Critical Review – Genitourinary Cancers

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Disclosures

- No pertinent C.O.I. with this presentation
- Advisory Boards/Honoraria/Consultant for:
  - BMS
  - Janssen
  - MSD
  - Pfizer
  - Roche

PROSTATE CANCER

ASCO NEWS IN PROSTATE CANCER

1. TITAN

2. ENZAMET (ANZUP 1304)

3. TOPARP-B

ASCO NEWS IN PROSTATE CANCER

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TITAN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

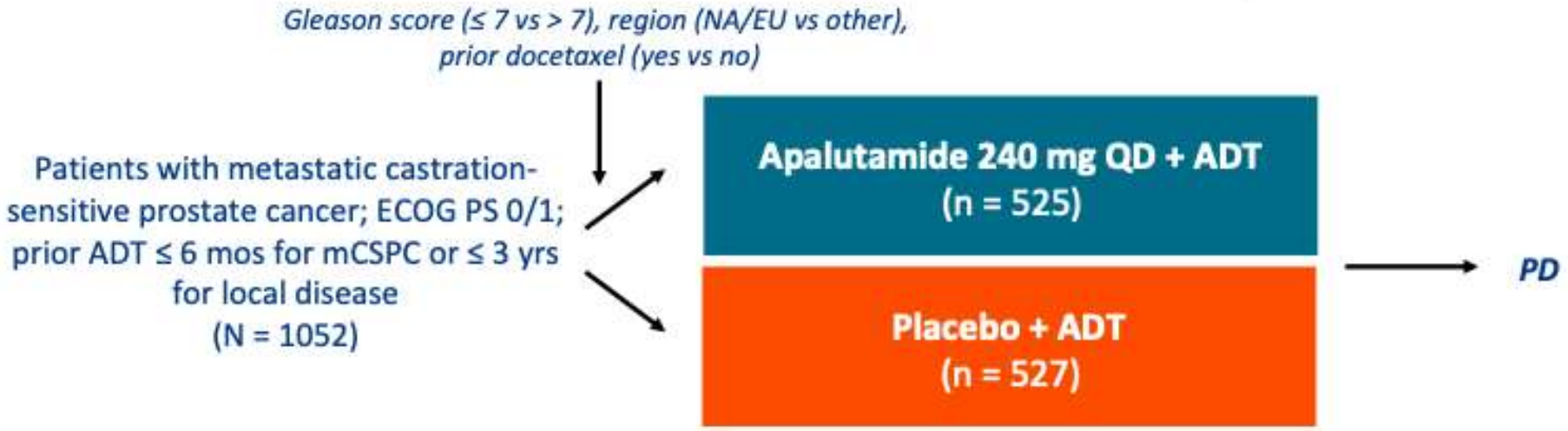
Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu, M.D., Hirotsugu Uemura, M.D., Dingwei Ye, M.D., Kris Deprince, M.D., Vahid Naini, Pharm.D., Jinhui Li, Ph.D., Shinta Cheng, M.D., Margaret K. Yu, M.D., Ke Zhang, Ph.D., Julie S. Larsen, Pharm.D., Sharon McCarthy, B.Pharm., and Simon Chowdhury, M.D., for the TITAN Investigators*

Chi et al NEJM 2019

TITAN – Study Design

- International, randomized, double-blind, placebo-controlled phase III trial



Primary endpoints: OS, radiographic PFS

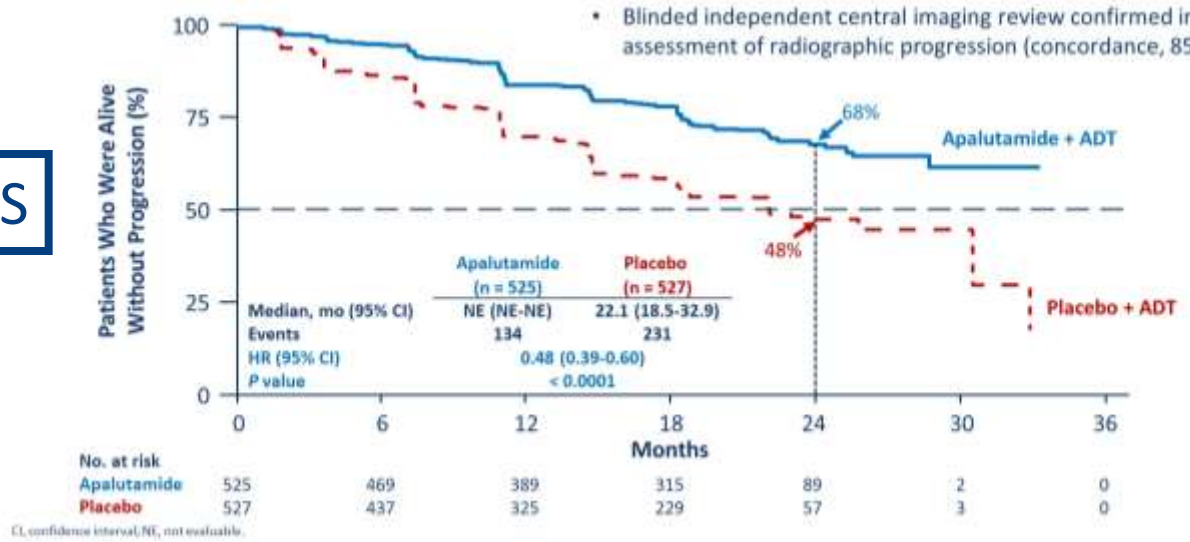
Secondary endpoints: time to pain progression, time to SRE, time to chronic opioid use, time to cytotoxic chemotherapy

Exploratory endpoints including: time to PSA progression, PFS2

Presented By Kim Chi at 2019 ASCO Annual Meeting

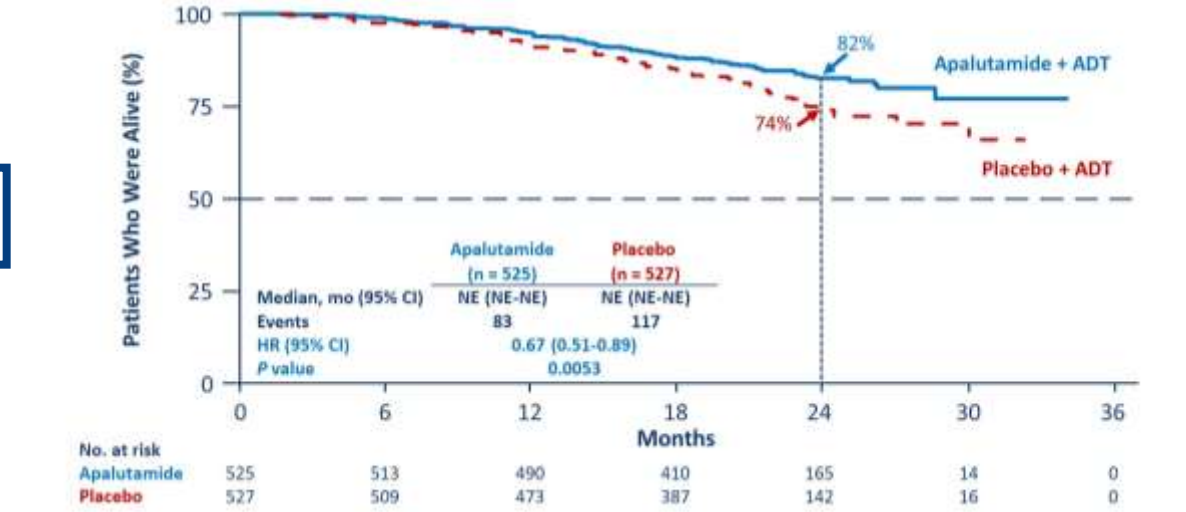
TITAN – Results

rPFS



Apalutamide significaIntly reduced risk of rPFS or death by 52%

OS



Apalutamide significaIntly reduced risk of death by 33%

Modified By Kim Chi at 2019 ASCO Annual Meeting

TITAN – Conclusions

- In patients with metastatic castration-sensitive prostate cancer, the addition of apalutamide to ADT significantly improved survival
  - rPFS: 52% reduction in risk of radiographic progression or death (HR: 0.48; 95% CI: 0.39-0.60; *P* < .0001)
  - OS: 33% reduction in risk of death (HR: 0.67; 95% CI: 0.51-0.89; *P* = .0053)
- Apalutamide in this setting also demonstrated prolonged time to initiation of cytotoxic chemotherapy and PSA progression and increased PFS2
- Apalutamide was well tolerated with adverse events consistent with previously reported data
- Investigators concluded that results support the addition of apalutamide to ADT for patients with metastatic castration-sensitive prostate cancer

Presented By Kim Chi at 2019 ASCO Annual Meeting

ASCO NEWS IN PROSTATE CANCER

1. TITAN

2. ENZAMET (ANZUP 1304)

3. TOPARP-B

ENZAMET

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

I.D. Davis, A.J. Martin, M.R. Stockler, S. Begbie, K.N. Chi, S. Chowdhury, X. Coskinas, M. Frydenberg, W.E. Hague, L.G. Horvath, A.M. Joshua, N.J. Lawrence, G. Marx, J. McCaffrey, R. McDermott, M. McJannett, S.A. North, F. Parnis, W. Parulekar, D.W. Pook, M.N. Reaume, S.K. Sandhu, A. Tan, T.H. Tan, A. Thomson, E. Tu, F. Vera-Badillo, S.G. Williams, S. Yip, A.Y. Zhang, R.R. Zielinski, and C.J. Sweeney, for the ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group*

Davis et al NEJM 2019

ENZAMET – Study Design

- Phase III, randomized, open-label, multicenter clinical trial

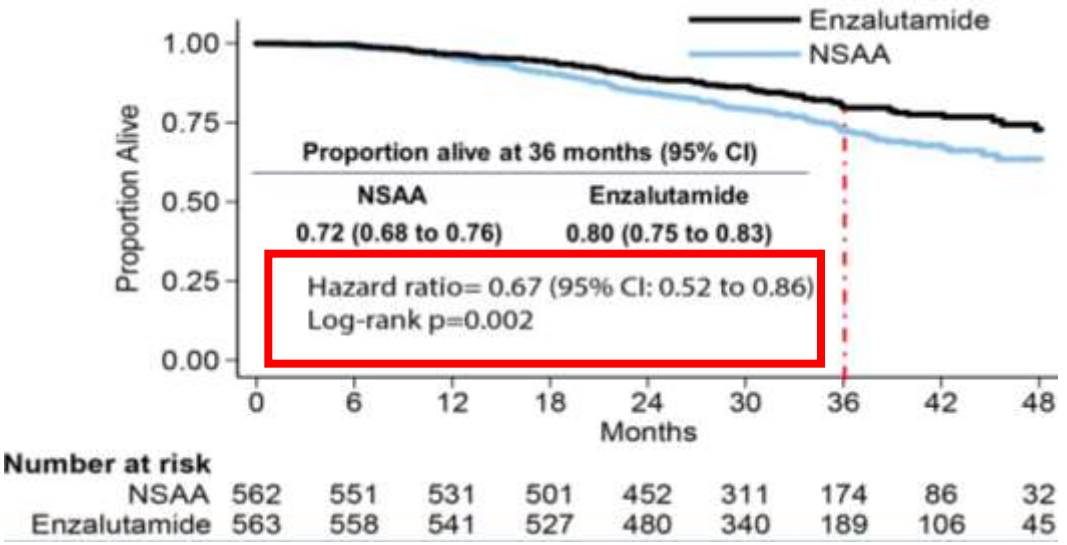
Stratified by volume of metastases (high vs low), antiresorptive therapy (yes vs no), ECOG PS (0/1 vs 2), comorbidities (ACE-27: 0/1 vs 2/3), study site, planned use of early docetaxel (yes vs no)

- Primary endpoint: OS
- Secondary endpoints: PSA PFS (including clinical progression if occurring first), clinical PFS, AEs, HRQoL

