatinib/ Everolimus

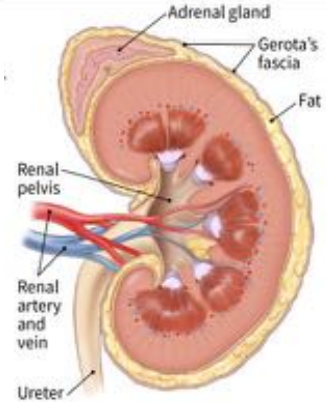
2018
Nivolumab/
Ipilimumab

2019
Pembrolizumab/ Axitinib
Avelumab/ Axitinib

2021
Nivolumab/ Cabozantinib
Lenvatinib/ Pembrolizumab

2021
Tivozanib

ONGOING (2022)
Ipi/ Nivo/ Cabozantinib
Tivozanib/ Nivolumab
Belzutifan/ Cabozantinib
Belzutifan/ Lenvatinib
Risk Adapted (PDIGREE/ PROBE)






mRCC= metastatic renal cell carcinoma, VEGF= Vascular endothelial growth factor , TKI= tyrosine kinase inhibitor, IFN= interferon, IL-2= Interleukin-2

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# Phase-3 Approved Front-Line Therapies

| | CLEAR | CHECKMATE- 9ER | CHECKMATE- 214* | KEYNOTE-426 |
|---|---|---|---|---|
| **DRUGS** | **Pembrolizumab +Lenvatinib (N=1069)** | **Nivolumab + Cabozantinib (N=651)** | **Nivolumab + Ipilimumab (N=1096)** | **Pembrolizumab + Axitnib (N=861)** |
| **mPFS (mo)** | **23.9** | 16.6 | 12 | 15.7 |
| **HR (95% CI)** | 0.39 | 0.56 | 0.73 | 0.68 |
| **Median OS (mo)** | NR | 37.7 | 38 | **45.7** |
| **HR (95% CI)** | 0.66 | 0.70 | 0.68 | 0.73 |
| **ORR/CR(%)** | **71/16.1** | 55.7/12.4 | 42/12 | 60.4/10 |
| **Sarcomatoid features (%)** | 7.9 | 11.5 | **14** | 12 |
| **% AEs leading to discontinuation** | **37.2** | **3.1** | 22 | 10.7 |
| **IMDC or MKSCC risk (F/I/P)** | **31**/59.2/9.3 | 22.6/57.6/19. 7 | 23/**61/17** | **31.9**/55.1/13 |
| **Median FU (mo)** | 27 | 24 | 67.7 | 42 |

Rini B et al. JCO, 2021; Powles T, et al. Presented at: ASCO GU;2022.; Hammer HJ, et al. Ann Oncol. 2021;32(Suppl_5):S678-S724.; Motzer et al. Presented at ASCO GU, 2021

# International Metastatic Database Consortium Risk Stratification

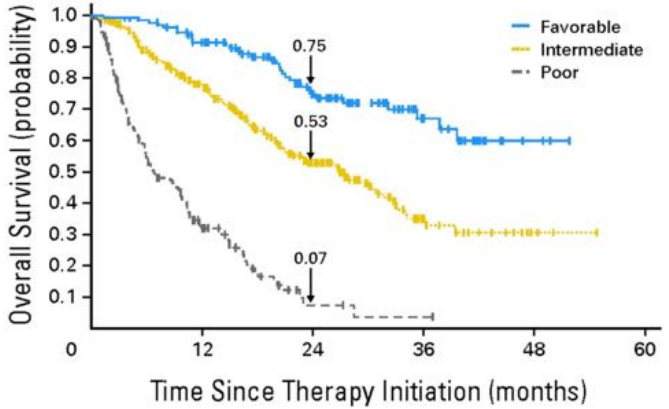
- **Clinical**

- Karnofsky Performance Status <80%
- Time from diagnosis to treatment <1 year

- **Laboratory**

- Hemoglobin <LLN
- Calcium > ULN
- Neutrophil count > ULN

- Platelet count > ULN




| No. of events/No. at risk | | | | | |
|---|---|---|---|---|---|
| Favorable | 11/133 | 16/110 | 4/62 | 2/22 | 0/3 |
| Intermediate | 61/301 | 50/182 | 17/82 | 2/18 | 0/3 |
| Poor | 94/152 | 19/36 | 1/3 | 0/1 | 0/0 |

**Favorable: 0 risk factors → means slow-growing and/or VEGF-responsive**
**Intermediate: 1-2 risk factors → medium growth rate and somewhat VEGF- responsive**
**Poor: 3-6 risk factors → fast-growing and VEGF-unresponsive**

Heng DYC, et al. *J Clin Oncol*. 2009;27(34):5794-9.

# Kidney Cancer: METASTATIC TRIPLET OR DOUBLET

## LBA8 - Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313)

**Date**
12 Sep 2022

**Session**
Presidential Symposium III

**Topics**
Clinical Research; Targeted Therapy; Immunotherapy; Renal Cell Cancer

**Presenters**
Toni Choueiri

**Citation**
Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

**Authors**
T.K. Choueiri[1], T.B. Powles[2], L. Albiges[3], M. Burotto[4], C. Szczylik[5], B. Zurawski[6], E. Yanez Riuz[7], M. Maruzzo[8], A. Suarez Zaizar[9], L.E. Fein[10], F.A. Barros Schutz[11], D.Y.C. Heng[12], F. Wang[13], F. Mataveli[13], Y. Chang[14], M. van Kooten Losio[15], C. Suarez Rodriguez[16], R.J. Motzer[17]

**FIRST trial to compare a triplet to a doublet**
**FIRST trial with ipilimumab/ nivolumab as the comparator**

Choueiri et al. Presented at ESMO, September 2022

# Kidney Cancer: METASTATIC TRIPLET vs. DOUBLET (COSMIC-313)

| | CLEAR Pembro +Len (N=1069) | CHECKMATE- 9ER Nivo+ Cabo (N=651) | CHECKMATE- 214* Nivo + Ipi (N=1096) | KEYNOTE-426 Pembro + Axitnib (N=861) | COSMIC-313 Nivo+Ipi+Cab0 (N=428) |
|---|---|---|---|---|---|
| **PFS (ITT) HR** | 0.39 | 0.56 | 0.73 | 0.68 | 0.73 |
| **PFS (int/poor) HR** | 0.36 | I: 0.58<br>P: 0.36 | 0.73 | 0.67 | **I: 0.63**<br>**P: 1.04** |
| **Median OS (mo)** | NR | 37.7 | 38 | **45.7** | Not reported |
| HR (95% CI) | 0.66 | 0.70 | 0.68 | 0.73 | Not reported |
| **ORR/CR (%)** | **71/16.1** | 55.7/12.4 | 42/12 | 60.4/10 | 43/3 |
| **Sarcomatoid features (%)** | 7.9 | 11.5 | **14** | 12 | |
| **% AEs leading to discontinuation** | **37.2%** | **3.1%** | 22% | 10.7% | **45%** |
| **IMDC or MKSCC risk (F/I/P)** | **31**/59.2/9.3 | 22.6/57.6/19. 7 | 23/**61/17** | **31.9**/55.1/13 | **0/75/25** |
| **Median FU (mo)** | 27 | 24 | 67.7 | 42 | 20.2 |

Pal. Presented at ESMO, September 2022

# Kidney Cancer: METASTATIC TRIPLET vs. DOUBLET (COSMIC-313)

| | Cabo+Nivo+Ipi (N=276) | Pbo+Nivo+Ipi (N=274) |
|---|---|---|
| Objective response rate (95% CI), % | 43 (37.2–49.2) | 36 (30.1–41.8) |
| Best overall response, n (%) | | |
| Complete response | 7 (3) | 9 (3) |
| Partial response | 112 (41) | 89 (32) |
| Stable disease | 119 (43) | 100 (36) |
| Progressive disease | 23 (8) | 55 (20) |
| Not evaluable | 15 (5) | 21 (8) |
| Disease control rate, % | 86 | 72 |
| Median time to objective response (range), mo | 2.4 (1.5–17.1) | 2.3 (1.9–16.8) |
| Median duration of response (95% CI), mo | NR (20.2–NE) | NR (NE–NE) |

**Low ORR, Low CR, no OS data**

Choueiri et al. Presented at ESMO, September 2022

# Kidney Cancer: METASTATIC TRIPLET OR DOUBLET

## Treatment Exposure and Discontinuation (Safety Population)

| | Cabo+Nivo+Ipi (N=426) | Pbo+Nivo+Ipi (N=424) |
|---|---|---|
| Median duration of exposure of study treatment (range), mo | 10.9 (0.2–28.5) | 10.3 (0.1–28.1) |
| Median average daily dose (range) of Cabo or Pbo, mg | 23.2 (3.6–40.0) | 36.1 (0.8–40.0) |
| Median Nivo infusions (range) received, no | 10 (1–27) | 9 (1–27) |
| Doses of Ipi received, % | | |
| 4 | 58 | 73 |
| 3 | 13 | 14 |
| 2 | 22 | 7 |
| 1 | 7 | 6 |
| Any dose hold due to an AE, % | 90 | 70 |
| Any dose reduction of Cabo or Pbo due to an AE, % | 54 | 20 |
| Treatment-related AE leading to discontinuation, % | | |
| Any study treatment | 45 | 24 |
| Cabo or Pbo | 28 | 14 |
| Nivo | 26 | 18 |
| Ipi | 30 | 12 |
| All treatment components (due to the same AE) | 12 | 5 |

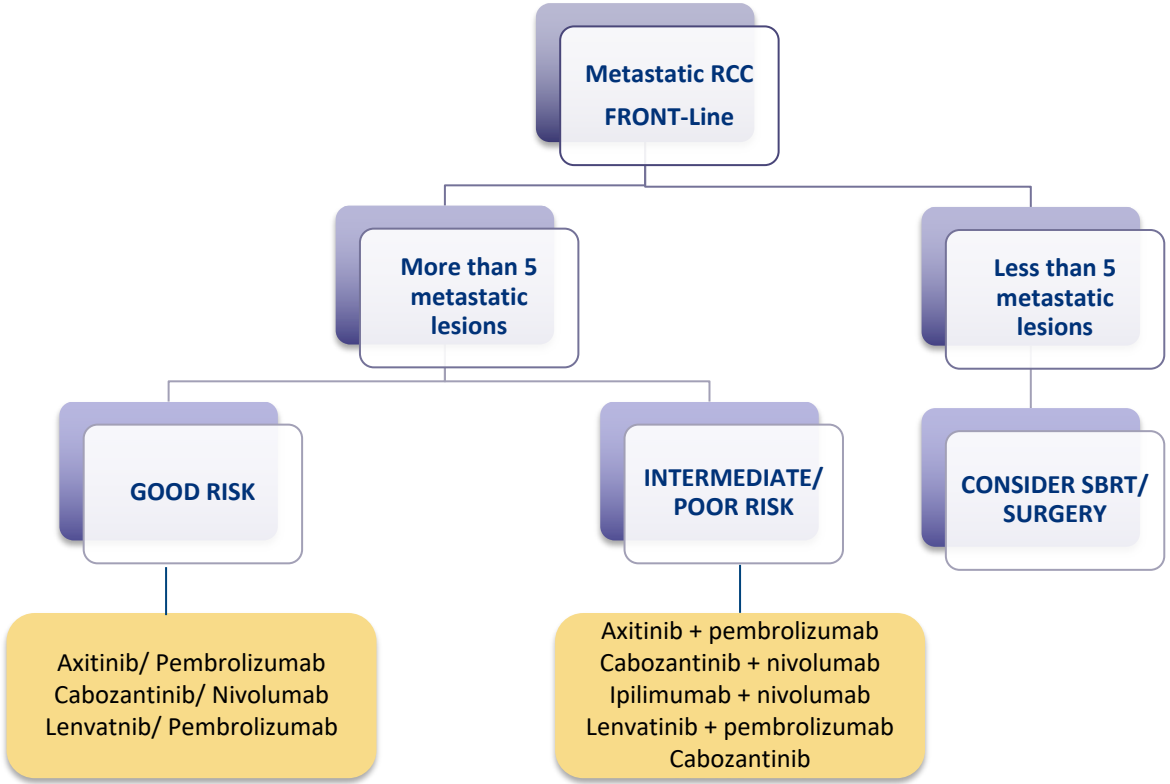
Data cut-off: Jan 31, 2022

Choueiri et al. Presented at ESMO, September 2022

# Kidney Cancer: METASTATIC TRIPLET OR DOUBLET: COSMIC 313

- Positive trial for PFS (HR 0.73) to support the triplet regimen
- However, looking at the HR in the FORREST PLOT: poor risk patients DO NOT benefit
- Low response rates
- Use of high dose corticosteroids ($\geq$ 40mg/day) in 58% patients and a 45% rate of discontinuation due to AEs
- TOXICITY GETS IN THE WAY!!!