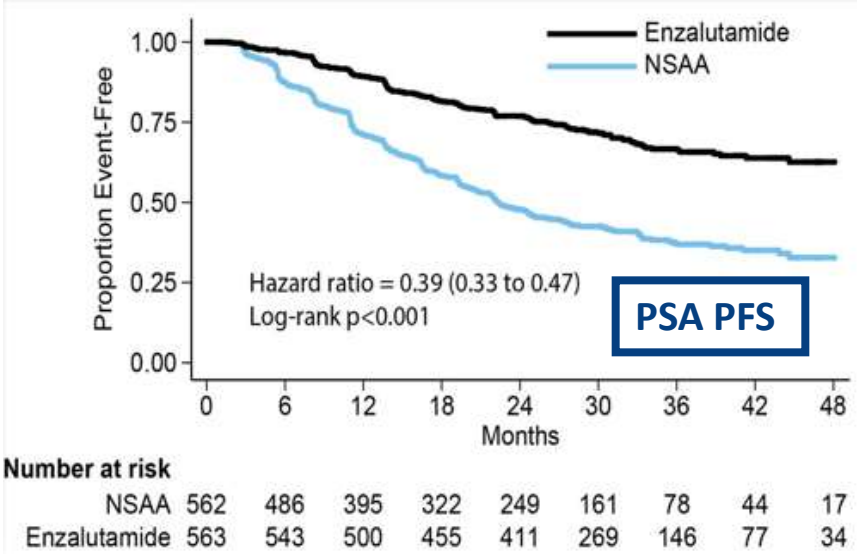
Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

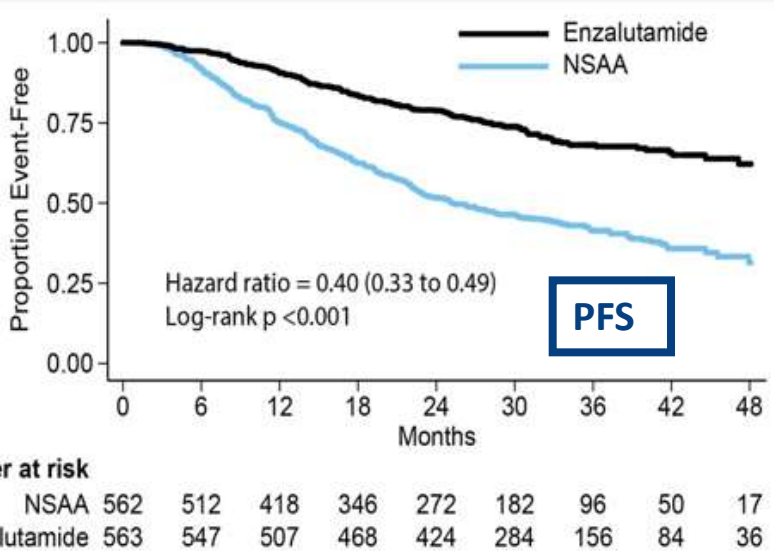
ENZAMET – Results

Primary endpoint: OS



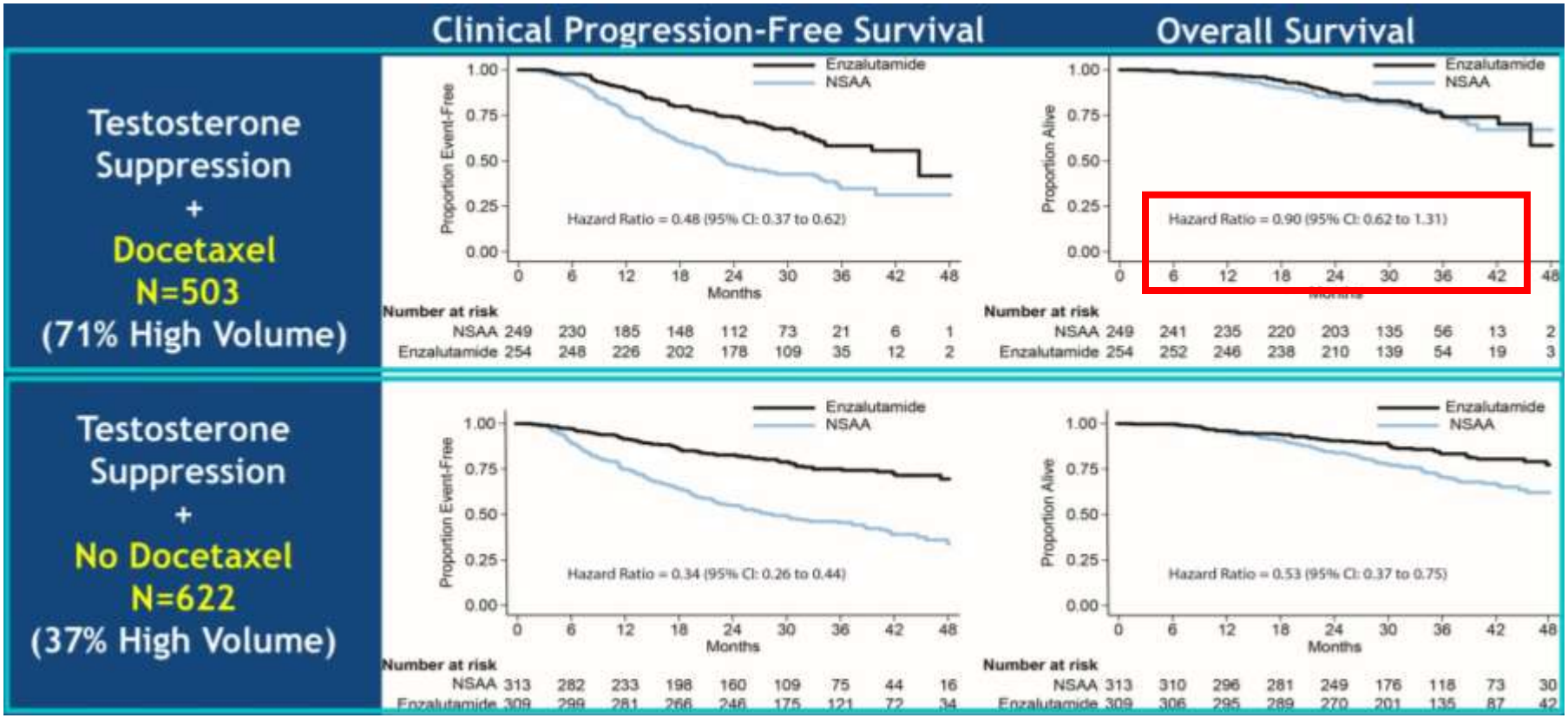
Secondary endpoint: PFS (PCWG2)





Modified By Christopher Sweeney at 2019 ASCO Annual Meeting

ENZAMET – Concurrent Docetaxel



Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

ENZAMET – Conclusions

- Enzalutamide demonstrated improved survival compared with standard NSAA in patients with mHSPC
  - 36-mo OS: 80% for enzalutamide vs 72% for NSAA (HR: 0.67; *P* = .002)
  - Similar OS benefit in patients with low and high volume of metastases
- Increased toxicity was shown with the addition of enzalutamide, as expected
  - Patients who were also treated with docetaxel experienced more chemotherapy-related toxicity
- The study investigators concluded that enzalutamide is an appropriate option for men with mHSPC starting on ADT

Davis et al NEJM 2019

Sweeney C 2019 ASCO Annual Meeting

Progress in Management of mHSPC

- 2015 paradigm shift → Docetaxel upfront
  - ADT + Docetaxel in newly diagnosed M1 disease (CHAARTED[1], STAMPEDE[2])

EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018 (http://uroweb.org)

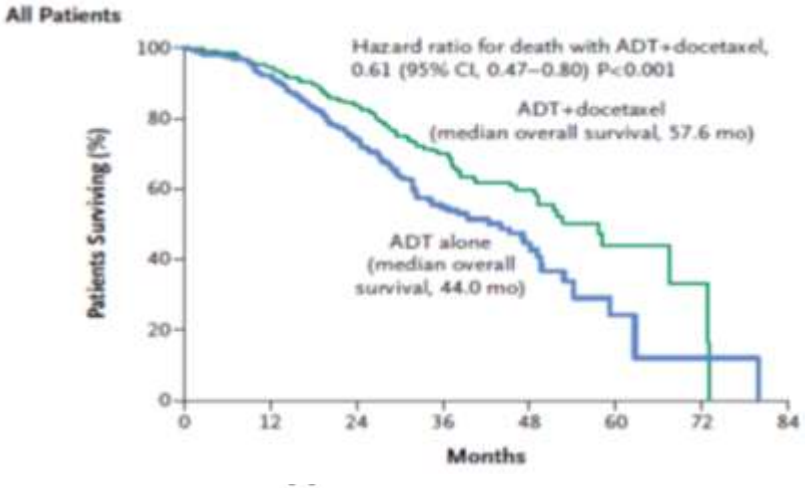
1. Sweeney et al NEJM 2015; 373:737
2. James et al Lancet 2016; 387:1163
3. Fizazi et al NEJM 2017; 377:352
4. James et al NEJM 2017; 377:338
5. Chi et al NEJM 2019
6. Armstrong et al ASCO GU abstr#687
7. Davis et al NEJM 2019

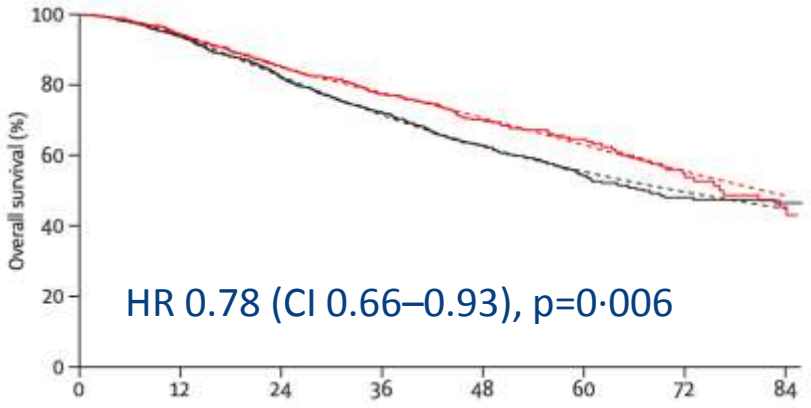
DOCETAXEL

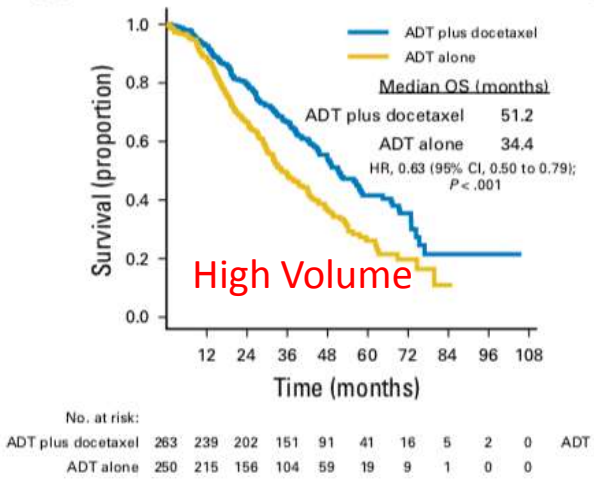
CHARTEED[1]

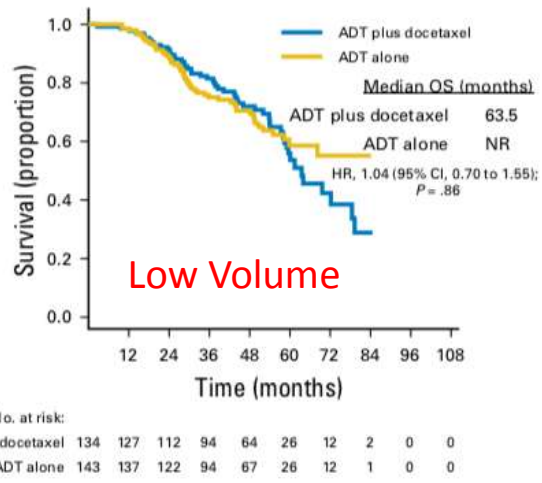
OS

STAMPEDE[2]









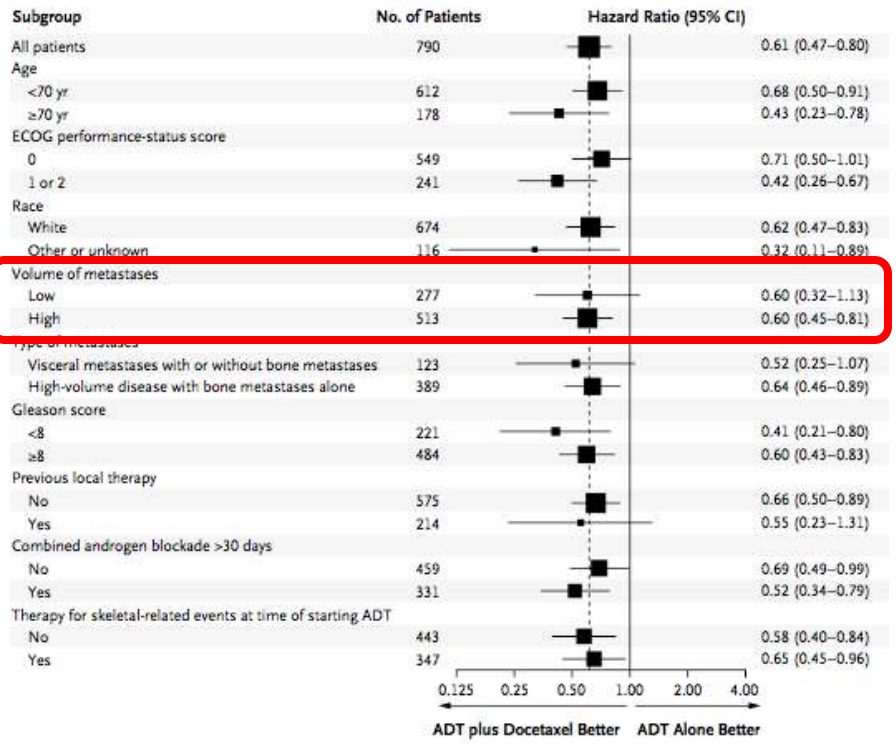
1. Sweeney NEJM 2015;373:737
2. James et al Lancet 2016; 387:1163
3. Kyriakopoulos CE et al. J Clin Oncol 2018;36(11):1080–7

DOCETAXEL - CHARTEED

Table 1. Baseline Characteristics of the Patients.*

Characteristic	ADT plus Docetaxel (N=397)	ADT Alone (N=393)
Age — yr		
Median	64	63
Range	36–88	39–91
Race — no. (%)†		
White	344 (86.6)	330 (84.0)
Black	39 (9.8)	37 (9.4)
Other	4 (1.0)	6 (1.5)
Unknown	10 (2.5)	20 (5.1)
ECOG performance status — no. (%)‡		
0	277 (69.8)	272 (69.2)
1	114 (28.7)	115 (29.3)
2	6 (1.5)	6 (1.5)
Volume of metastases — no. (%)§		
Low	134 (33.8)	143 (36.4)
High	263 (66.2)	250 (63.6)
Visceral metastases — no. (%)	57 (14.4)	66 (16.8)
Gleason score — no. (%)¶		
4–6	21 (5.3)	21 (5.3)
7	96 (24.2)	83 (21.1)
8–10	241 (60.7)	243 (61.8)
Unknown	39 (9.8)	46 (11.7)
PSA level at start of ADT — ng/ml		
Median	50.9	52.1
Range	0.2–8540.1	0.1–8056.0
Prior treatment for prostate cancer — no. (%)		
No local therapy	289 (72.8)	286 (72.8)
Primary radiation	27 (6.8)	33 (8.4)
Prostatectomy	81 (20.4)	73 (18.6)
Missing data	0	1 (0.3)
Adjuvant ADT — no. (%)	18 (4.5)	16 (4.1)
Time from start of ADT to randomization — mo‖		
Median	1.2	1.3
Range	0.03–3.9	0.03–3.9
No ADT before randomization — no. (%)	51 (12.8)	52 (13.2)

High volume:
-Visceral mets and/or
-≥ 4 bone mets (at least 1 beyond pelvis and vertebral column)



Sweeney NEJM 2015;373:737

Progress in Management of mHSPC

- 2015 paradigm shift → Docetaxel upfront
  - ADT + Docetaxel in newly diagnosed M1 disease (CHAARTED[1], STAMPEDE[2])
- 2017 → Abiraterone acetate upfront
  - ADT + Abiraterone in newly diagnosed M1 disease (LATITUDE[3], STAMPEDE[4])

EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018 (http://uroweb.org)

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5. Chi et al NEJM 2019
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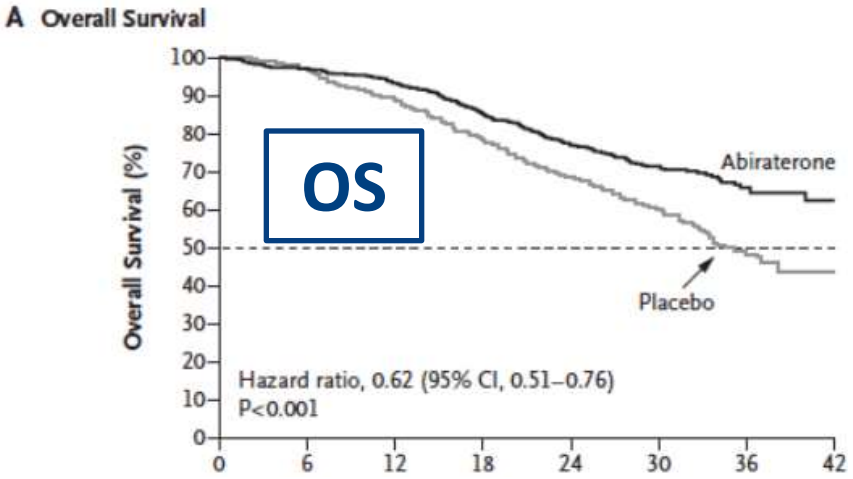
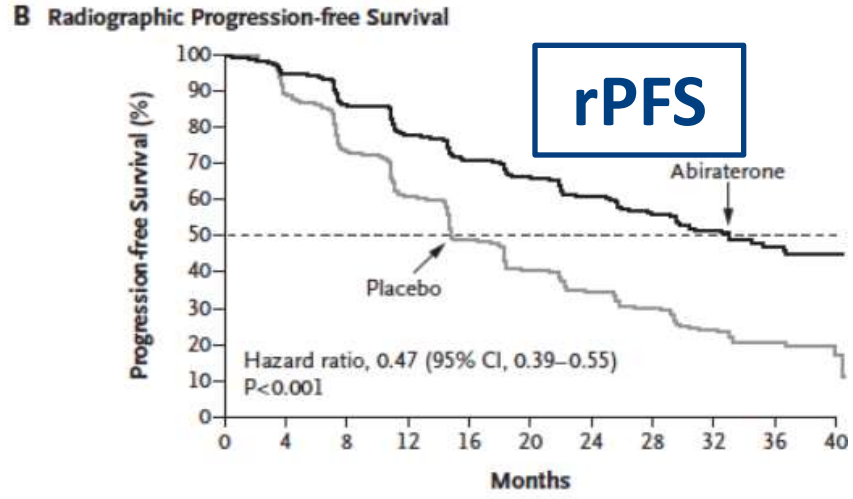
7. Davis et al NEJM 2019

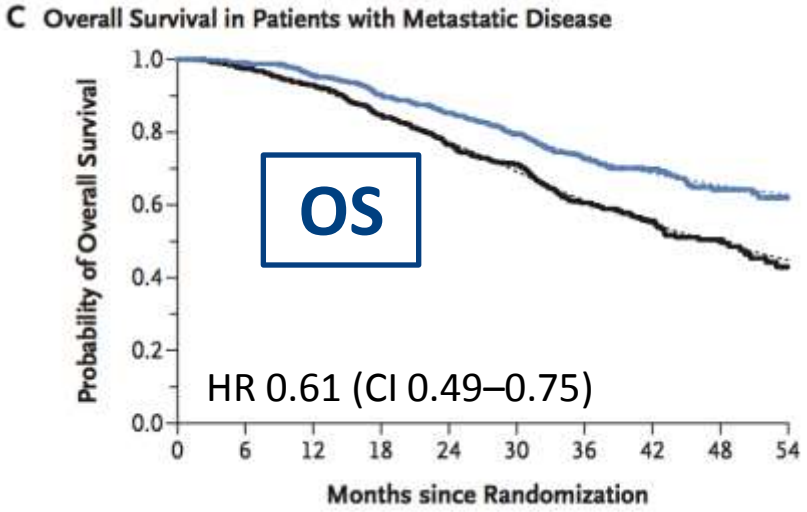
ABIRATERONE

LATITUDE[1]





STAMPEDE[2]



1. Fizazi et al NEJM 2017; 377:352
2. James et al NEJM 2017; 377:338

ABIRATERONE

LATITUDE[1]

	Abiraterone Group (n=597)	Placebo Group (n=602)
Age (yr), n (%)		
n	597	602
<65	221 (37)	233 (39)
65–69	112 (19)	134 (22)
70–74	141 (24)	115 (19)
≥75	123 (21)	120 (20)
Median	68.0	67.0
Range	38–89	33–92
Gleason score at initial diagnosis, n (%)		
n	597	602
<7	4 (0.7)	1 (0.2)
7	9 (2)	15 (2)
≥8	584 (98)	586 (97)
Baseline pain score (BPI-SF Item 3), n (%)		
n	570	579
0–1	284 (50)	288 (50)
2–3	123 (22)	137 (24)
≥4	163 (29)	154 (27)
Patients with ≥3 bone metastases at screening, n/N (%)	580/597 (98.2)	585/602 (97.2)
Patients with high risk at screening, n (%)		
n	597	601
Gleason score ≥8 + ≥3 bone lesions	573 (96)	569 (95)
Gleason score ≥8 + measurable visceral disease	82 (14)	87 (14)
≥3 bone lesions + measurable visceral disease	84 (14)	85 (14)
Gleason score ≥8 + ≥3 bone lesions + measurable visceral disease	71 (12)	70 (12)
Extent of disease, n (%)		
n	596	600
Bone	580 (97)	585 (98)
Liver	32 (5)	30 (5)
Lungs	73 (12)	72 (12)
Node	283 (47)	287 (48)
Prostate mass	151 (25)	154 (26)
Viscera	18 (3)	13 (2)
Soft tissue	9 (2)	15 (3)
Other	2 (0.3)	0
Patients with previous prostate cancer therapy, n (%)		
n	560	560

STAMPEDE[2]

Table 1. Characteristics of the Patients.*

Characteristic	ADT Alone (N=957)	Combination Therapy (N=960)
Age at randomization — yr		
Median (IQR)	67 (62 to 72)	67 (63 to 72)
Range	39 to 84	42 to 85
PSA level before ADT — ng/ml		
Median (IQR)	56 (19 to 165)	51 (19 to 158)
Range	0 to 10,530	0 to 21,460
WHO performance status — no. (%)†		
0	744 (78)	745 (78)
1 or 2	213 (22)	215 (22)
Disease group — no. (%)		
Newly diagnosed node-negative, nonmetastatic disease	256 (27)	253 (26)
Newly diagnosed node-positive, nonmetastatic disease	187 (20)	182 (19)
Newly diagnosed metastatic disease	476 (50)	465 (48)
Previously treated nonmetastatic disease	12 (1)	25 (3)
Previously treated metastatic disease	26 (3)	35 (4)
Gleason score — no. (%)‡		
≤7	223 (23)	221 (23)
8 to 10	721 (75)	715 (74)
Unknown	13 (1)	24 (2)
Planned or current long-term ADT — no. (%)		
Orchiectomy	5 (1)	3 (<1)
Bicalutamide	5 (1)	5 (1)
Dual androgen blockade	4 (<1)	1 (<1)
LHRH-based§	943 (99)	951 (99)
Time to initiation of ADT from randomization — days¶		
Median (IQR)	−45 (−67 to −23)	−44 (−63 to −24)
Range	−85 to 39	−85 to 28
Planned antiandrogen use — no. (%)		
No	50 (5)	61 (6)
Short-term antiandrogen	902 (94)	895 (93)
Long-term antiandrogen	5 (1)	4 (<1)
Radiotherapy planned — no. (%)‖		
No	561 (59)	564 (59)
Yes	396 (41)	396 (41)
Hypertension — no. (%)		
No	571 (60)	557 (58)
Yes, but still fit for trial	385 (40)	401 (42)
Cardiovascular assessment not received	1 (<1)	2 (<1)