# Metastatic Kidney Cancer: TREATMENT LANDSCAPE IN 2022




**Metastatic RCC**
**SUBSEQUENT LINES**

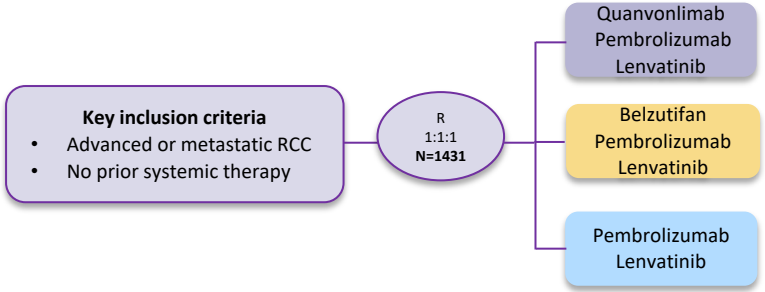
**SWITCH FROM 1st LINE Cabozantinib**
Lenvatinib + Everolimus
Nivolumab
Tivozanib (after 2 lines)
Belzutifan (category 2B in NCCN)

**CLINICAL TRIALS!!**

NCCN [nccn.org]

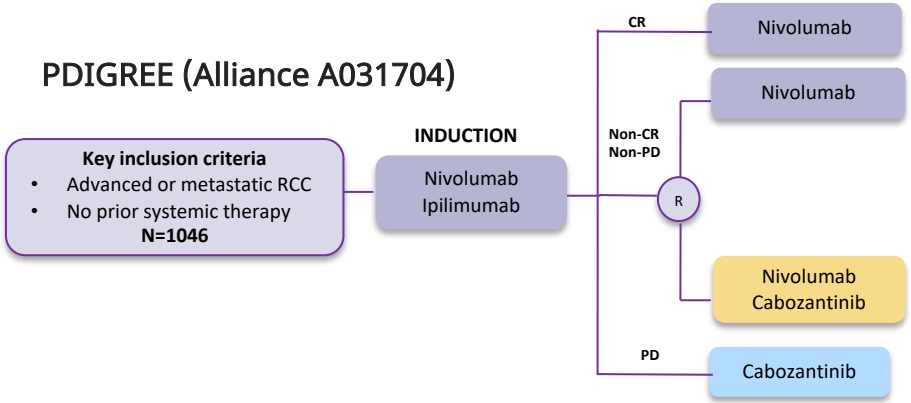
# Metastatic Kidney Cancer: Next Steps (Trials)

- Trials evaluating other Triplets

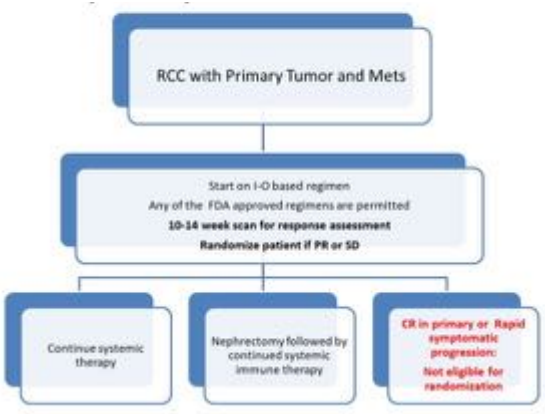



- Trials evaluating a "Risk-Adapted" Approach

PDIGREE (Alliance A031704)

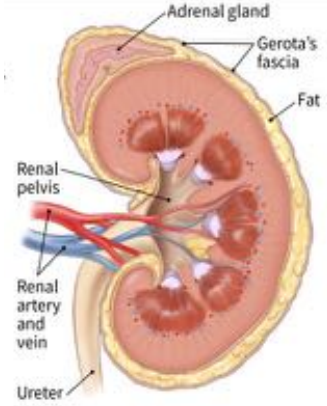



PROBE (SWOG S1931)




Choueiri, et al. Poster presented at: GU ASCO 2022
Zhang et al. Poster presented at GU ASCO 2022
Vaishampayan. Poster presented at GU ASCO 2022

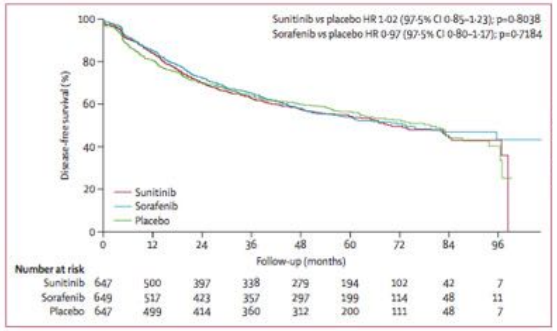
# Kidney Cancer: Perioperative Management



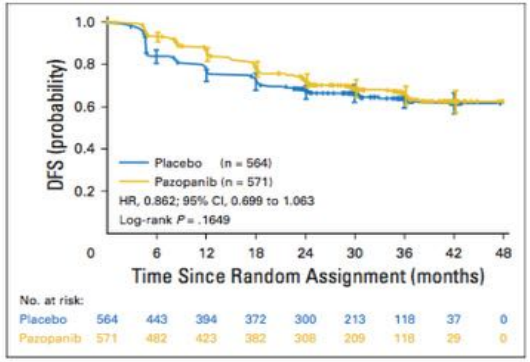

- Remains controversial in 2022!
- Rapidly evolving landscape
- Identification of  patients most likely to benefit remains a challenge (no biomarkers)

# Perioperative Management: VEGF-TKI Trials

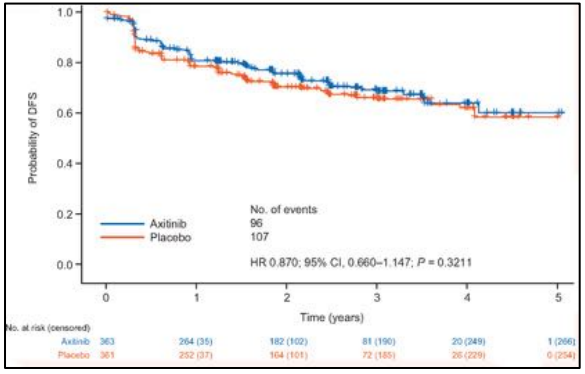
## ASSURE DFS



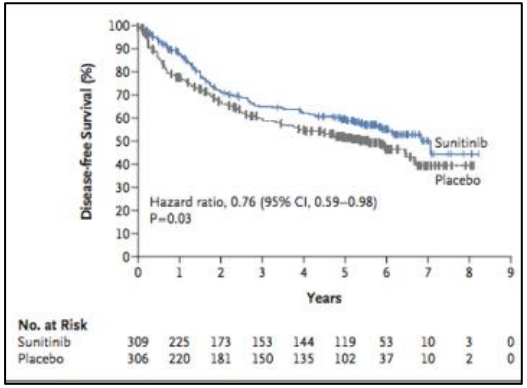

## PROTECT DFS




## ATLAS DFS



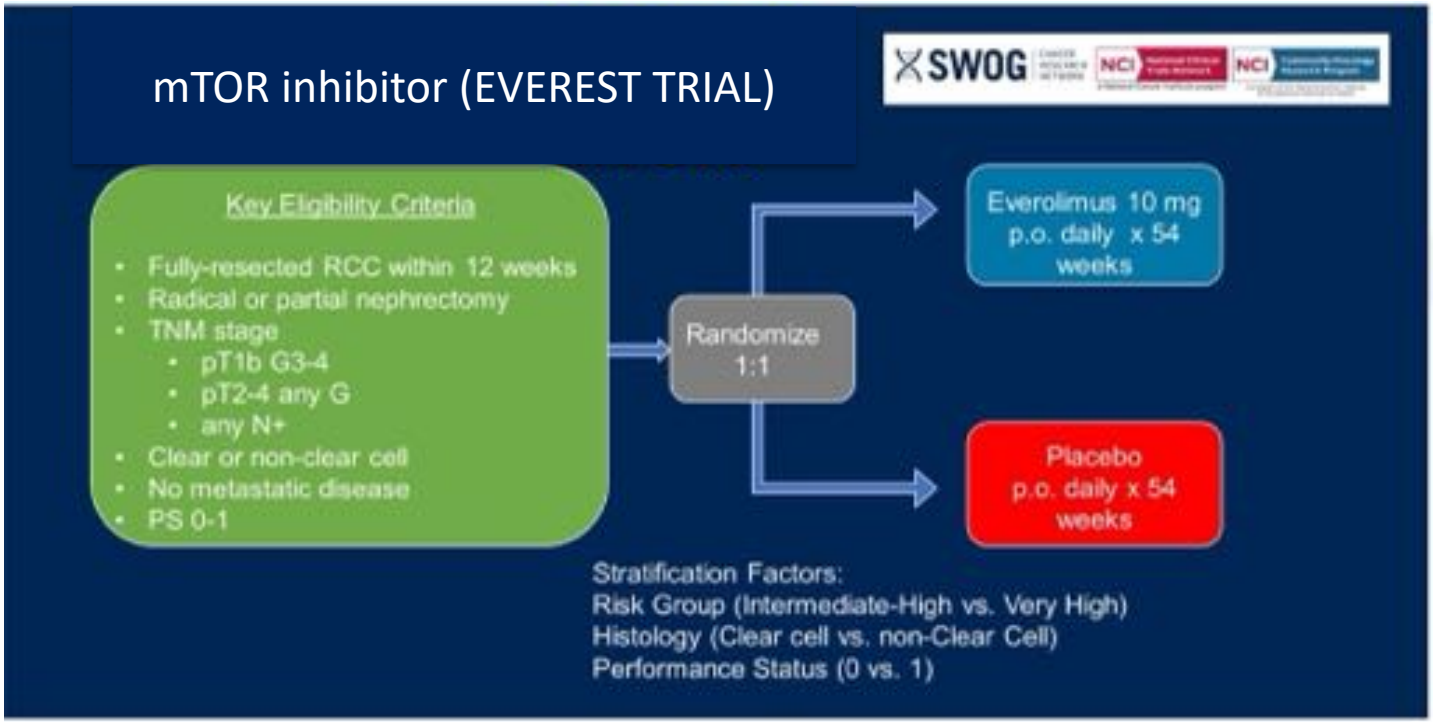

## S-TRAC DFS




- Heterogeneity
- ASSURE- lower T stage, clear and non clear
- PROTECT/ S-TRAC- pT3, higher grade and higher risk tumors
- S-TRAC the only positive trial for DFS (HR 0.76)
- Sunitinib approved by the FDA but not the EMA
- OS benefit not seen in any

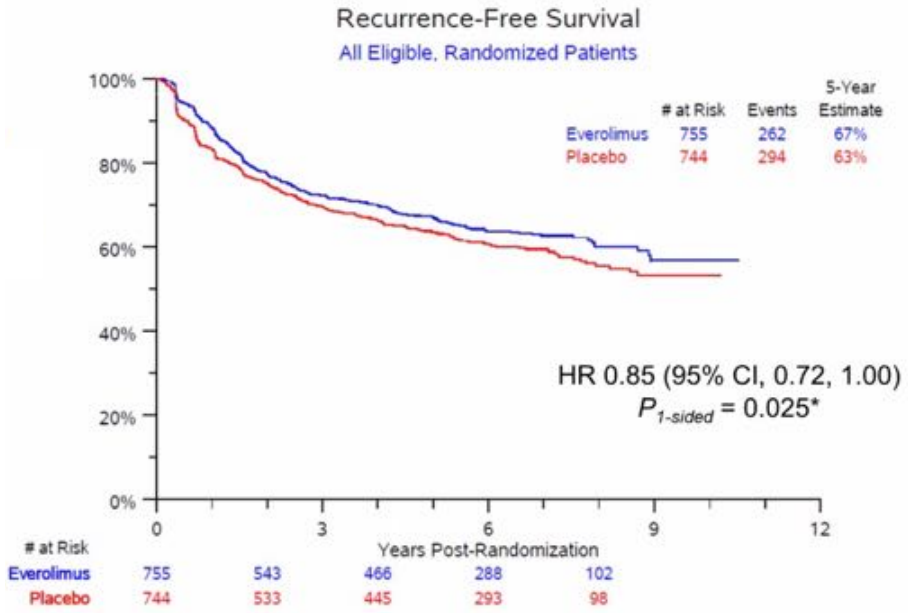
Haas NB, et al. *Lancet.* 2016;387(10032):2008-16. Motzer RJ, et al. *J Clin Oncol*. 2017;35(35):3916-3923. Ravaud A, et al. *N Engl J Med*. 2016;375(23):2246-2254. Gross- Goupil M, et al. *Ann Oncol*. 2018;29(12):2371-2378.

# Kidney Cancer: Perioperative Management (EVEREST TRIAL)




Ryan CW, et al. *J Clin Oncol*. 2022;40(17_suppl):LBA4500. Presented at: ASCO 2022.

# Kidney Cancer: Perioperative Management (EVEREST TRIAL)




- *p-value did not cross the prespecified boundary for statistical significance
- DID NOT reach its primary RFS endpoint

Ryan CW, et al. *J Clin Oncol*. 2022;40(17_suppl):LBA4500. Presented at: ASCO 2022.