1. Fizazi et al NEJM 2017; 377:352
2. James et al NEJM 2017; 377:338

Progress in Management of mHSPC

- 2015 paradigm shift → Docetaxel upfront
  - ADT + Docetaxel in newly diagnosed M1 disease (CHAARTED[1], STAMPEDE[2])
- 2017 → Abiraterone acetate upfront
  - ADT + Abiraterone in newly diagnosed M1 disease (LATITUDE[3], STAMPEDE[4])
- 2019 ASCO GU and ASCO → Apalutamide, Enzalutamide
  - TITAN: Apalutamide[5]
  - ARCHES: Enzalutamide[6]
  - ENZAMET: Enzalutamide[7]

EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018 (http://uroweb.org)

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5. Chi et al NEJM 2019
6. Armstrong et al ASCO GU abstr#687
7. Davis et al NEJM 2019

APALUTAMIDE - TITAN

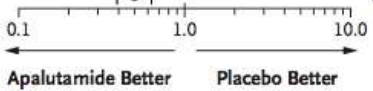
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Apalutamide (N=525)	Placebo (N=527)
Median age (range) — yr	69 (45–94)	68 (43–90)
ECOG performance-status score — no. (%)†		
0	328 (62.5)	348 (66.0)
1	197 (37.5)	178 (33.8)
2	0	1 (0.2)
Gleason score at initial diagnosis — no. (%)‡		
<7	41 (7.8)	39 (7.4)
7	133 (25.3)	130 (24.7)
>7	351 (66.9)	358 (67.9)
Metastatic stage at initial diagnosis — no. (%)		
M0	85 (16.2)	59 (11.2)
M1	411 (78.3)	441 (83.7)
MX	29 (5.5)	27 (5.1)
Disease volume — no. (%)		
Low	200 (38.1)	192 (36.4)
High	325 (61.9)	335 (63.6)
Previous treatment with docetaxel — no. (%)§	58 (11.0)	55 (10.4)
Previous therapy for localized prostate cancer — no. (%)¶	94 (17.9)	79 (15.0)
Median prostate-specific antigen level (range) — μg/liter	5.97 (0–2682)	4.02 (0–2229)

DISEASE VOLUME → CHAARTED:

High volume:
-Visceral mets and/or
-≥ 4 bone mets (at least 1 beyond pelvis and vertebral column)

Previous docetaxel use					
Yes	10/58	19/55	NE	22.1	0.47 (0.22–1.01)
No	124/467	212/472	NE	22.0	0.49 (0.39–0.62)
Age					
<65 yr	40/149	85/182	NE	18.4	0.45 (0.31–0.66)
65–74 yr	61/243	105/232	NE	22.0	0.47 (0.34–0.64)
≥75 yr	33/133	41/113	NE	32.9	0.65 (0.41–1.03)
Baseline PSA above median					
Yes	92/285	119/241	NE	15.4	0.51 (0.39–0.67)
No	42/240	112/286	NE	30.5	0.39 (0.27–0.56)
Baseline LDH above ULN					
Yes	21/60	30/60	22.4	14.6	0.57 (0.33–1.00)
No	109/443	191/442	NE	23.0	0.48 (0.38–0.61)
Baseline ALP above ULN					
Yes	69/177	98/180	22.4	14.7	0.54 (0.40–0.74)
No	64/346	133/345	NE	30.5	0.42 (0.31–0.57)
Disease volume					
High	109/325	173/335	NE	14.9	0.53 (0.41–0.67)
Low	25/200	58/192	NE	30.5	0.36 (0.22–0.57)
Metastasis stage at initial diagnosis					
M0	17/85	23/59	NE	NE	0.41 (0.22–0.78)
M1	108/411	196/441	NE	22.0	0.49 (0.39–0.63)



Chi et al NEJM 2019

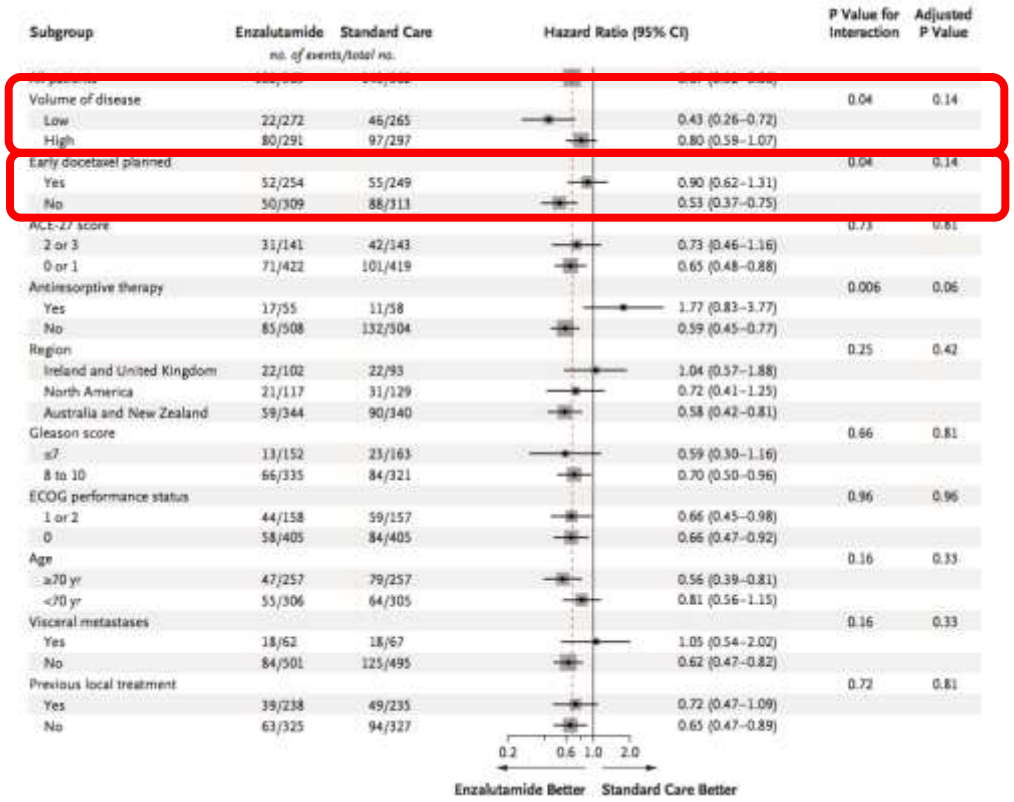
ENZALUTAMIDE - ENZAMET

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Enzalutamide (N=563)	Standard Care (N=562)
Age — yr		
Mean	68.9±8.1	68.8±8.3
Median (IQR)	69.2 (63.2–74.5)	69.0 (63.6–74.5)
Planned use of early docetaxel — no. (%)	254 (45)	249 (44)
Volume of disease — no. (%)		
High	291 (52)	297 (53)
Low	272 (48)	265 (47)
Visceral metastases — no. (%)	62 (11)	67 (12)
No. of months since diagnosis of metastasis		
Mean	2.9±6.9	3.1±7.2
Median (IQR)	1.9 (0.9–2.8)	1.9 (1.0–2.8)
Gleason score — no. (%)†		
≤7	152 (27)	163 (29)
8–10	335 (60)	321 (57)
Missing data	76 (13)	78 (14)
Previous therapy — no. (%)		
Adjuvant androgen-deprivation therapy	58 (10)	40 (7)
Antiandrogen therapy‡	285 (51)	316 (56)
LHRHA‡	411 (73)	418 (74)
Bilateral orchiectomy	5 (1)	8 (1)
Docetaxel‡	95 (17)	83 (15)

DISEASE VOLUME → CHAARTED:

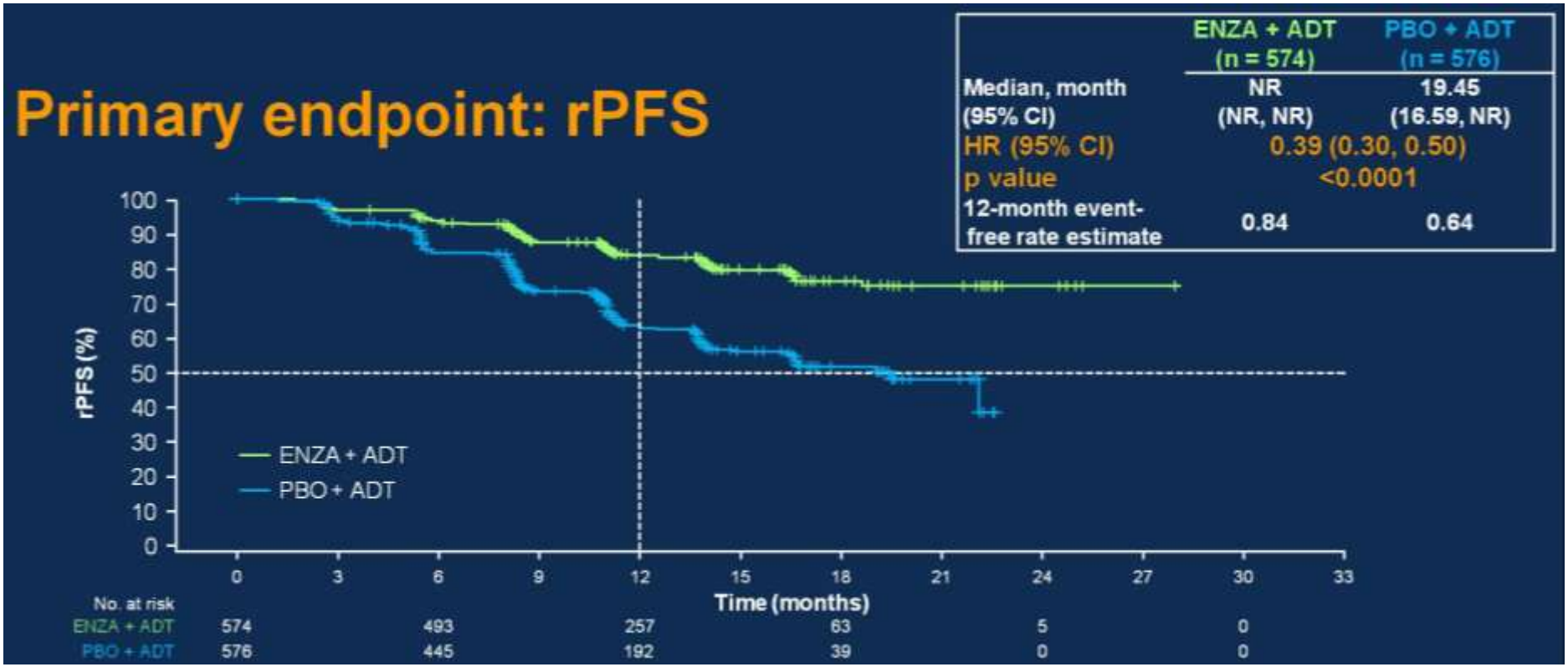
High volume:
-Visceral mets and/or
-≥ 4 bone mets (at least 1 beyond pelvis and vertebral column)



Davis et al NEJM 2019

ENZALUTAMIDE - ARCHES

rPFS



Armstrong et al ASCO GU abstr#687

HOW TO CHOOSE BETWEEN UP-FRONT TREATMENTS IN mHSPC

	DOCETAXEL	ABIRATERONE	ENZALUTAMIDE APALUTAMIDE
Duration of treatment	➢ Short term treatment	➢ Long term treatment	➢ Long term treatment
Toxicities	➢ Peripheral neuropathy, hair loss	➢ Liver enzymes, electrolytes	➢ CNS (seizure), falls
Corticosteroids	➢ Use of corticosteroids	➢ Use of corticosteroids	➢ No use of corticosteroids
Setting	➢ High volume	➢ Any	➢ Any