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# Perioperative Management: Immune Checkpoint Inhibitor Trials

| | KEYNOTE - 564 PEMBROLIZUMAB | PROSPER (EA8143) NIVOLUMAB | IMMotion 010 ATEZOLIZUMAB | CHECKMATE-914 NIVO/ IPI |
|---|---|---|---|---|
| **RANDOMIZATION** | Adjuvant Pembrolizumab Vs. Placebo | Neoadjuvant and adjuvant Nivolumab vs. surgical SOC | Adjuvant Atezolizumab Vs. Placebo | Adj Nivolumab + Ipilimumab vs Placebo (nivolumab alone added) |
| **HISTOLOGY** | cRCC with a component of clear cell histology w or w/out sarcomatoid histology | Clear and nonclear cell | Component of either ccRCC histology or sarcomatoid histology | ccRCC predominant with or without sarcomatoid histology |
| **SACRCOMATOID?** | YES | YES | YES | YES |
| **T/N** | pT2, grade 4 and higher Any N | cT2 and higher Any N | pT2, grade 4 and higher Any N | pT2 grade3-4 and higher Any N |
| **OLIGOMETS** | M1 resected within 12 months of primary tumor | 0.70 | -Lung or soft tissue oligomets >12 months | NO |
| **PFS HR P-value** | **0.63** **p<0.0001** | 0.97 p= 0.43 | 0.93 p= 0.49 | 0.92 P= 0.53 |

Choueiri et al. Presented at ASCO GU 2022; Allaf M, et al. Presented at: ESMO;2022; Pal M, Lancet 9-11-22. Bex A, et al. Presented at: ESMO 2022; Motzer RJ, et al. Presented at: ESMO;2022

# Kidney Cancer: Perioperative Management FINAL CONCLUSIONS

- Pembrolizumab and sunitinib showed improvement in DFS and are approved in the adjuvant setting
- Detailed biomarker analysis even from the “negative” studies will be helpful to elucidate tumor/host factors that may determine response
- Standardization of eligibility criteria for future studies will be helpful

# Presentation Outline

- KIDNEY CANCER
- UROTHELIAL CARCINOMA
  - Current Status of approved drugs for metastatic urothelial carcinoma
  - Recent updates and upcoming trials
  - The state of perioperative therapies
  - Treatment decisions

- PROSTATE CANCER

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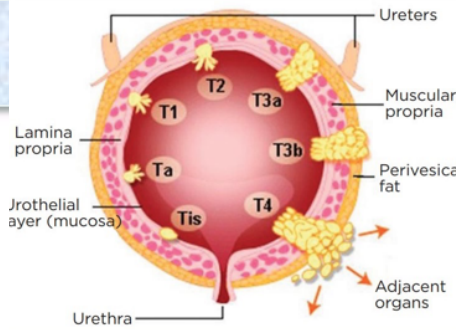
# Bladder Cancer: Change in Landscape




**1978**
**Cisplatin**

**2006**
**Cisplatin Gemcitabine**
1st line

CHECKPOINT INHIBITORS

**2016**
**Atezolizumab**
2nd line platinum ineligible

**2017**
**Atezolizumab**
1st line platinum ineligible
**Pembrolizumab**
1st line platinum ineligible AND 2nd line after platinum
**Durvalumab**
2nd line after platinum
**Avelumab**
2nd line after platinum
**Nivolumab**
2nd line after platinum

**2019**
**Enfortumab vedotin-ejvf**
2nd/ 3rd line after platinum/IO

**2019**
**Erdafitnib**
2nd line after platinum

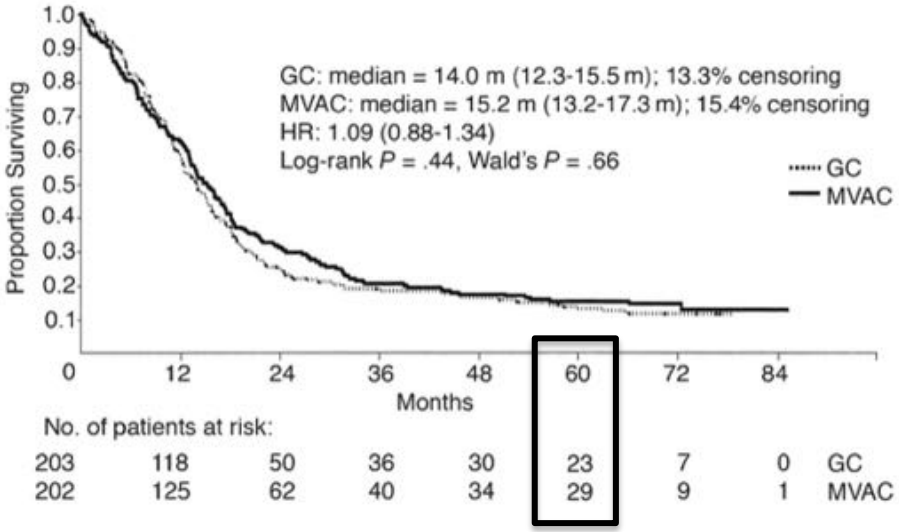
**2020**
**Avelumab Maintenance**
After response achieved with platinum

**2021**
**Sacituzumab govitecan**
3rd line after platinum and IO

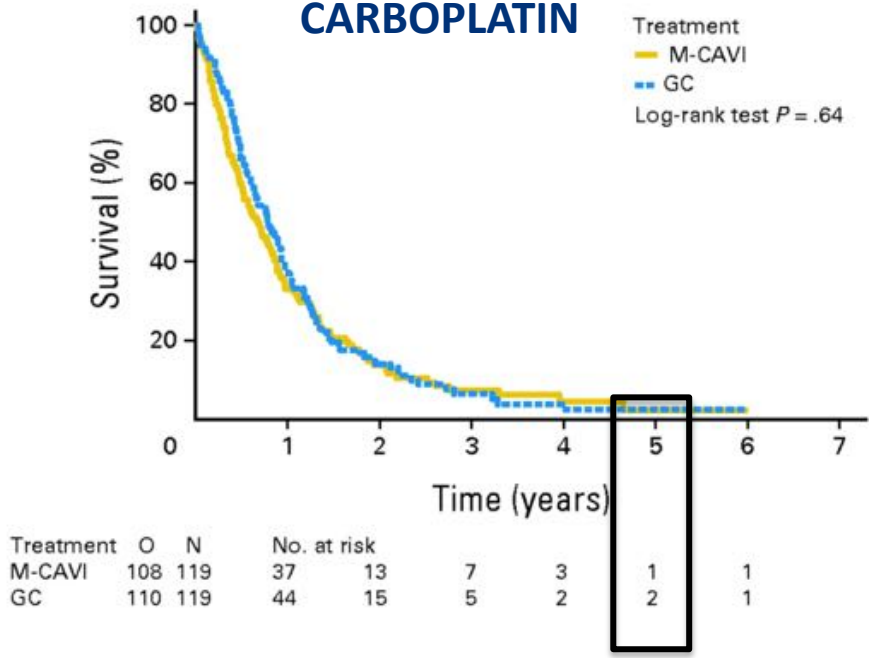
**ONGOING (2022)**

# Cisplatin-based chemotherapy has been the mainstay

## CISPLATIN




## CARBOPLATIN




von der Maase H, et al. *J Clin Oncol*. 2005;23(21):4602-8.
De Santis M, et al. *J Clin Oncol*. 2012;30(2):191-9.

MVAC= Methotrexate/ vinblastine/ Adriamycin/ cisplatin
MCAVI: methotrexate/carboplatin/vinblastine M-CAVI)
GC: Gemcitabine/ cisplatin or carboplatin

# Cisplatin Eligibility?

- ECOGPS=2
- Creatinine clearance < 60 mL/min
- Grade ≥ 2 hearing loss
- Grade ≥ 2 neuropathy
- New York Heart Association Class III CHF

Galsky MD, et al. *Lancet Oncol*. 2011;12(3):211-4

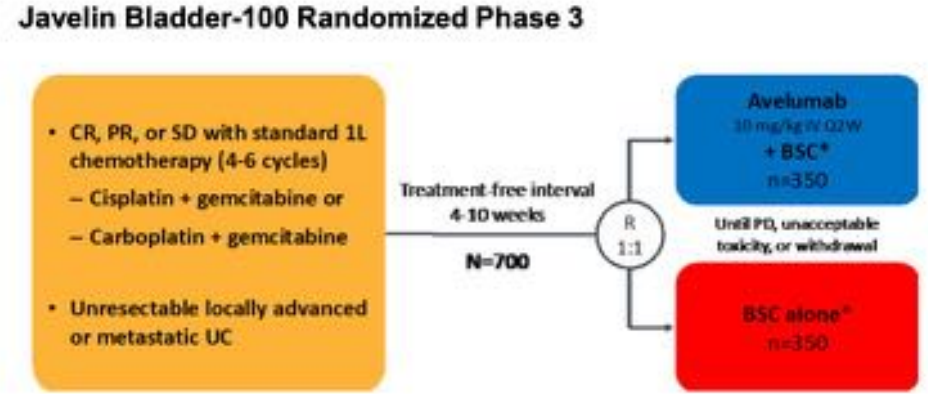
ECOG PS = Eastern Cooperative Oncology Group Performance Status; CHF = chronic heart failure

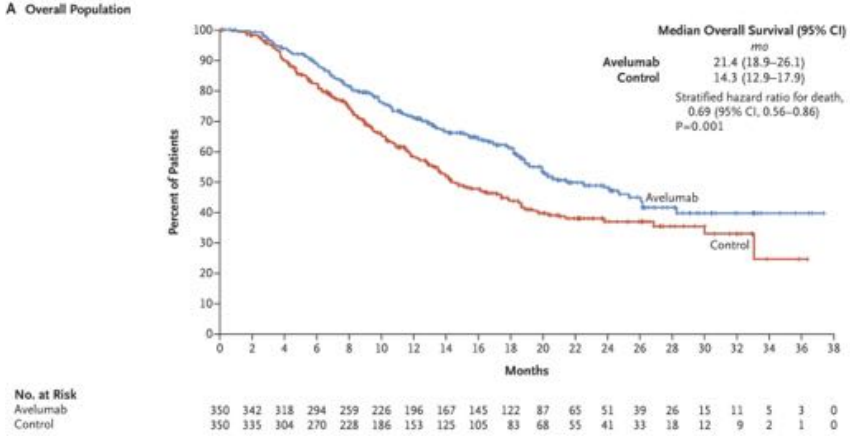
# Advent of Immunotherapy in Locally Advanced/ Metastatic UC

| Agent | Checkpoint | Post platinum | Front-line Cisplatin ineligible |
|---|---|---|---|
| **ATEZOLIZUMAB** | PD-L1 | Accelerated | **PD-L1 high or platinum inelgible** |
| **NIVOLUMAB** | PD-1 | Accelerated | |
| **DURVALUMAB** | PD-L1 | Accelerated | |
| **AVELUMAB** | PD-L1 | Accelerated | |
| **PEMBROLIZUMAB** | PD-1 | Level 1 | **Full approval only in platinum ineligible** |

Patel and Galsky MD. ACS A Cancer Journal for Clinicians. 2020

# Further Development of Immunotherapy in UC
# SWITCH MAINTAINENCE IO (JAVELIN 100)




Grivas et al. Presented at ASCO 2020. Powles T, et al. *N Engl J Med*. 2020;383(13):1218-1230

# Further Development of Immunotherapy in UC

- **Role of chemotherapy/ IO combination ?** **NOT YET**
  - IMvigor 130 ARM A (Atezo+ platinum/gem vs. placebo+ platinum/gem): Improved PFS (HR 0.82); OS pending
  - KEYNOTE 361 (Pembro+ Chemo vs. Chemo): Improved PFS (HR 0.78); OS did not reach predefined threshold for stat. significance

- **Role of IO alone in the upfront setting ?**
  - DANUBE (Durvalumab vs. Chemotherapy):
  - IMvigor 130 ARM B (Atezo alone arm):
  - KEYNOTE 361 (Pembro alone arm)

  } **NO**

- **Role of PD-L1+ CTLA4 inhibitor**
  - DANUBE: (Durvalumab + Tremilimumab vs. Chemo) **NO**

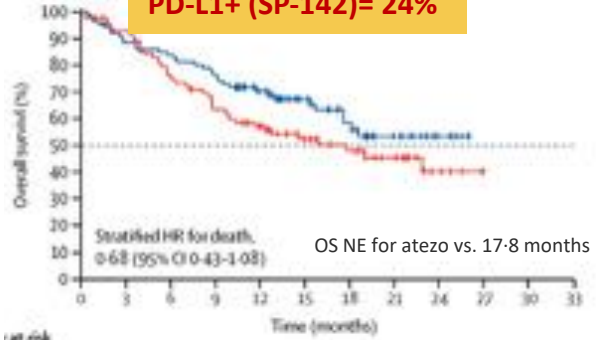
Galsky MD, et al. *Lancet*. 2020;395(10236):1547-1557
Alva A, et al. *Ann Oncol*. 2020;31(Suppl_4):S1142-S1215
Powles T, et al. *Lancet Oncol*. 2020;21(12):1574-1588

# Upfront IO in PD-L1 positive patients?

| DRUG | Biomarker | Scoring |
|---|---|---|
| **Pembrolizumab** | 22C3 | Tumor cell+ Immune cell |
| **Atezolizumab** | SP142 | Immune cell |
| **Nivolumab** | 28-8 | Tumor cell |
| **Durvalumab** | SP263 | Tumor cell+ Immune cell |
| **Avelumab** | 73-10 | Tumor cell+ Immune cell |