TREATMENT OPTIONS IN mHSPC

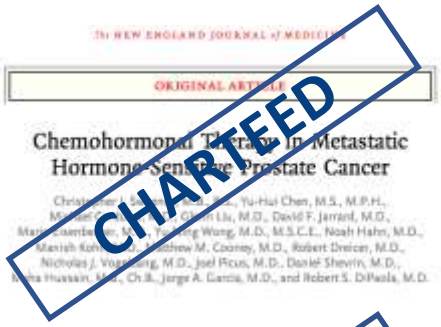
DOCETAXEL

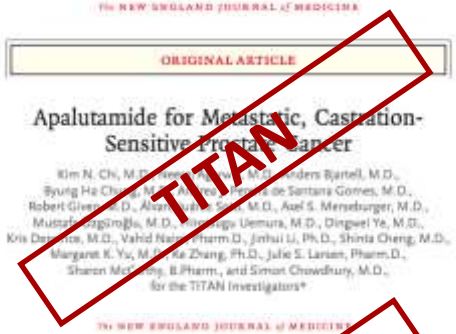
ABIRATERONE

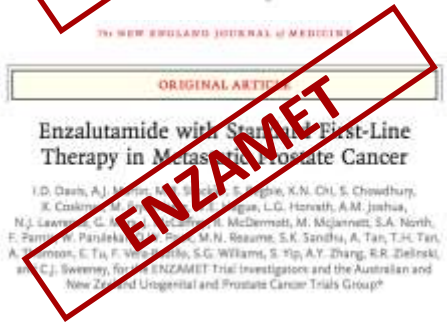
ENZALUTAMIDE

APALUTAMIDE

2015 → 2017 → 2019







ASCO NEWS IN PROSTATE CANCER

1. TITAN

2. ENZAMET (ANZUP 1304)

3. TOPARP-B

TOPARP-B

TOPARP-B: A Phase II Randomized Trial of the Poly(ADP)-Ribose Polymerase (PARP) Inhibitor Olaparib for Metastatic Castration Resistant Prostate Cancers (mCRPC) with DNA Damage Repair (DDR) Alterations.

Joaquin Mateo, Nuria Porta, Ursula Brigid McGovern, Tony Elliott, Robert J Jones, Isabel Syndikus, Christy Ralph, Suneil Jain, Mohini Anna Varughese, Omi Parikh, Simon J. Crabb, Susana Miranda, George Seed, Claudia Bertan, Aude Espinasse, Peter Chatfield, Diletta Bianchini, Emma Hall, Suzanne Carreira, Johann S. De Bono

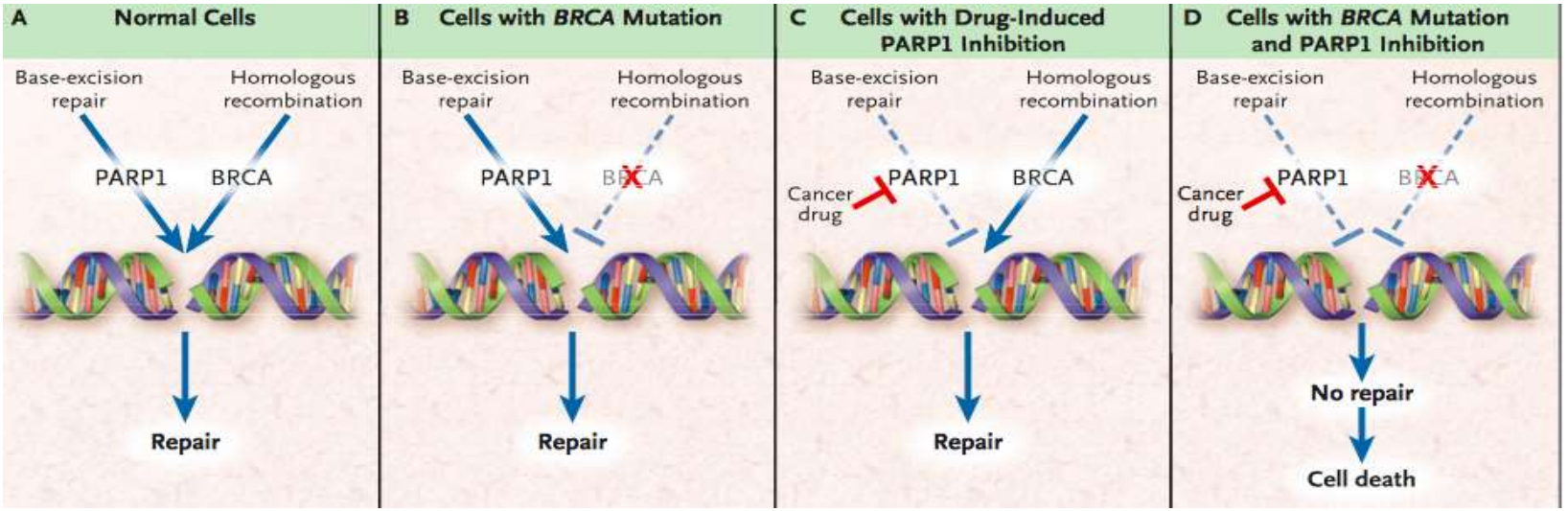
An investigator-initiated trial on behalf of the TOPARP investigators

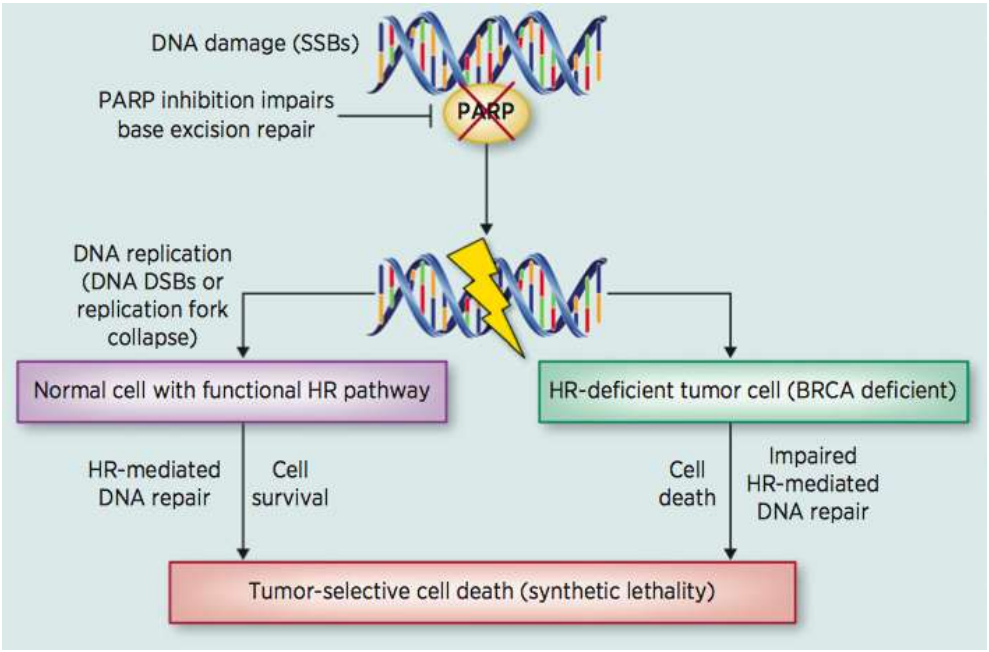
ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

Presented By Joaquin Mateo at 2019 ASCO Annual Meeting

BACKGROUND: DNA repair defects – Predictive Value





PARP inhibitor

- **PARP1 mediates:**
- DNA repair responses to alkylating agents
- Cellular survival in BRCA deficient cells
- AR-dependent prostate cancer cellular proliferation

Banerjee et al. Nat Rev Clin Oncol 2010;7:508–19
Feng et al. Mol Cell. 2015;58(6):925-34.

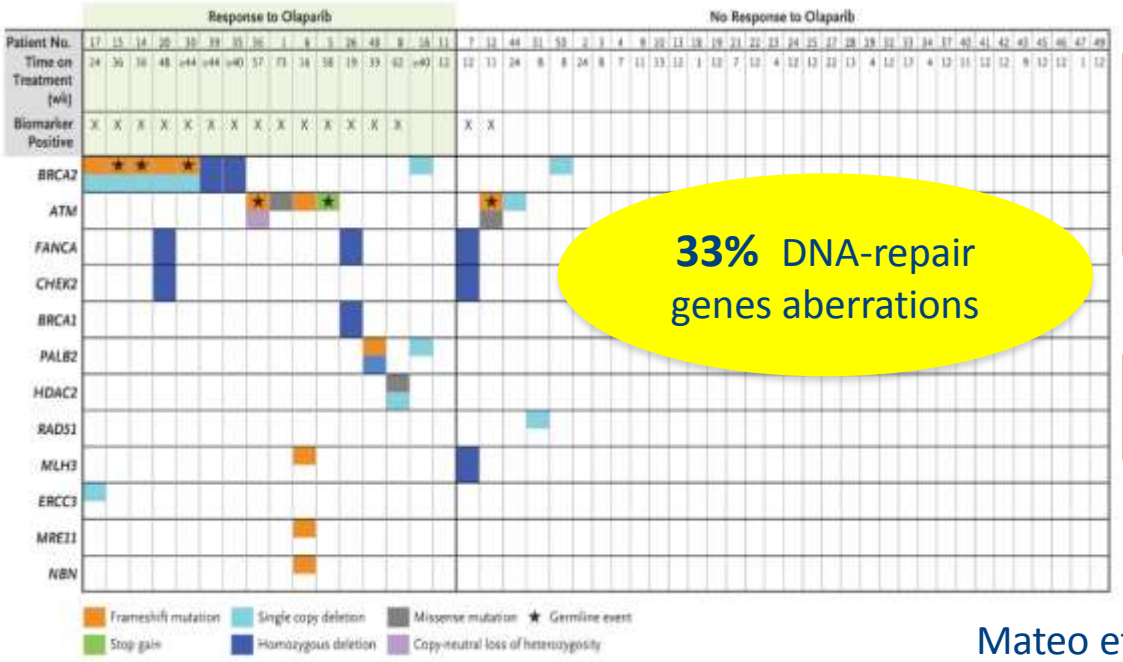
BACKGROUND: DNA repair defects – TOPARP-A

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

TOPARP-A was an open-label, single-group, two-stage, phase 2, multisite study, designed to **investigate the the activity of the PARPi Olaparib in mCRPCs with DNA-repair defects**



33% DNA-repair genes aberrations

- **Response Rate 33%**
- ≥50% Reductions in the PSA level 22%
- Reduction in CTC count 29%
- Radiologic partial response 19%