## IMvigor 130 ARM B (Atezo alone vs. chemo)

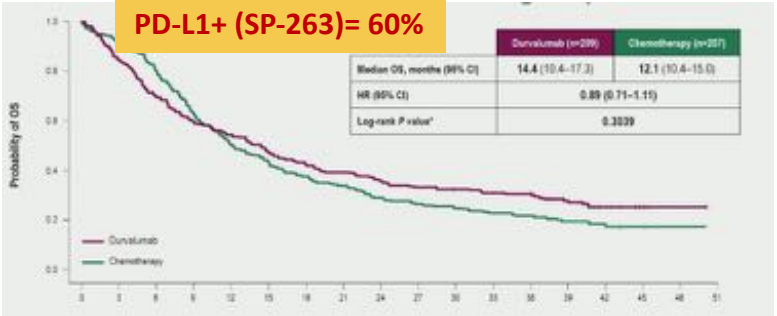
**PD-L1+ (SP-142)= 24%**




OS NE for atezo vs. 17·8 months

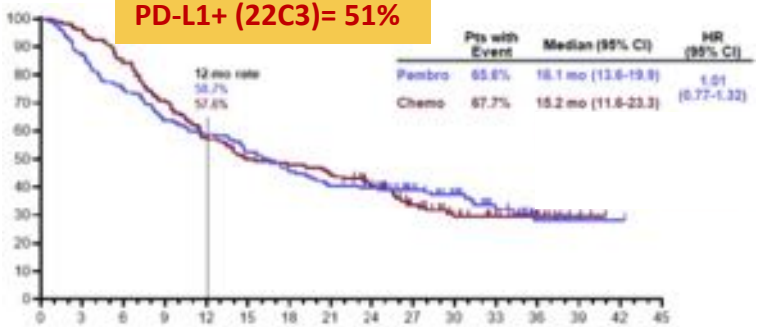
## DANUBE (Durvalumab vs. Chemotherapy)

**PD-L1+ (SP-263)= 60%**

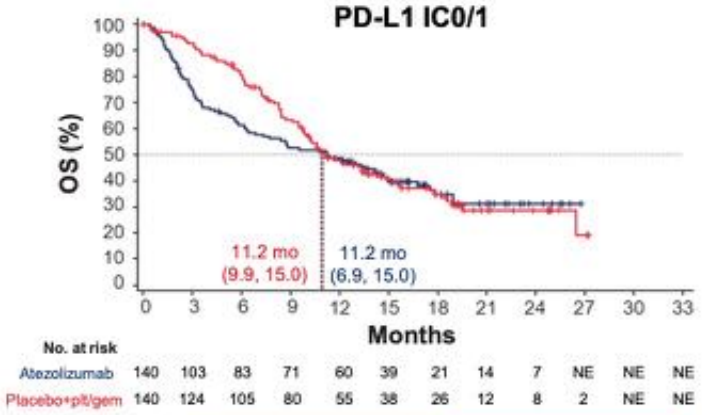



## KEYNOTE 361 (Pembro alone arm): NO

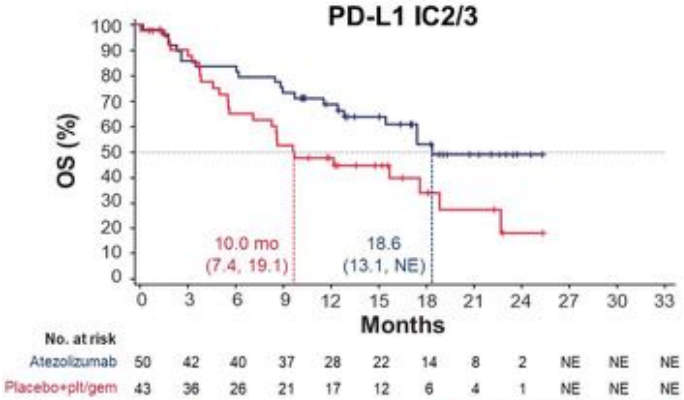
**PD-L1+ (22C3)= 51%**



# Atezolizumab in Cisplatin Ineligible + PD-L1 positive patients?



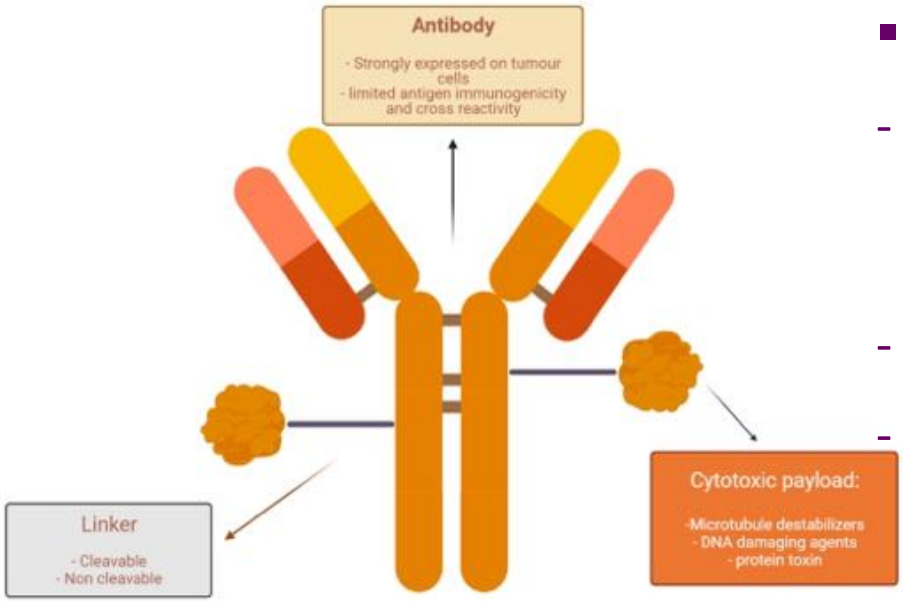

| | Atezolizumab (Arm B) (n=140) | Placebo + plt/gem (Arm C) (n=140) |
|---|---|---|
| OS events | 85 | 85 |
| OS HR (95% CI) | 1.11 (0.82, 1.51) | |
| ORR (95% CI), %[a] | 16 (10, 23) | 42 (34, 51) |




| | Atezolizumab (Arm B) (n=50) | Placebo + plt/gem (Arm C) (n=43) |
|---|---|---|
| OS events | 21 | 26 |
| OS HR (95% CI) | 0.53 (0.30, 0.94) | |
| ORR (95% CI), % | 38 (25, 53) | 33 (19, 49) |

Galsky MD et al. Presented at ASCO 2021

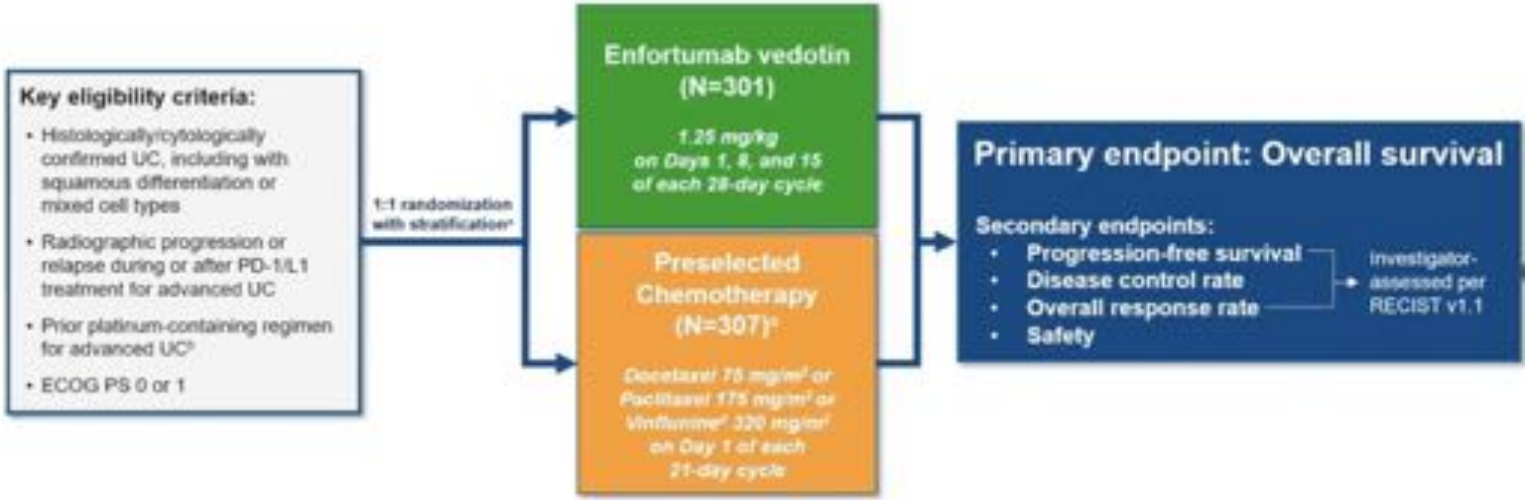
# Antibody Drug Conjugates




- **ENFORTUMAB VEDOTIN**
- **Target:** Nectin-4 (transmembrane cell adhesion molecule overexpressed in epithelial cancers)
- **Linker:** Protease cleavable
- **Payload:** Monomethyl auristatin E (MMAE)

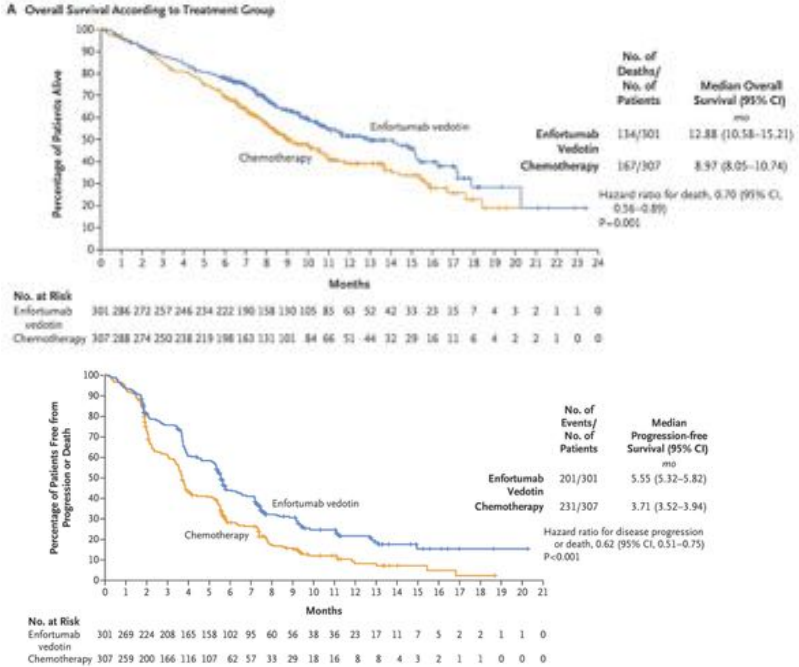
Ungaro et al. MDPI. 2022

# Enfortumab Vedotin: EV-301




Powels et al. Presented at GU-ASCO 2021; NEJM 2021

# Enfortumab Vedotin: Phase-III Trial (EV-301): Improved OS and PFS

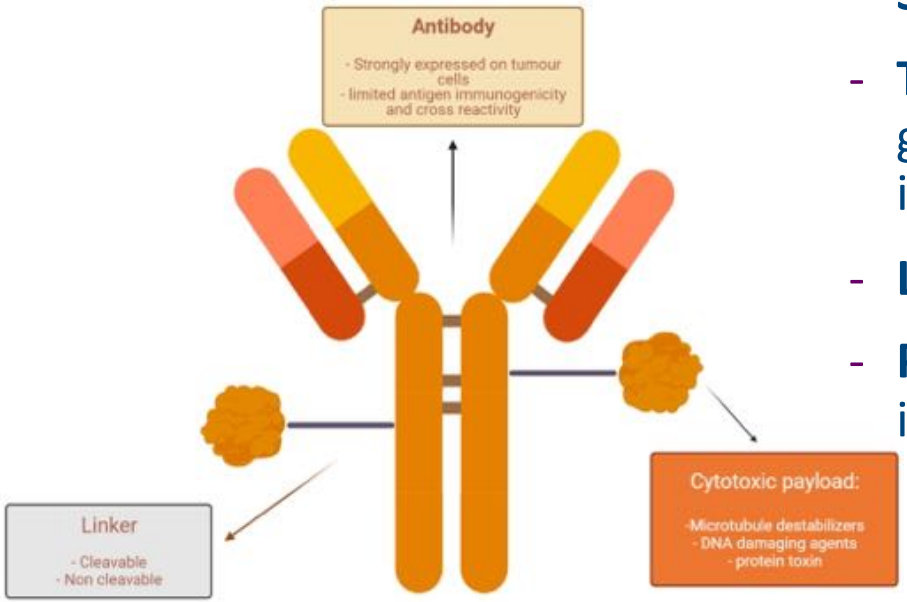



**FDA Approved for:**

- Patients who have have previously received IO and platinum-based chemotherapy
- Patients ineligible for cisplatin-based chemotherapy and have previously received one or more prior lines of therapy

Powels et al. Presented at GU-ASCO 2021; NEJM 2021

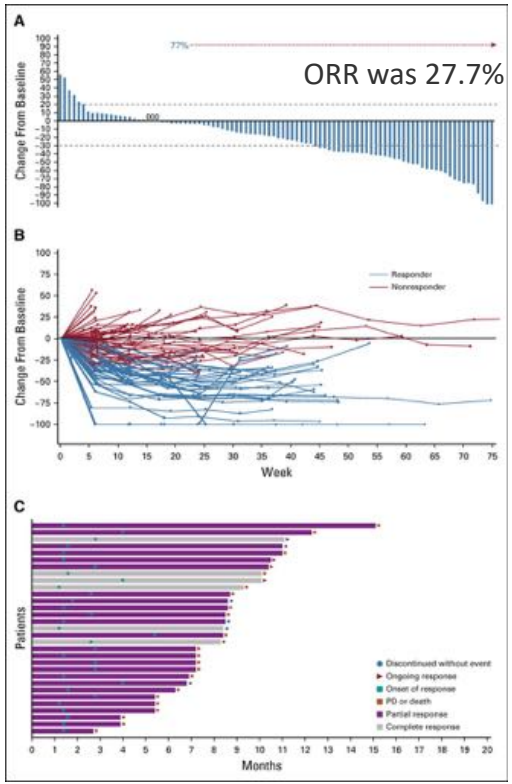
# Antibody Drug Conjugates




- **SACITUZUMAB GOVITECAN**
- **Target:** Trop-2, an epithelial cell-surface glycoprotein highly expressed in muscle-invasive disease
- **Linker:** Hydrolysable
- **Payload:** SN-38, the active metabolite of irinotecan