- **RR 88% in biomarker-positive** vs 6% in biomarker-negative pts

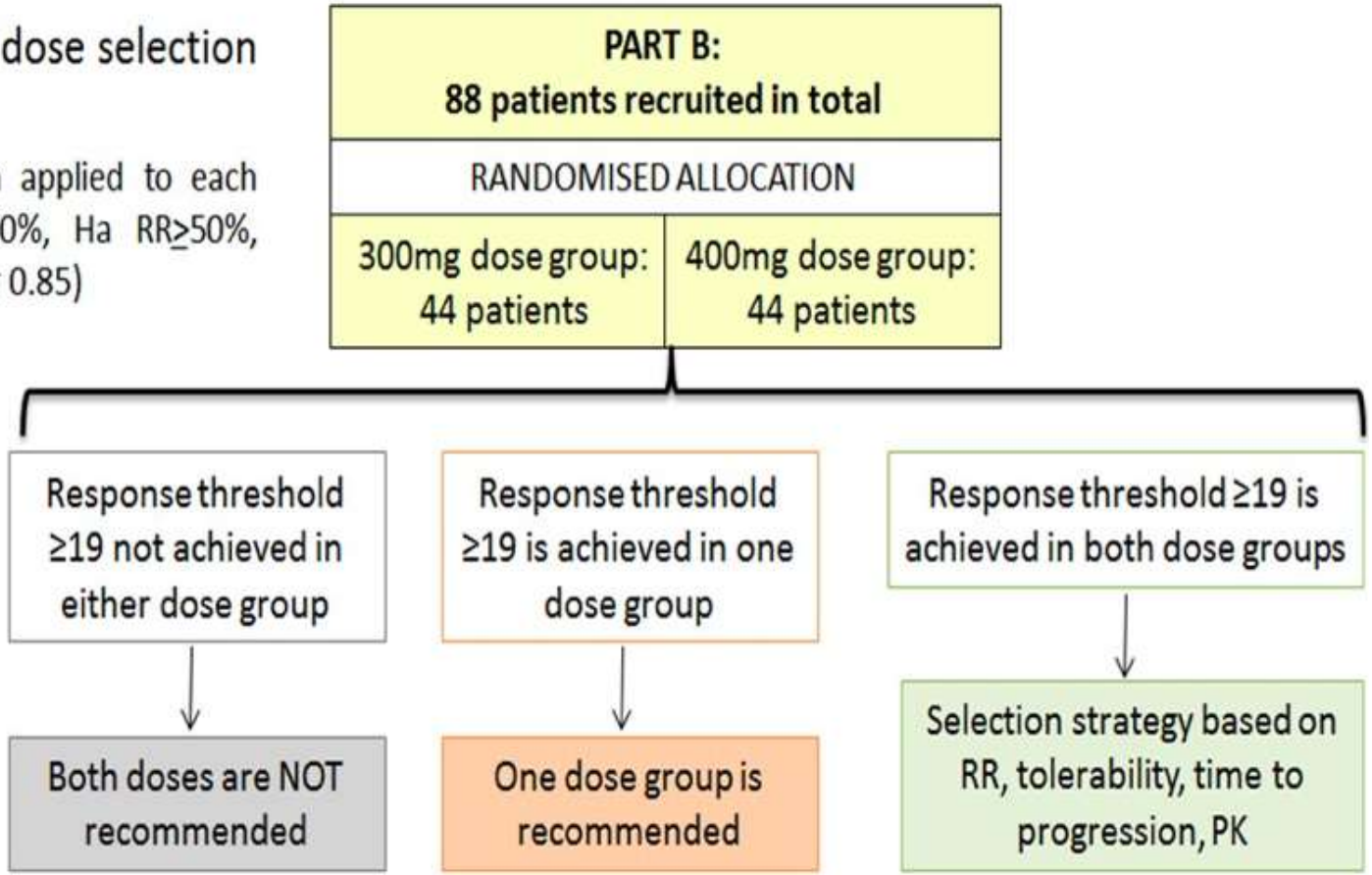
Mateo et al. N Engl J Med. 2015, 373(18):1697-1708

TOPARP-B

mCRPC after at least 1 but not more than 2 lines of taxane-based chemotherapy

Part B: optimal dose selection

1-stage approach applied to each group (Ho RR≤30%, Ha RR≥50%, alpha 0.05, power 0.85)



Modified By Joaquin Mateo at 2019 ASCO Annual Meeting

TOPARP-B – Results

Results: primary endpoint analyses (n=92)

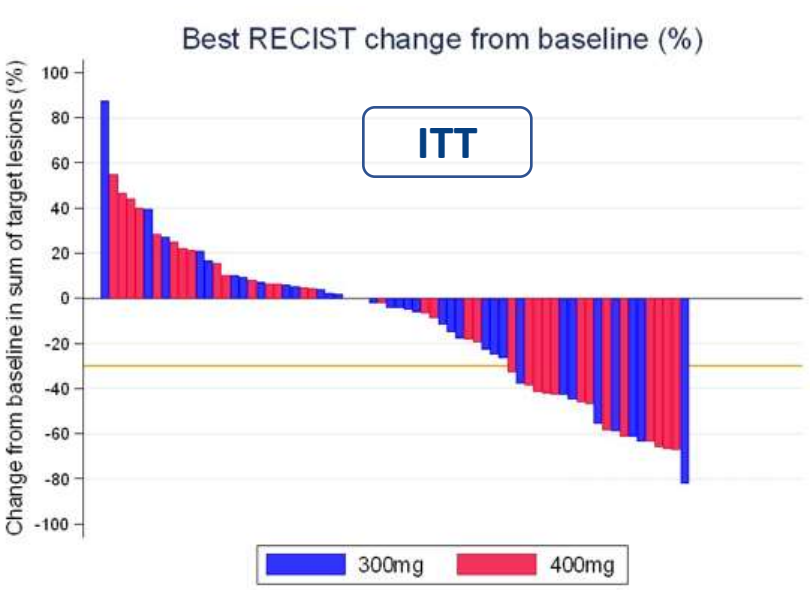
	Total (n=92)			Dose group					
				300mg (n=46)			400mg (n=46)		
	resp/n	%	95% CI	resp/n	%	95% CI	resp/n	%	95% CI
Composite Response (confirmed)	**43/92**	**46.7%**	**36.3-57.4**	**18/46**	**39.1%**	**25.1-54.6**	**25/46**	**54.3%**	**39.0-69.1**
RECIST Response	14/70	20.0%	11.4-31.3	6/37	16.2%	6.2-32.0	8/33	24.2%	11.1-42.3
PSA Response ≥50%	30/89	33.7%	24.0-44.5	13/43	30.2%	17.2-46.1	17/46	37.0%	23.2-52.5
CTC conversion	28/55	50.9%	37.1-64.6	13/27	48.1%	28.7-68.1	15/28	53.6%	33.9-72.5
RECIST / PSA response	32/92	34.8%	25.1-45.4	13/46	28.3%	16.0-43.5	19/46	41.3%	27.0-56.8

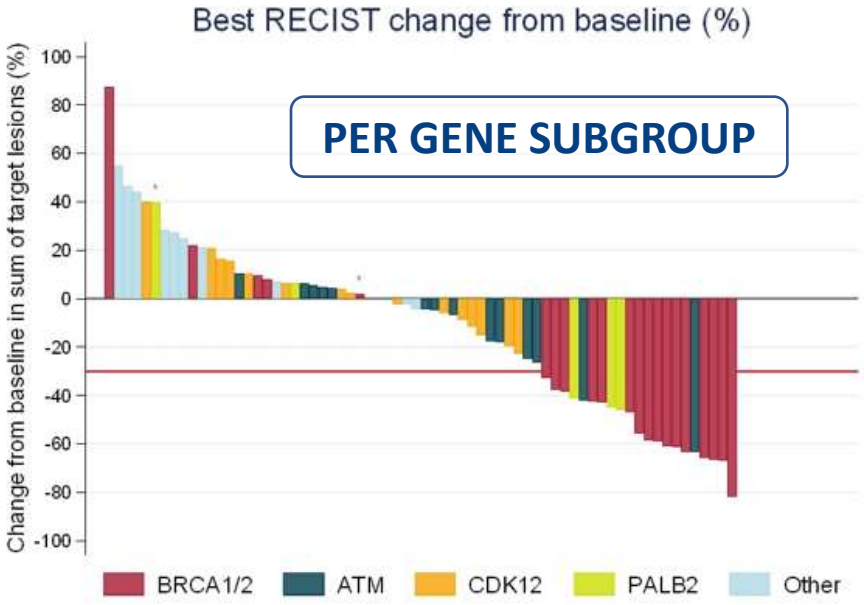
Results: primary endpoint per gene subgroup (n=92)

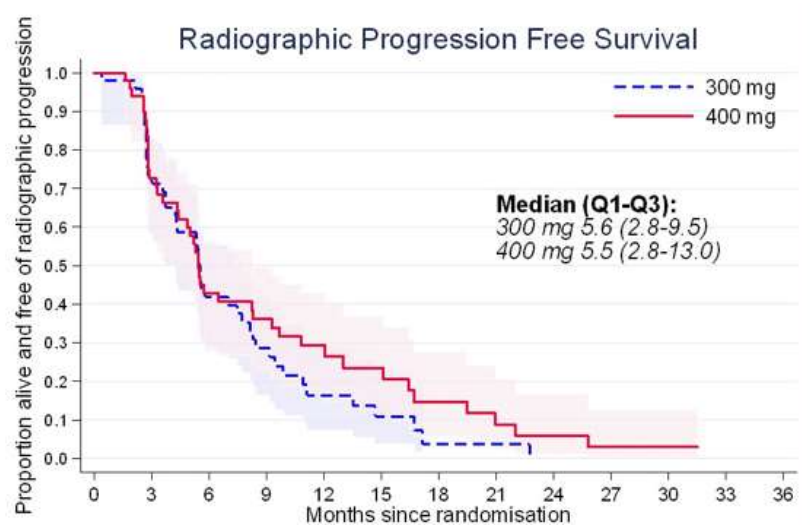
	Group 1: **BRCA1/2 (n=30)**		Group 2: **ATM (n=19)**		Group 3: **CDK12 (n=20)**		Group 4: **PALB2 (n=7)**		Group 5: **Other (n=20)**	
	resp/n	%	resp/n	%	resp/n	%	resp/n	%	resp/n	%
Composite Response (confirmed)	**25/30**	**83.3%**	**7/19**	**36.8%**	**5/20**	**25.0%**	**4/7**	**57.1%**	**4/20**	**20.0%**
RECIST Objective Response	11/21	52.4%	1/12	8.3%	0/18	0.0%	2/6	33.3%	0/17	0.0%
PSA response ≥50%	23/30	76.7%	1/19	5.3%	0/20	0.0%	4/6	66.7%	2/17	11.8%
CTC conversion	17/22	77.3%	5/10	50.0%	5/12	41.7%	0/2	0.0%	3/11	27.3%
RECIST / PSA response	24/30	80.0%	2/19	10.5%	0/20	0.0%	4/7	57.1%	2/20	10.0%

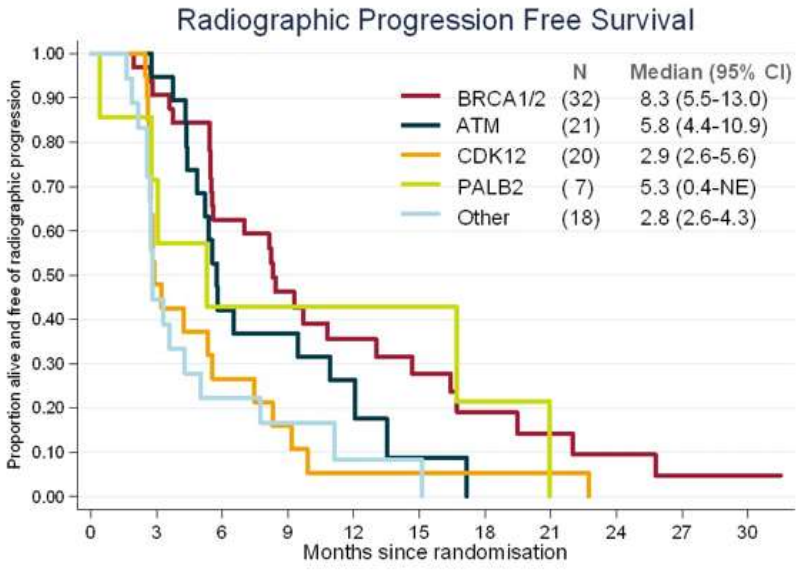
Modified By Joaquin Mateo at 2019 ASCO Annual Meeting