Ungaro et al. MDPI. 2022

# Sacituzumab Govitecan: TROPHY-U-1 (Phase-II trial)




Tagawa et al. JCO. 2021

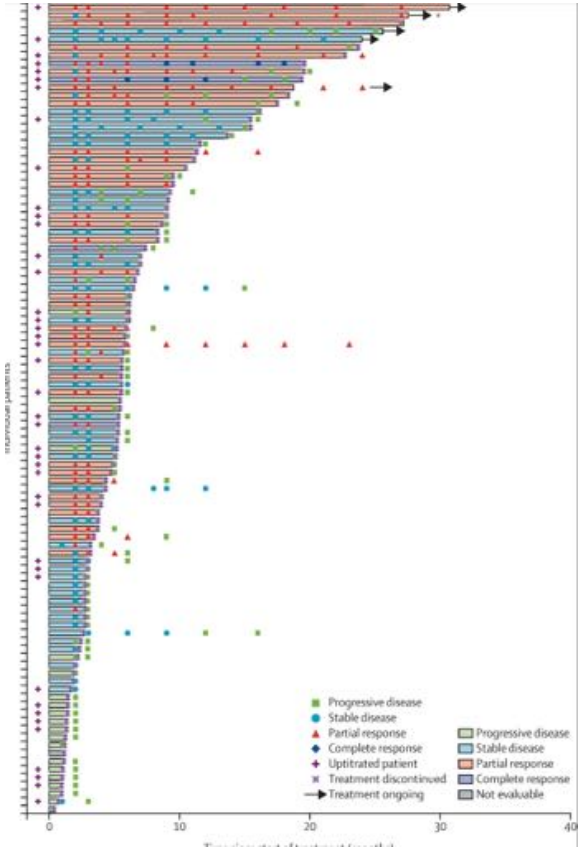
**FDA Approved for:**

- Patients who have have previously received IO and platinum-based chemotherapy

**Results of TROPHY-U-2 (Phase-III): Pending**

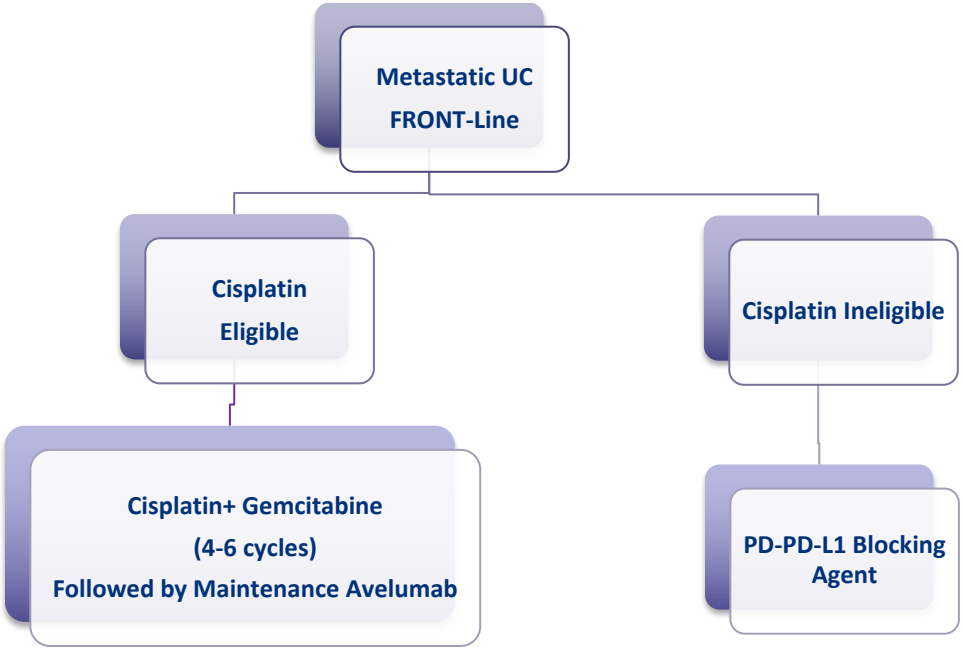
# FGFR3 Inhibitors

- **FGFR3 mutated in 15-20% patients**
- Targeted therapy: **ERDAFITINIB**
- ORR 33%
- **FDA approved patients with**
  - locally advanced or metastatic urothelial carcinoma
  - with susceptible FGFR3 or FGFR2 genetic alterations
  - progressed during or following platinum-containing chemotherapy




Siefker-Radtke et al. Lancet Oncology, 2022

# Metastatic Urothelial Cancer: TREATMENT LANDSCAPE IN 2022



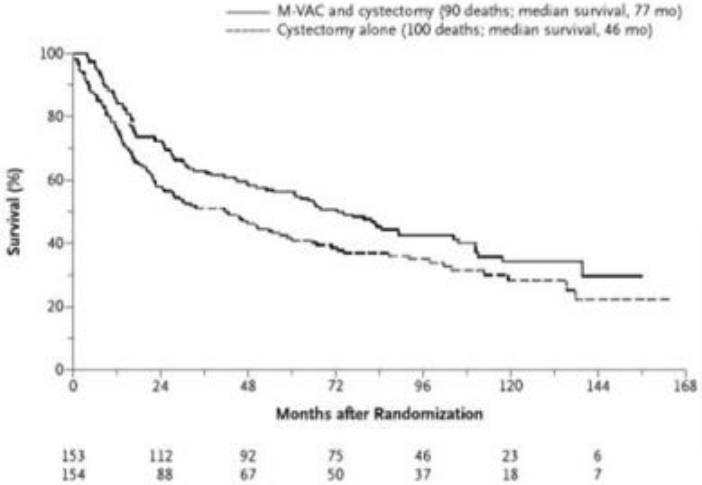

Metastatic UC
SUBSEQUENT
LINES

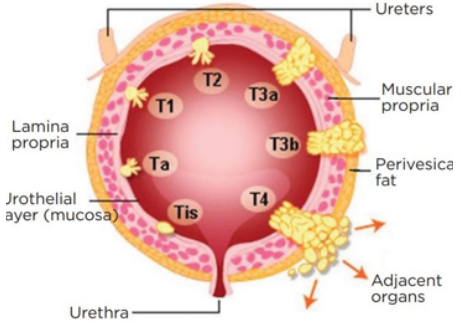
**SWITCH FROM 1st LINE**
PD-1/ PD-L1 Blockade
Enfortumab Vedotin
Erdafitinib
Sacituzmab

**CLINICAL TRIALS!!**

NCCN [nccn.org]

# Urothelial Cancer: Perioperative Management




## UPTO 50% PATIENTS CISPLATIN INELIGIBLE

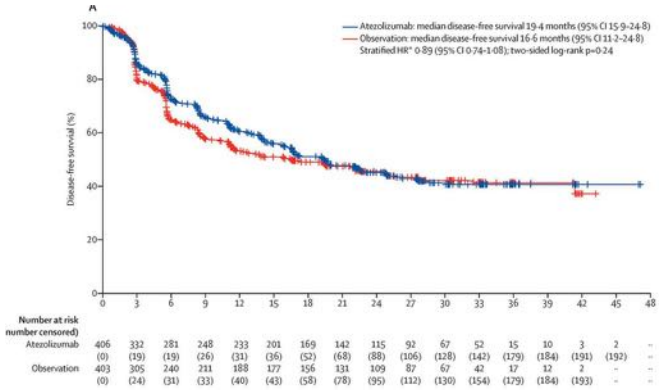
- ECOGPS=2
- Creatinine clearance < 60 mL/min
- Grade ≥ 2 hearing loss
- Grade ≥ 2 neuropathy
- New York Heart Association class III CHF

**NEOADJUVANT PLATINUM BASED CHEMOTHERAPY IS THE GOLD STANDARD !**

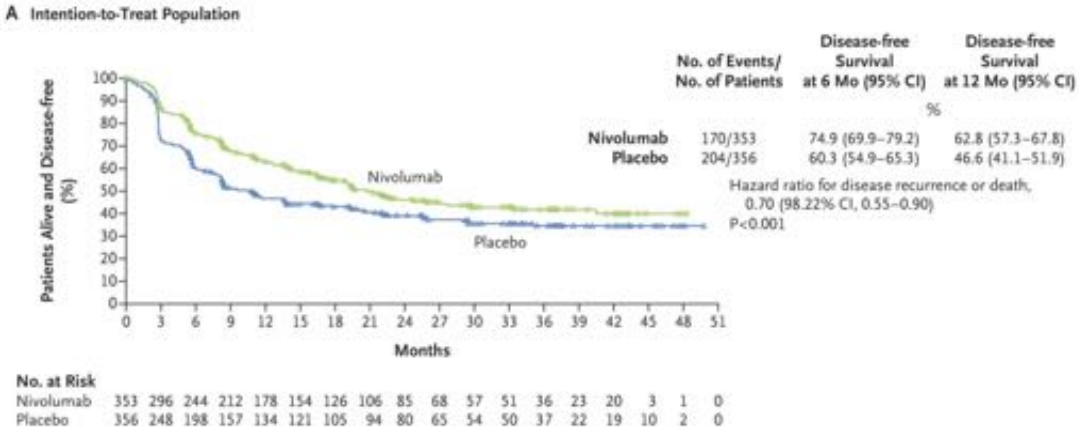
Grossman. NEJM, 2003
Galsky. Lancet Oncol, 2011

# Urothelial Cancer: Adjuvant IO Therapies?

**IMvigor010 (Atezolizumab)**



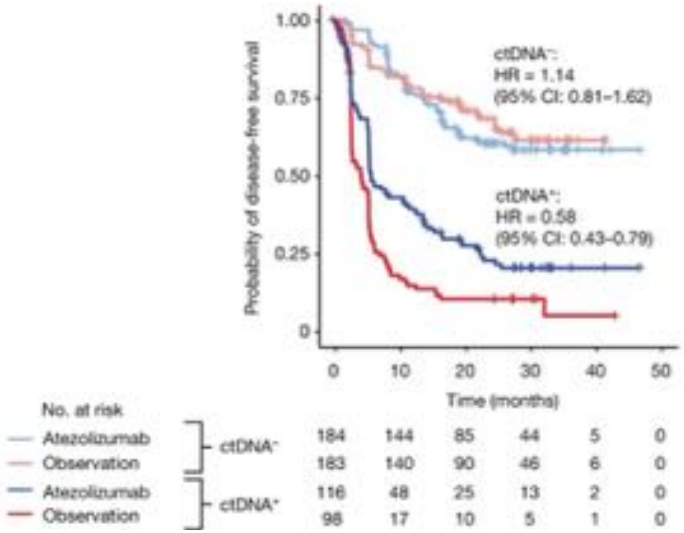

**CHECKMATE-274 (Nivolumab)**

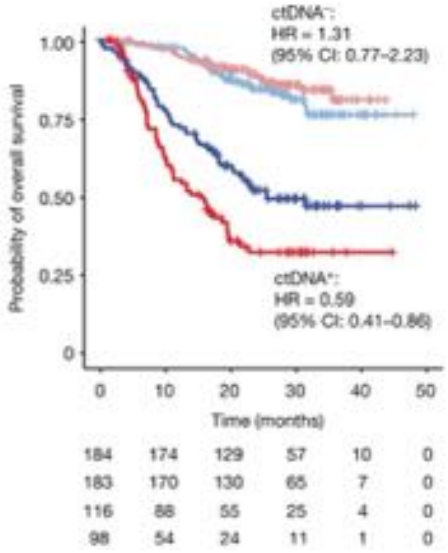



**AMBASSADOR (Pembrolizumab) PENDING**

Bellmunt J, et al. Lancet Oncol. 2021;22(4):525-537.
Bajorin DF, et al. *N Engl J Med.* 2021;384(22):2102-2114.

# Urothelial Cancer: Adjuvant IO Therapies?




**IMvigor010 (Atezolizumab) ctDNA negative patients have better outcomes compared to ctDNA positive patients**

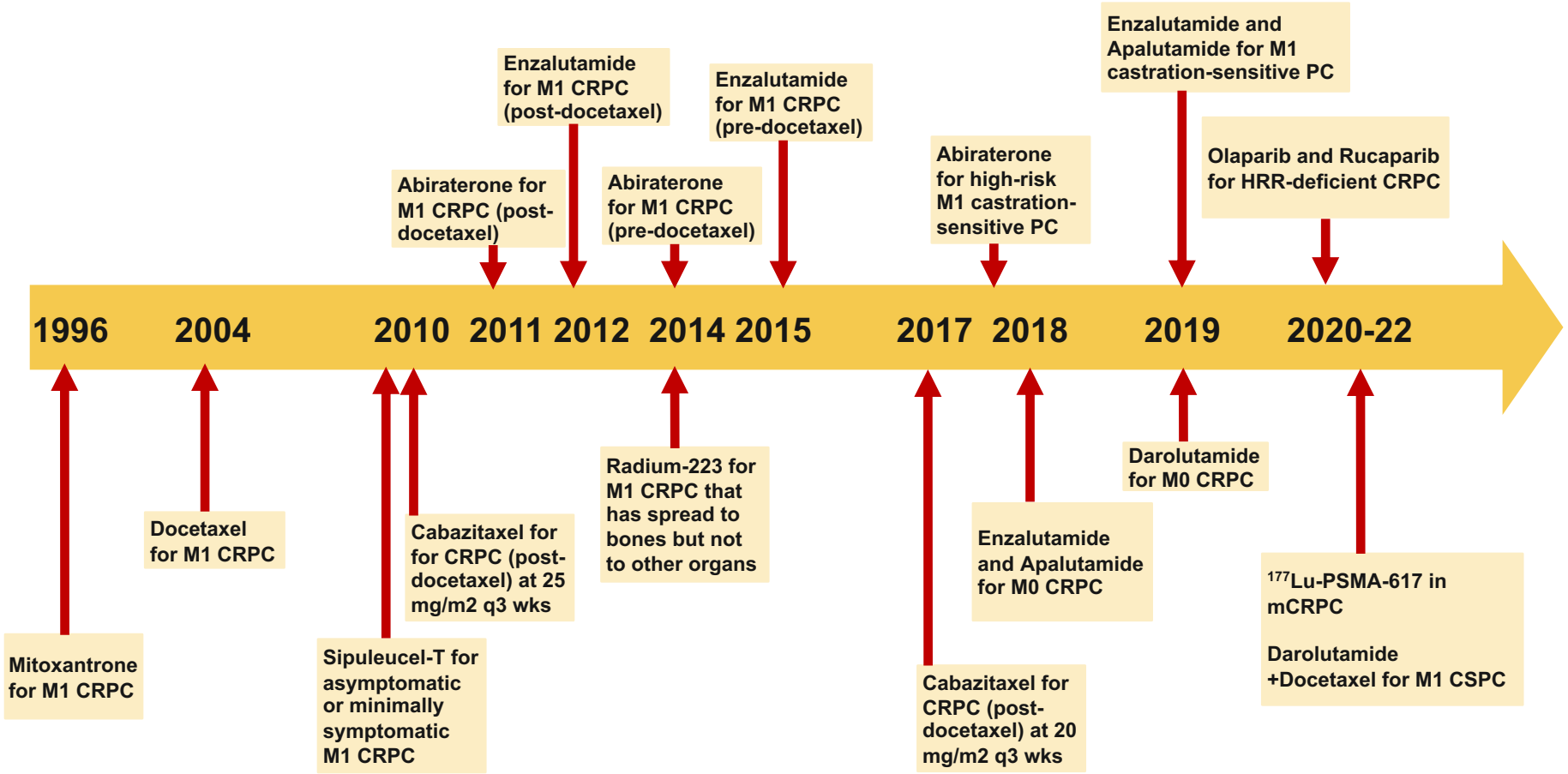
Powels et al. Nature. 2021

# Presentation Outline

- KIDNEY CANCER
- UROTHELIAL CARCINOMA
- PROSTATE CANCER
  - Current status of approved drugs
  - Recent updates and upcoming trials
  - Treatment decisions

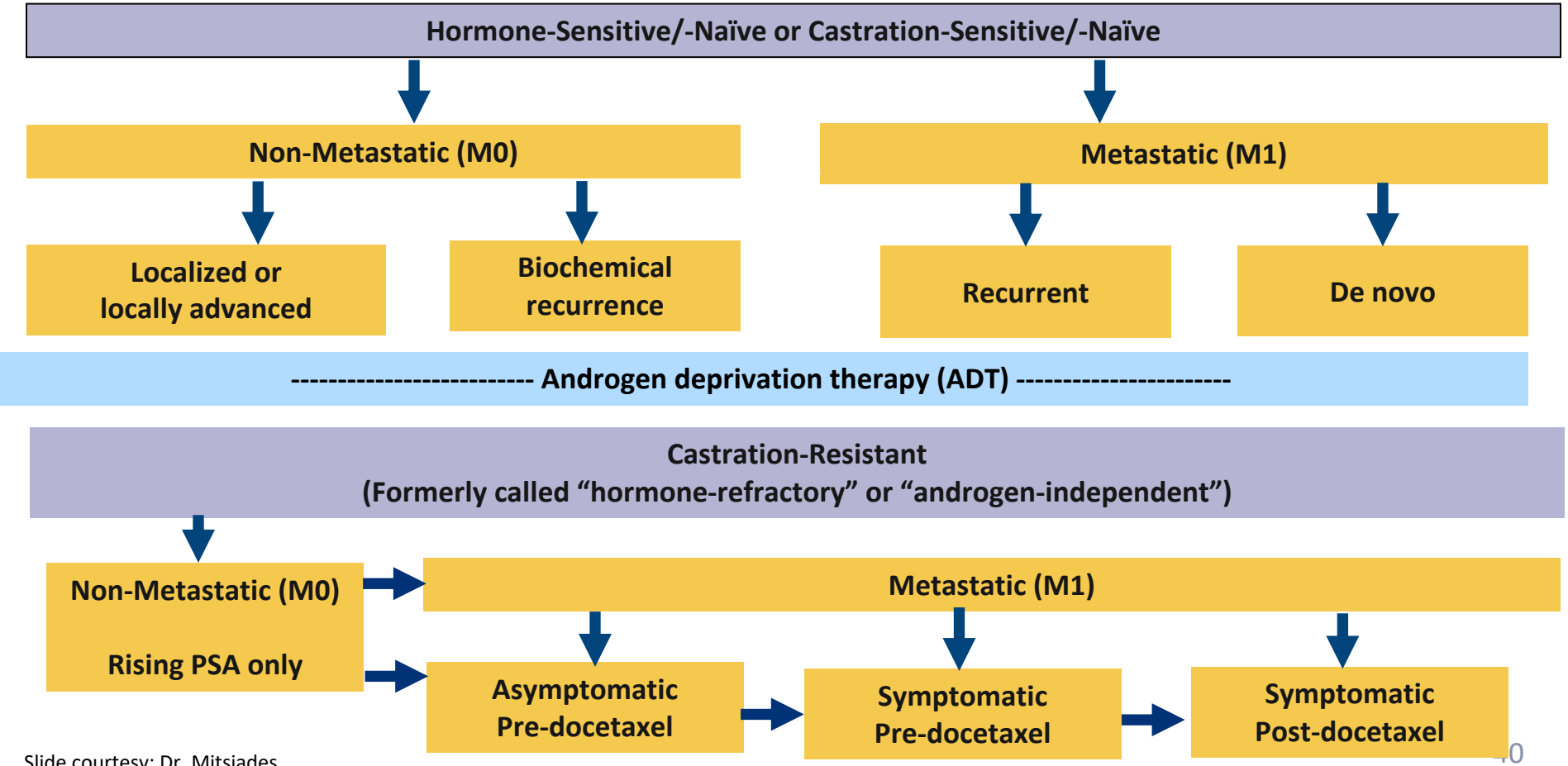
UCDAVIS COMPREHENSIVE CANCER CENTER

# Timeline of FDA approvals in Prostate Cancer



UCDAVIS COMPREHENSIVE CANCER CENTER

# Prostate Cancer Disease States




Slide courtesy: Dr. Mitsiades

# Enhancing frontline ADT: a) Docetaxel

## M1 Disease

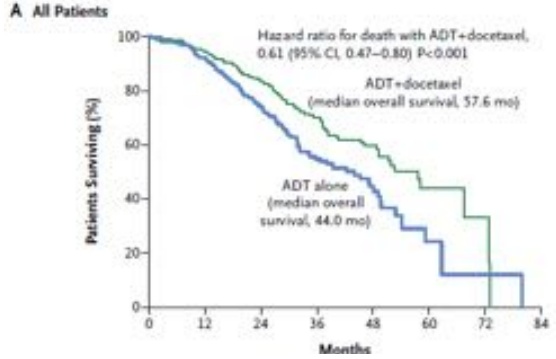
| OS Hazard Ratio (HR) | |
|---|---|
| CHAARTED[a] | **0.61 (0.47-0.80)** |
| STAMPEDE[b] | **0.76 (0.62-0.93)** |
| GETUG-15[c] | 0.90 (0.69-1.81) |
| | |
| Failure-free survival HR | |
| CHAARTED[a] | **0.61 (0.51-0.73)** |
| STAMPEDE[b] | **0.61 (0.53-0.71)** |
| GETUG-15[c] | **0.70 (0.57-0.86)** |

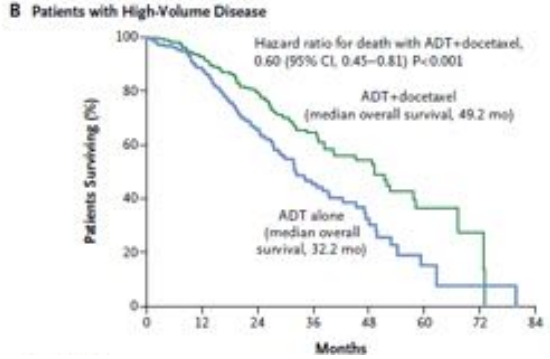
## M0 Disease

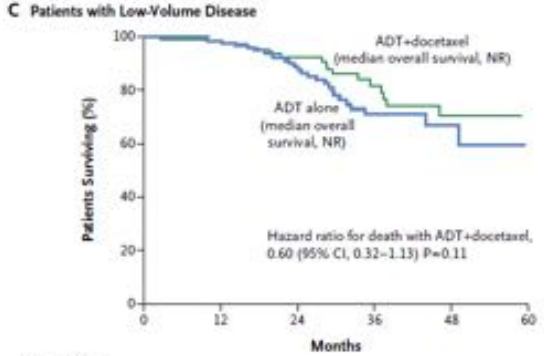
| OS HR | |
|---|---|
| STAMPEDE[b] | 0.95 (0.62-1.46) |
| GETUG-12[d] | 0.94 (0.60-1.48) |
| | |
| Failure-free survival | |
| STAMPEDE[b] | **0.60 (045-0.80)** |
| GETUG-12[d] | **0.71 (0.54-0.94)** |

(a) CJ Sweeney, et al. N Engl J Med, 373 (2015), pp. 737-746
(b) ND James, et al. Lancet 2016;387(10024):1163-77
(c) G Gravis, et al. Lancet Oncol, 14 (2013), pp. 149-158; G Gravis, et al. Proc Am Soc Clin Oncol, 33 (suppl 7) (2015) abstr 140.
(d) K Fizazi, et al. Proc Am Soc Clin Oncol, 32 (suppl) (2014) abstr 5005.

# CHAARTED: ADT + 6 cycles of Docetaxel



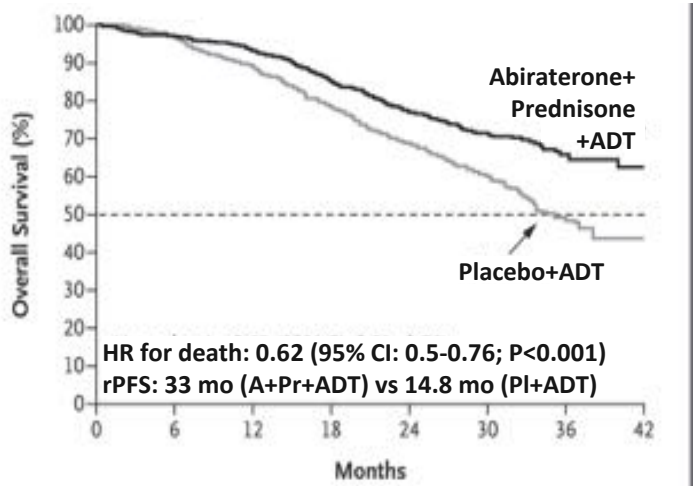




**Stratification: high vs. low volume metastasis (high volume: visceral metastases OR four or more bone lesions with at least one beyond the vertebral bodies and pelvis)**

CJ Sweeney, et al. N Engl J Med, 373 (2015), pp. 737-746

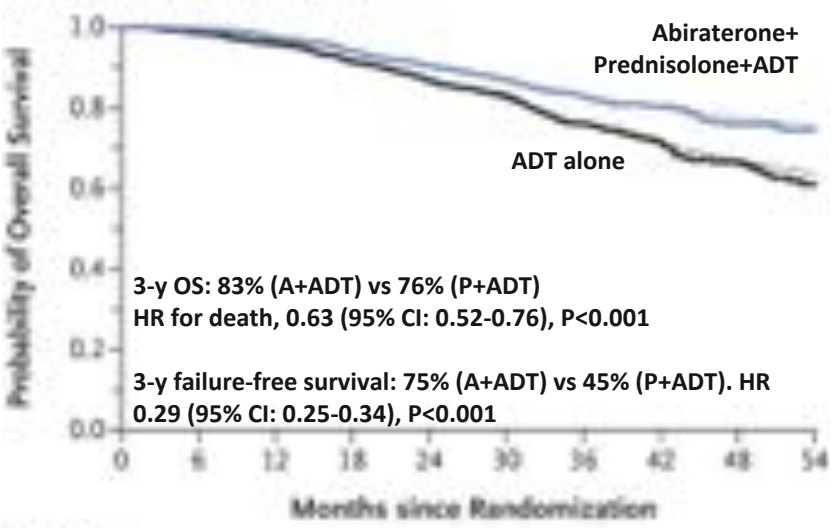
# Enhancing frontline ADT: b) Abiraterone

## LATITUDE




Patients had at least two of three risk factors: Gleason≥8, at least three bone lesions, or visceral metastasis.