TOPARP-B – Results



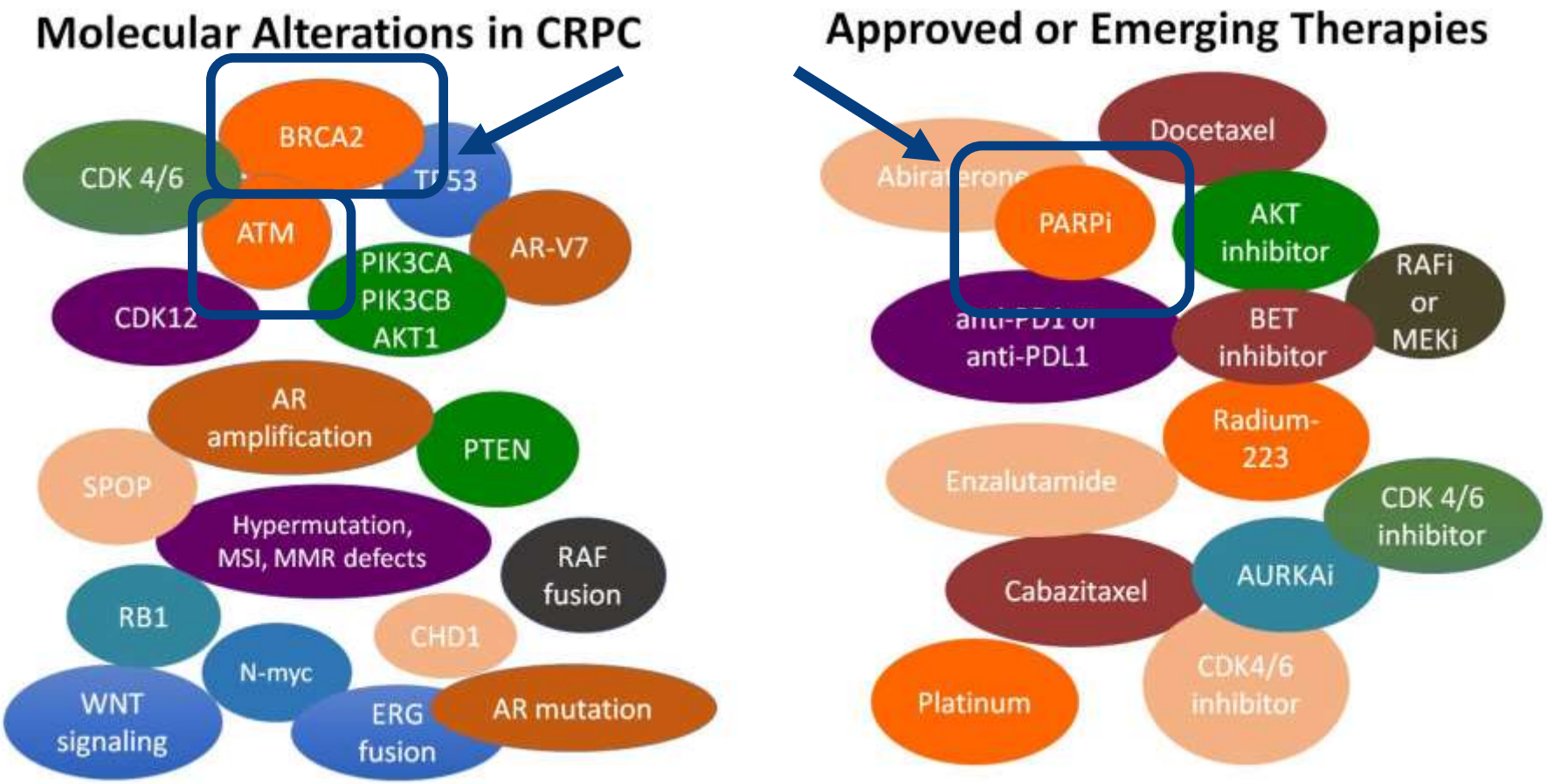






Modified By Joaquin Mateo at 2019 ASCO Annual Meeting

Increased genomic testing has led to more biomarkers driven trials



Modified by Beltran H, 2019 ASCO Genitourinary Symposium

KIDNEY CANCER

ASCO NEWS IN KIDNEY CANCER

1. UPDATE ON CARMENA

2. UPDATE ON KEYNOTE 426

ASCO NEWS IN KIDNEY CANCER

1. UPDATE ON CARMENA

2. UPDATE ON KEYNOTE 426

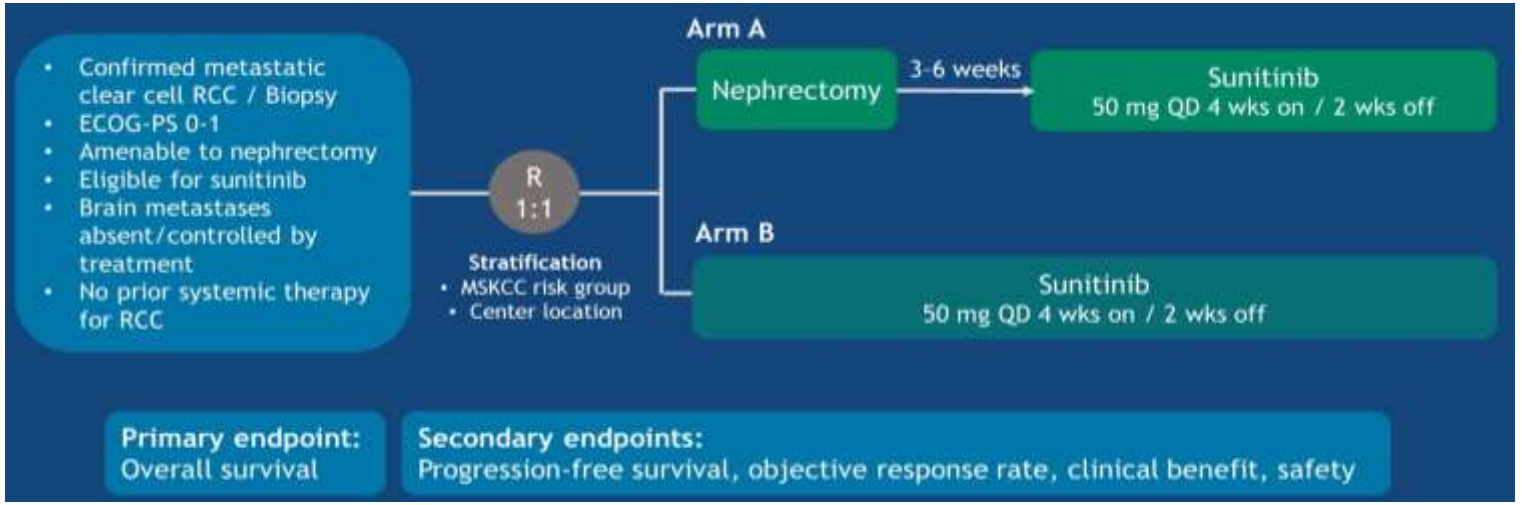
UPDATE ON CARMENA

Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): Update on Carmena trial with focus on intermediate IMDC-risk population

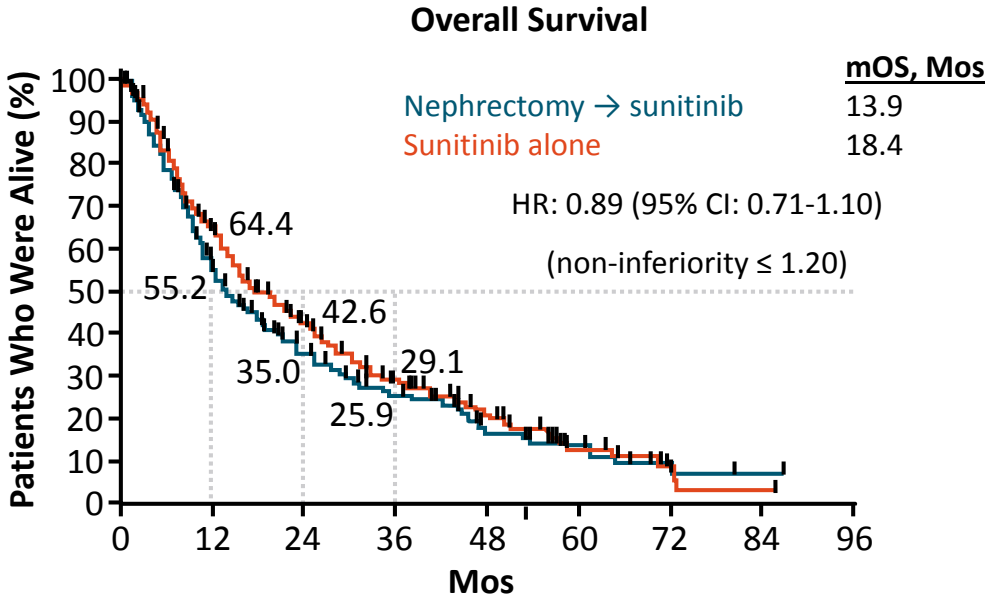
Arnaud Méjean, Simon Thezenas, Christine Chevreau, Karim Bensalah, Lionnel Geoffrois, Antoine Thiery-Vuillemin, Luc Cormier, Herve Lang, Laurent Guy, Gwenaelle Gravis, Frederic Rolland, Claude Linassier, Marc-Olivier Timsit, Laurence Albiges, Stephane Oudard, Thierry Lebret, Jean-Marc Treluyer, Sandra Colas, Bernard Escudier, Alain Ravaud

Presented By Arnaud Mejean at 2019 ASCO Annual Meeting

CARMENA



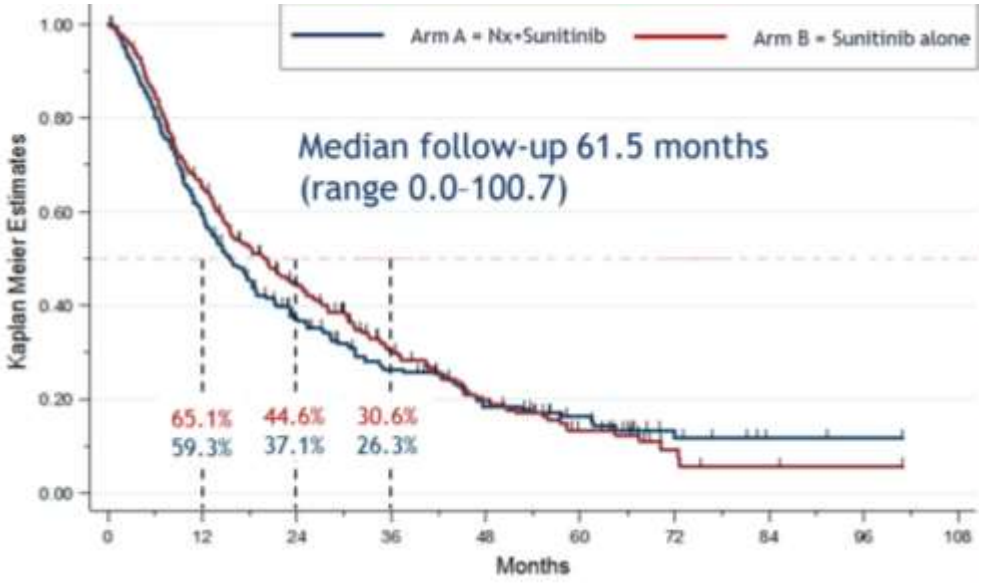
- Sunitinib alone not inferior to nephrectomy → sunitinib (upper boundary of 95% CI ≤ 1.20)
- mOS longer with sunitinib alone vs nephrectomy → sunitinib:
  - MSKCC intermediate-risk: 23.4 vs 19.0 mos (HR: 0.92)
  - MSKCC poor-risk: 13.3 vs 10.2 mos (HR: 0.86)



Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018

UPDATE ON CARMENA

Updated OS



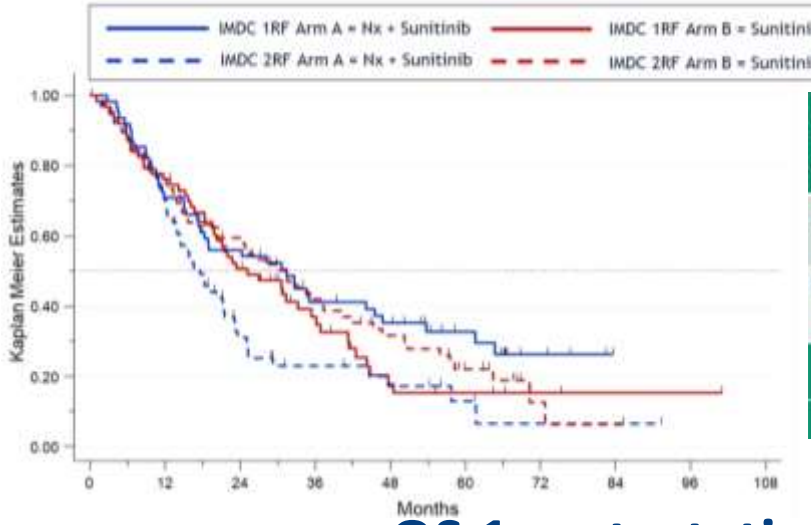
With longer FU of 61.5 months, Carmena trial confirms that CN is not superior to sunitinib alone in ITT population, both with MSKCC and IMDC risk groups for treating mRCC.