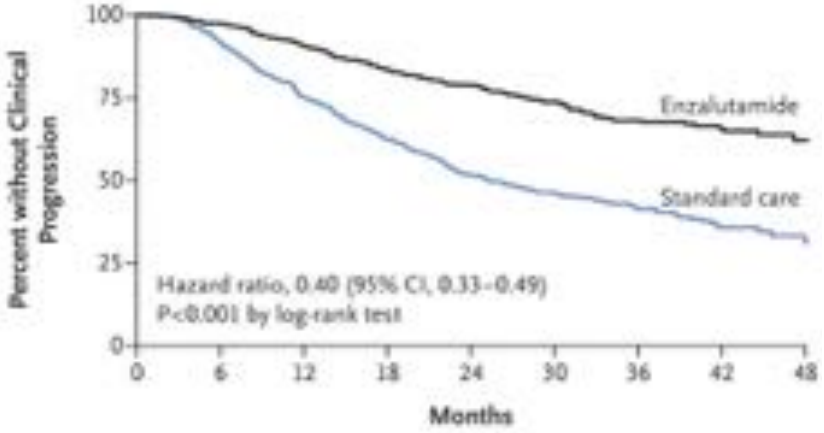
## STAMPEDE (arm G)

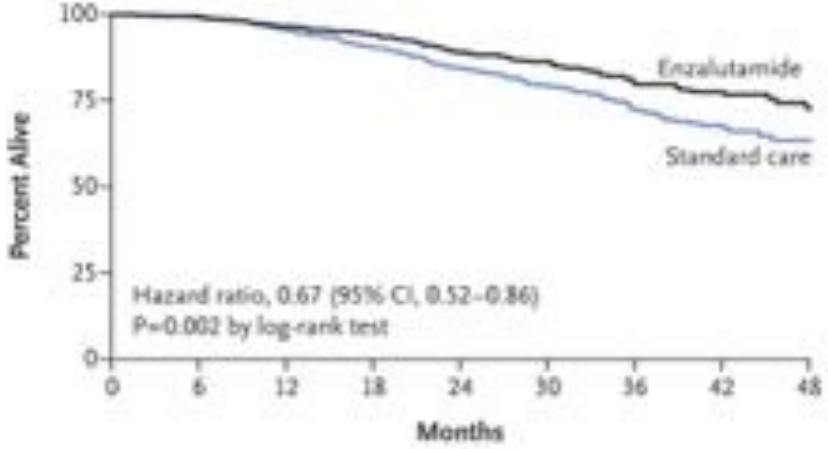



Patients had M1 disease (52%), N1 (or indeterminate) M0 disease (20%), and N0M0 disease (28%). XRT was mandatory for N0M0 and optional for N1M0 disease.

# Enhancing frontline ADT: c) Enzalutamide

## ENZAMET



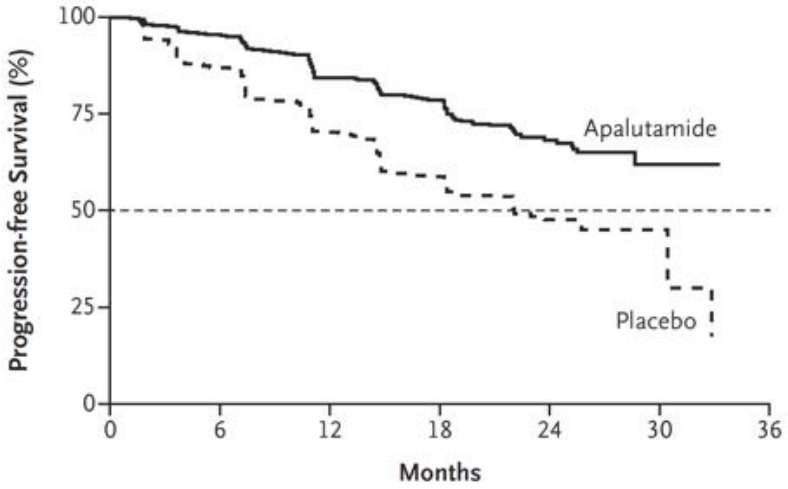



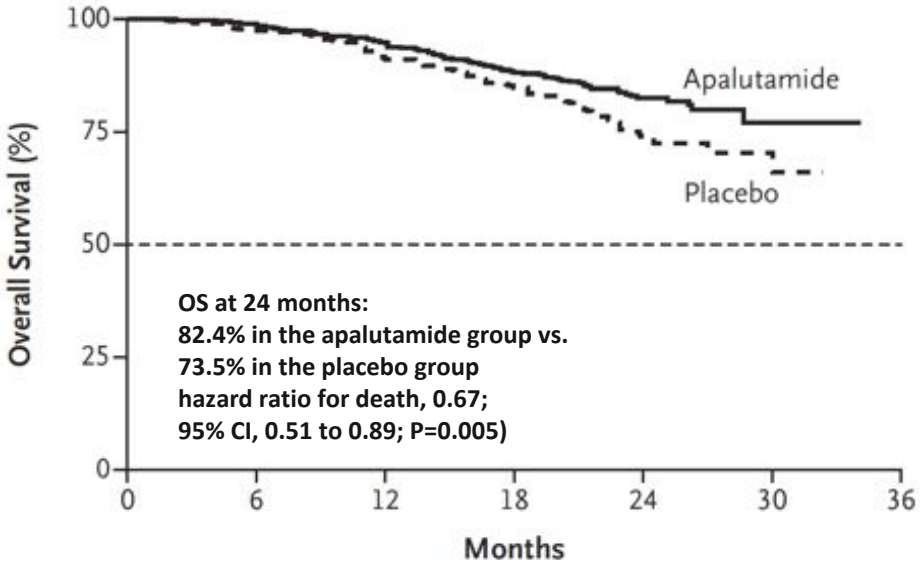

**High-volume disease in 52% of the patients**
**The results were unaffected by adjustments for volume of disease and use of early docetaxel**

ID Davis et al. N Engl J Med 2019;381:121-131.

# Enhancing frontline ADT: d) Apalutamide

## TITAN



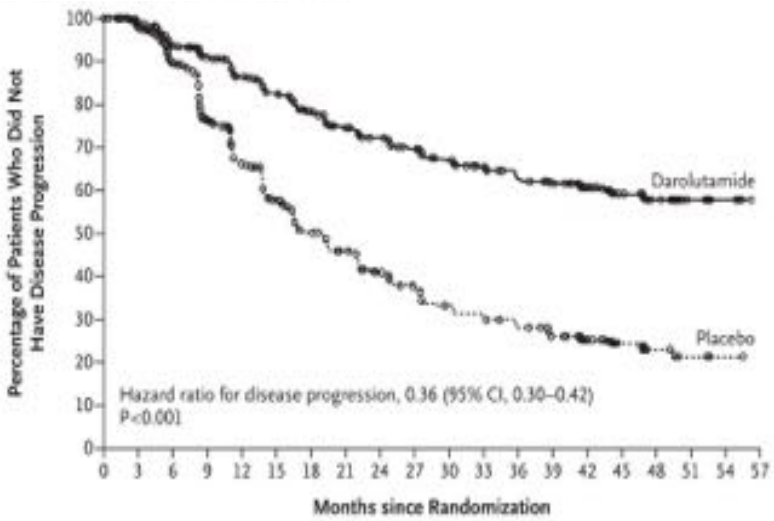



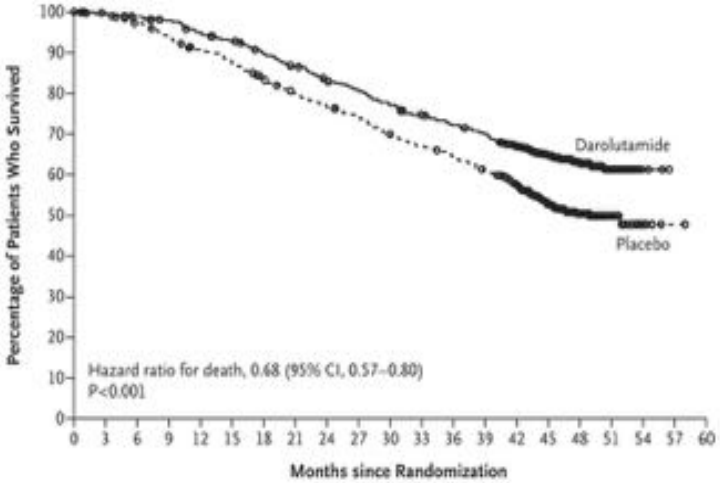

**62.7% had high-volume disease, and 37.3% had low-volume disease**
**10.7% had received previous docetaxel therapy**

Chi KN et al. NEJM 2019;381(1):13-24

# Enhancing frontline ADT: e) Darolutamide +Docetaxel

## ARASENS




MR Smith et al. N Engl J Med 2022;386:1132-1142.

# Summary and Thoughts on augmenting frontline ADT

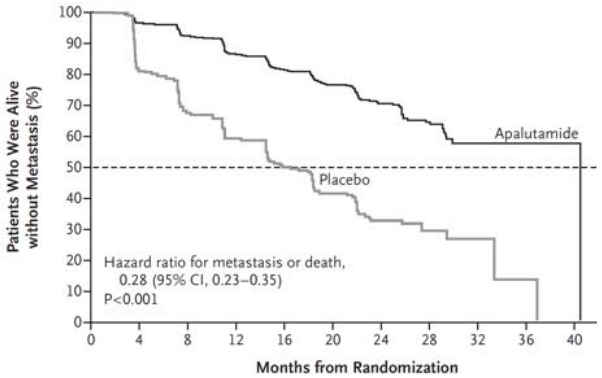
- Several options for M1 CSPC: ADT+Docetaxel (high volume disease), ADT+Abi, ADT+Enza, ADT+Apa and ADT+darolutamide+docetaxel

- Rapidly evolving field. Triplet or doublet therapy? Sequential?

- Adverse effects and other considerations:
  - Docetaxel: Peripheral neuropathy, myelosuppression, fatigue.
  - Abiraterone: HTN, hypokalemia, edema, liver toxicity, fatigue. Need for steroids
  - Enzalutamide/Apalutamide: Risk of seizure.
  - Darolutamide: Lower risk of seizures.

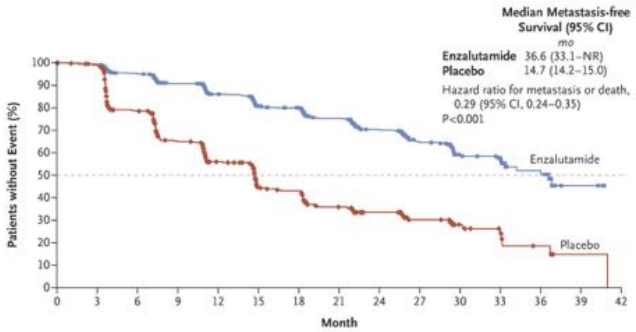
# CRPC: Non-metastatic (PSA only)

## SPARTAN



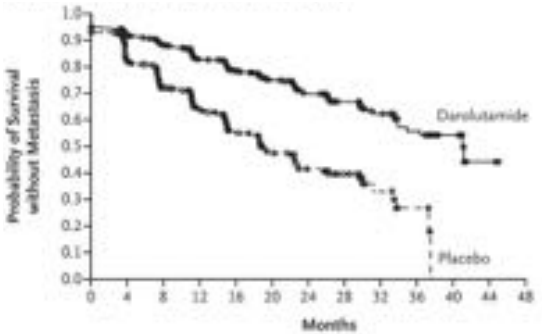

**APALUTAMIDE***

## PROSPER




**ENZALUTAMIDE***

## ARAMIS




**DAROLUTAMIDE**

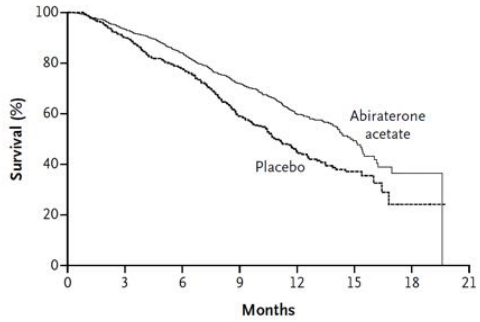
**Significant fracture risk in both studies ***
**11.7% (apalutamide) vs. 6.5% (placebo) / 10% (enzalutamide) vs. 5% (placebo)**

**Darolutamide not associated with a higher incidence of seizures, falls, fractures, cognitive disorder**


Smith MR, et al. NEJM 2018;378(15):1408-1418
Hussain M, et al. NEJM 2018;378(26):2465-2474
Fizazi K, NEJM 2019;380(13):1235-1246.

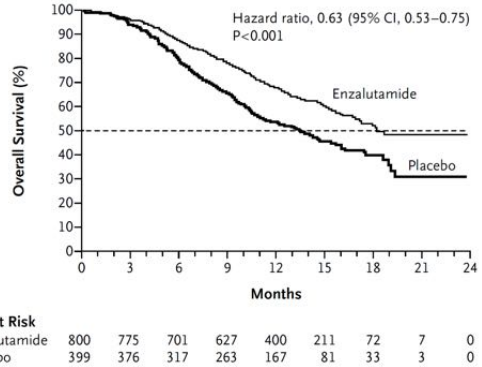
# Castration-Resistant PC: Metastatic

## COU-AA-301



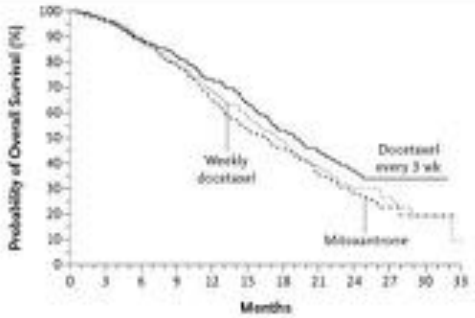

**ABIRETARONE**

## AFFIRM

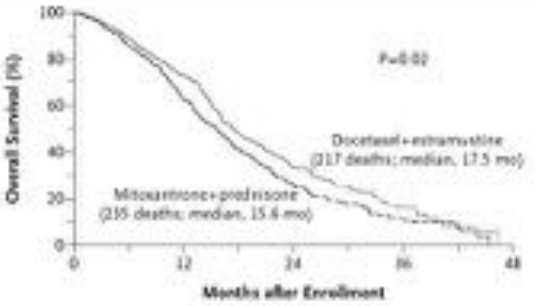



**ENZALUTAMIDE**

## TAX-327




## SWOG 9916

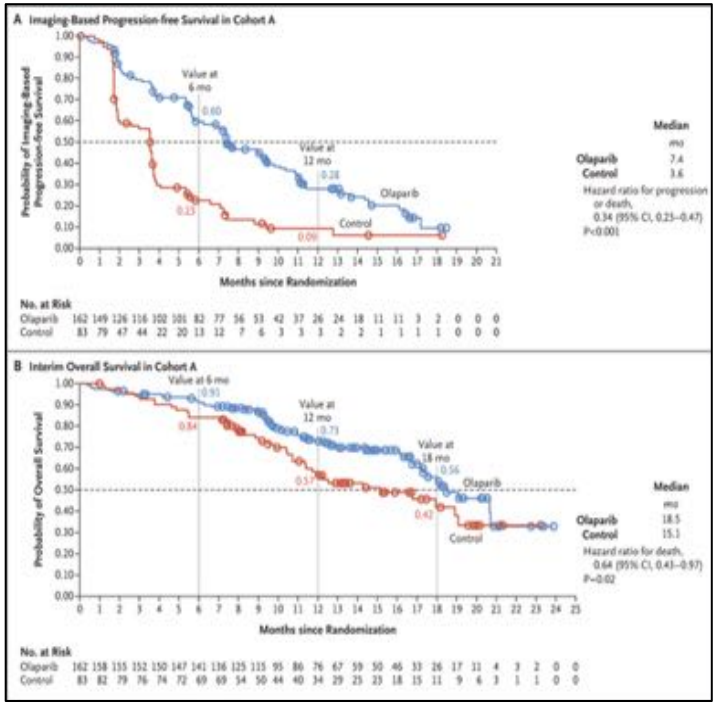



**DOCETAXEL**


de Bono JS, et al. NEJM 2011;364(21):1995-2005
Scher H. et al. NEJM 2012;367(13):1187-97
Tannock IF et al. N Engl J Med 2004;351:1502-1512.
Petrylak DP, et al. N Engl J Med. 2004;351(15):1513-20.

# PARP inhibitors in CRPC

## PROFOUND




**OLAPARIB**

**Mutations:**

**Cohort A:**

**BRCA1, BRCA2, ATM**

**Cohort B:**

**BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L**

**PROfound is the first positive phase III biomarker-selected study evaluating a molecularly targeted treatment in patients with mCRPC**

de Bono et al. NEJM 2020;382:2091-2102)

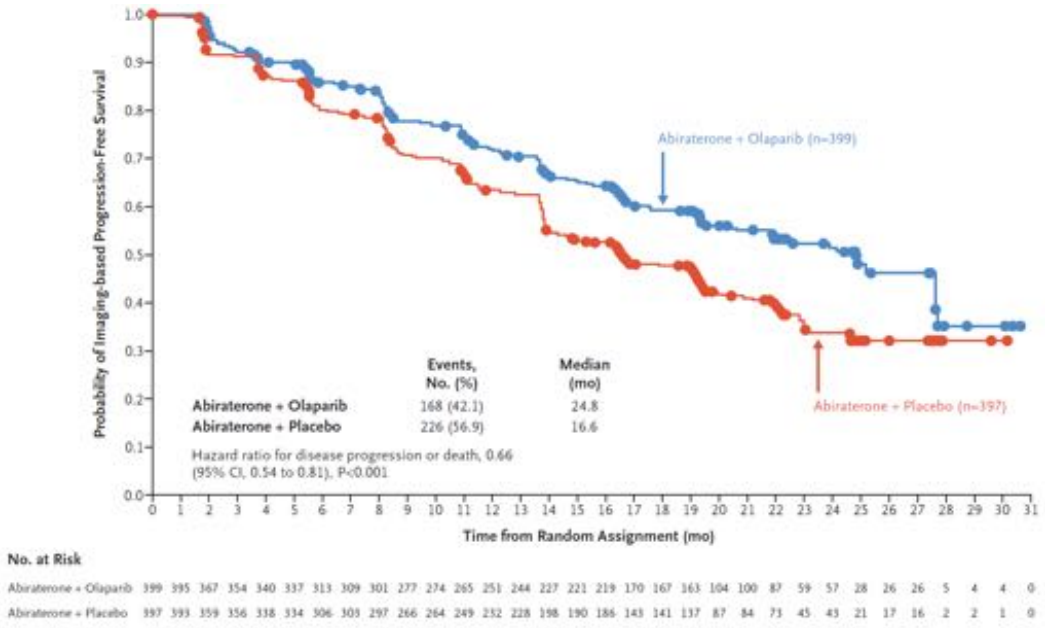
# Guidelines and FDA approvals for PARP inhibitors in PC

- **Olaparib** as a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene, **who have previously been treated with ADT**

- Patients with **PPP2R2A mutations in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, olaparib is not recommended in patients with a PPP2R2A mutations.**

- FDA approval 5/15/2020: **Rucaparib** for mCRPC with BRCA mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy

# Are we going to challenge the concept? (NHT + PARPi in all comers?)

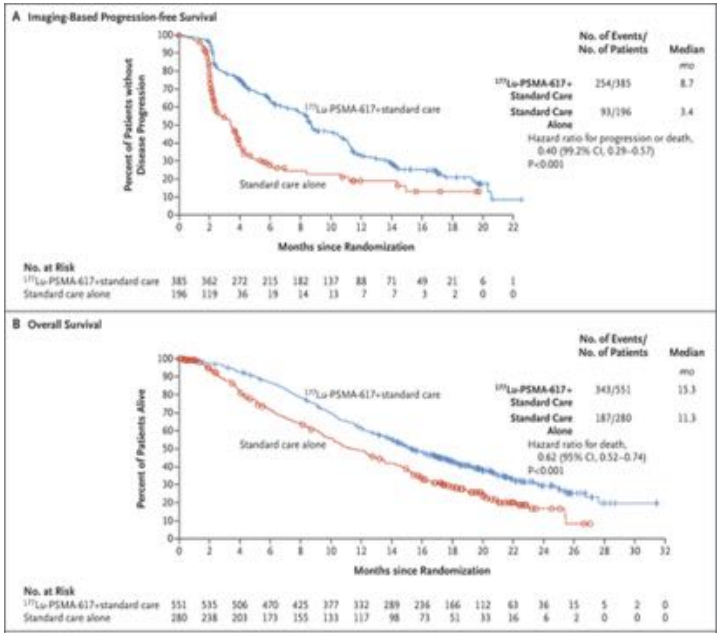


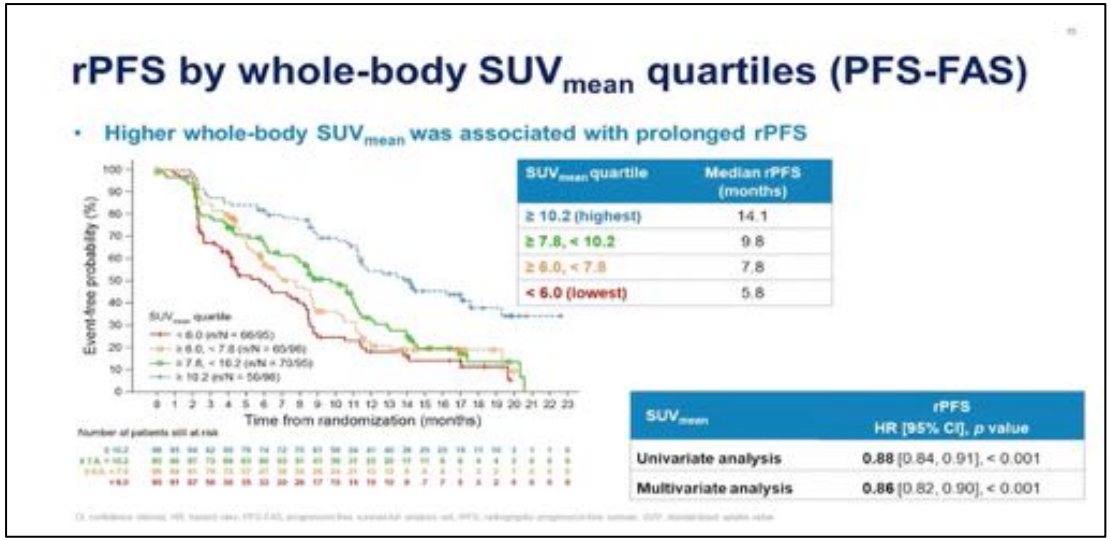

**Patients with mCRPC, regardless of HRR gene mutation status, received either abiraterone and olaparib or abiraterone and placebo in the first-line setting.**

Noel W. Clarke, et al. NEJM Evid; Volume 1(9):EVIDoa2200043, August 23, 2022

# Other upcoming treatment options in prostate cancer

## VISION

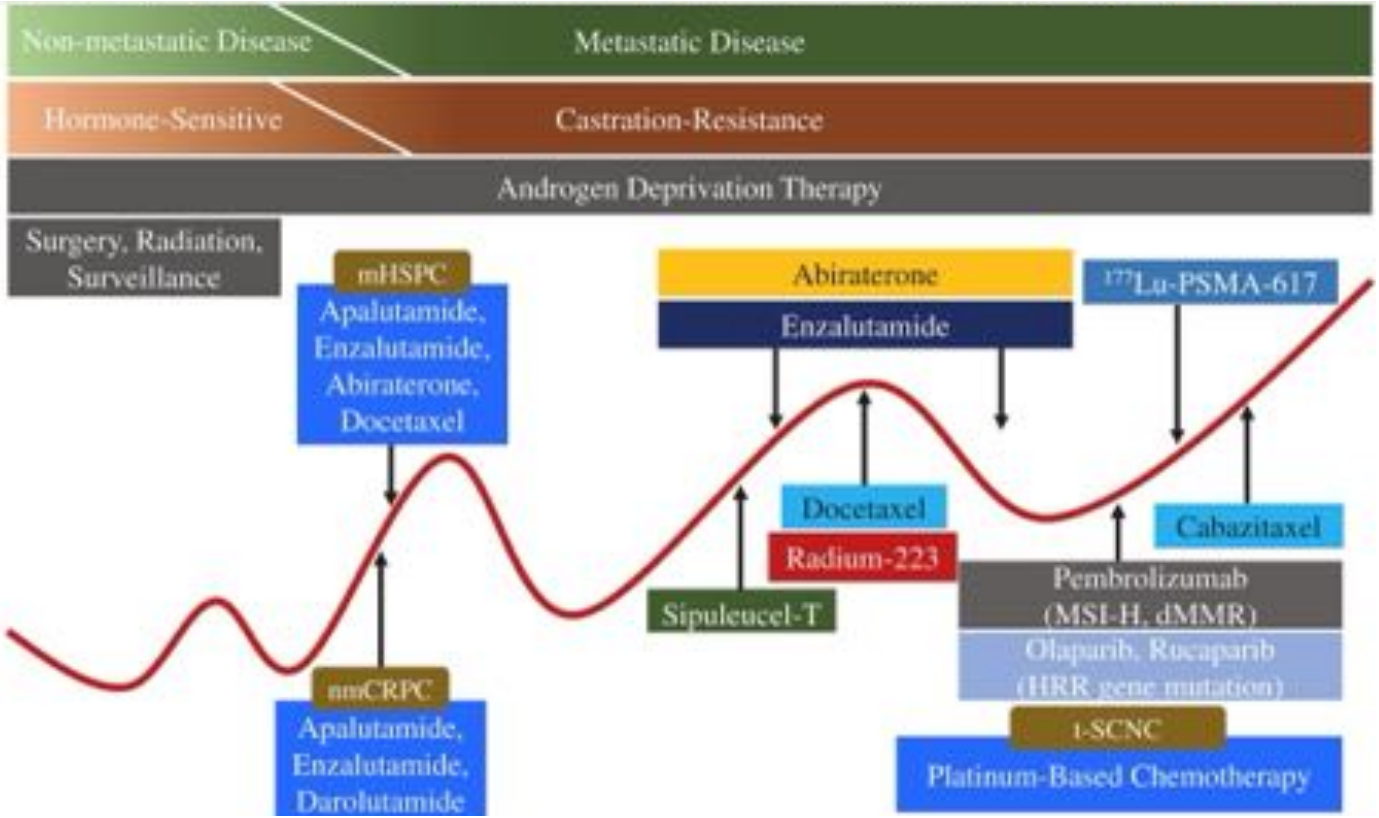



**177Lu-PSMA-617 in mCRPC**

O Sartor et al. N Engl J Med 2021;385:1091-1103.
Armstrong AJ et al. JCO. 2022

# Summary




Yasutaka Yamada, Himisha Beltran. Cancer Letters, 2021

Thank You!

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