→ CN should NOT be considered as the SOC

Modified By Arnaud Mejean at 2019 ASCO Annual Meeting

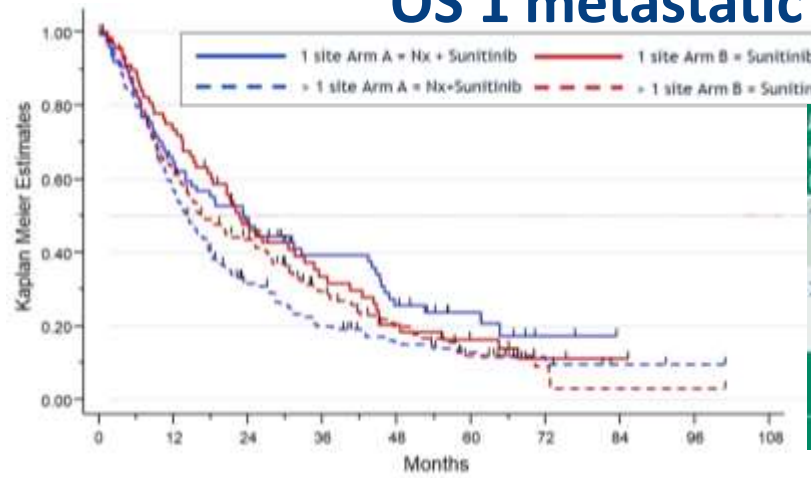
UPDATE ON CARMENA

OS IMDC intermediate patients: 1 vs 2 risk factors



Median OS, months (95% CI)	Arm A: Nephrectomy + Sunitinib (n=127)	Arm B: Sunitinib alone (n=139)	HR (95% CI)	p
IMDC 1 risk factor	(n=63) **31.4** (17.3-45.5)	(n=63) **25.2** (19.6-35.4)	1.29 (0.85-1.98)	0.232
IMDC 2 risk factors	(n=64) **17.6** (13.7-21.5)	(n=76) **31.2** (20.5-40.4)	0.63 (0.44-0.97)	0.033
HR (95% CI)	1.68 (1.10-2.57)	0.88 (0.59-1.30)		
p	0.015	0.515		

OS 1 metastatic site vs more than 1



Median OS, months (95% CI)	Arm A: Nephrectomy + Sunitinib (n=226)	Arm B: Sunitinib alone (n=224)	HR (95% CI)	p
1 site	(n=75) **23.2** (13.9-43.4)	(n=68) **22.7** (17.5-33.1)	1.09 (0.75-1.59)	0.655
>1 site	(n=148) **14.4** (11.8-17.6)	(n=155) **16.7** (13.8-24.8)	0.87 (0.70-1.20)	0.284
HR (95% CI)	1.42 (1.03-1.96)	1.19 (0.86-1.64)	1.01 (0.74-1.37)	
p	0.032	0.292		

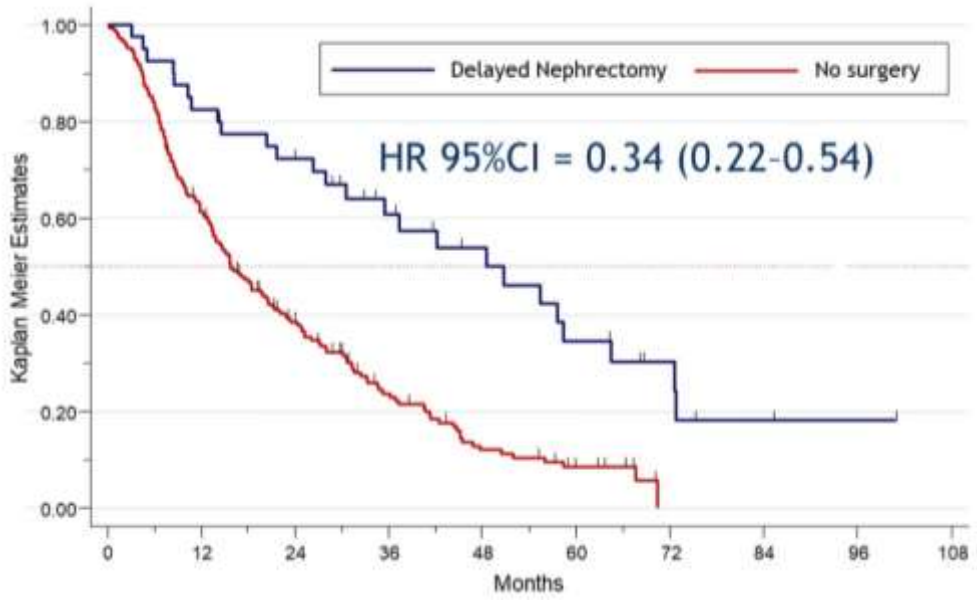
CN might be beneficial for patients with only one IMDC risk factor, especially in case of one metastatic site

Modified By Arnaud Mejean at 2019 ASCO Annual Meeting

UPDATE ON CARMENA

OS in patients with secondary nephrectomy in sunitinib alone arm

Secondary nephrectomy: 18% of patients in sunitinib alone arm (n=40) for emergency treatment of the primary tumor (17.5%) or for CR or near CR in metastatic sites (>6 months)



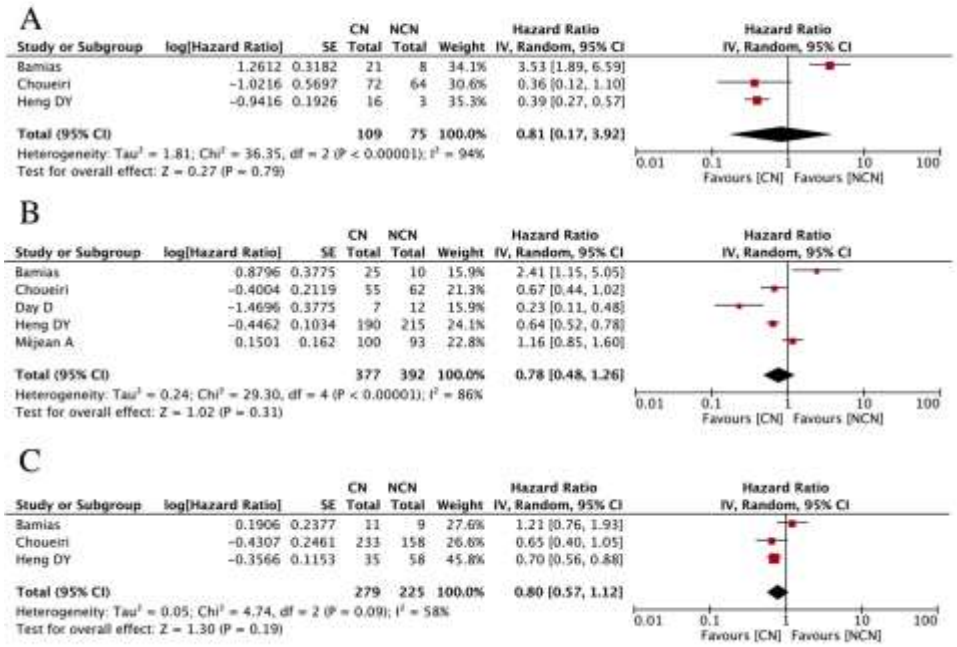
	Median OS, months (95% CI)
Sunitinib and delayed nephrectomy (n=40)	**48.5** (27.9-64.4)
Sunitinb alone without nephrectomy (n=183)	**15.7** (13.3-20.5)
HR (95% CI)	0.34 (0.22-0.54)

Delayed nephrectomy after initial systemic treatment in good responders patients is associated with long OS

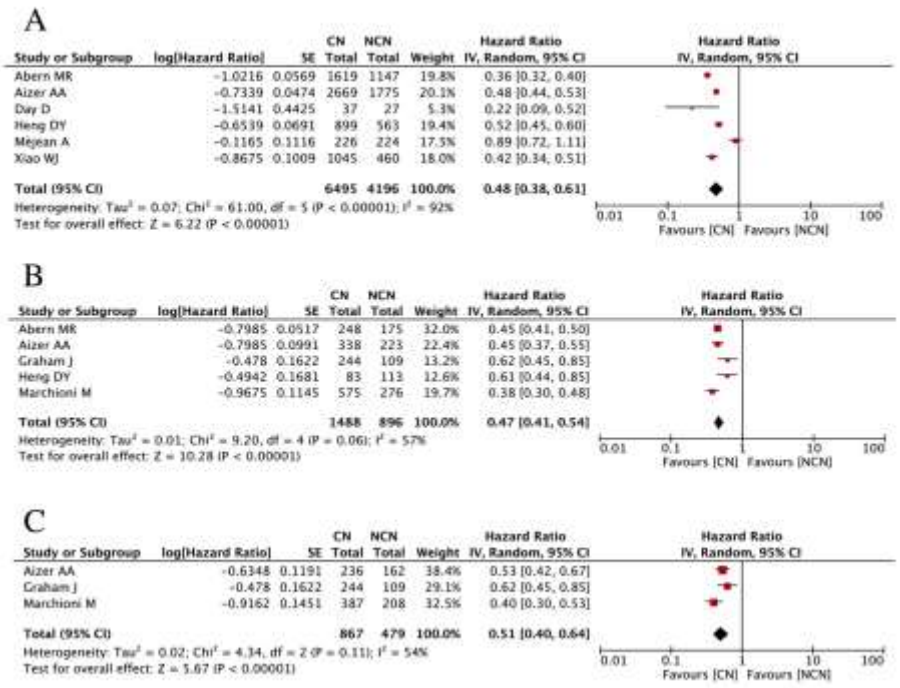
Modified By Arnaud Mejean at 2019 ASCO Annual Meeting

SHOULD CARMENA REALLY CHANGE OUR ATTITUDE TOWARDS CYTOREDUCTIVE NEPHRECTOMY IN METASTATIC RENAL CELL CARCINOMA WITH PRIMARY SITE?

Cytoreductive Nephrectomy vs No Cytoreductive Nephrectomy in patients with brain metastases, poor prognosis and poor performance status.



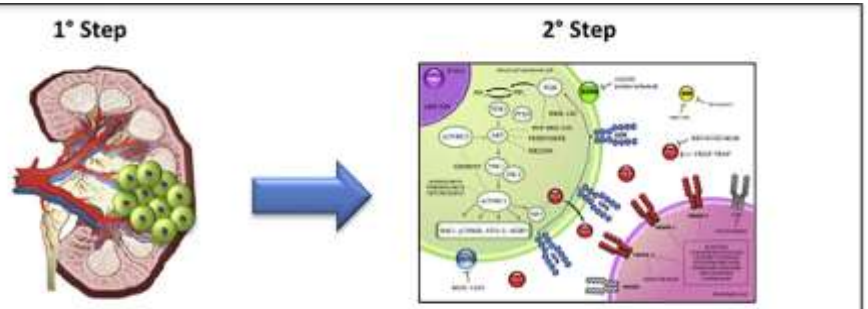
Cytoreductive Nephrectomy vs No Cytoreductive Nephrectomy in patients with ccRCC, nccRCC, and papillary RCC



Massari F et al., Tageted Oncology 2018

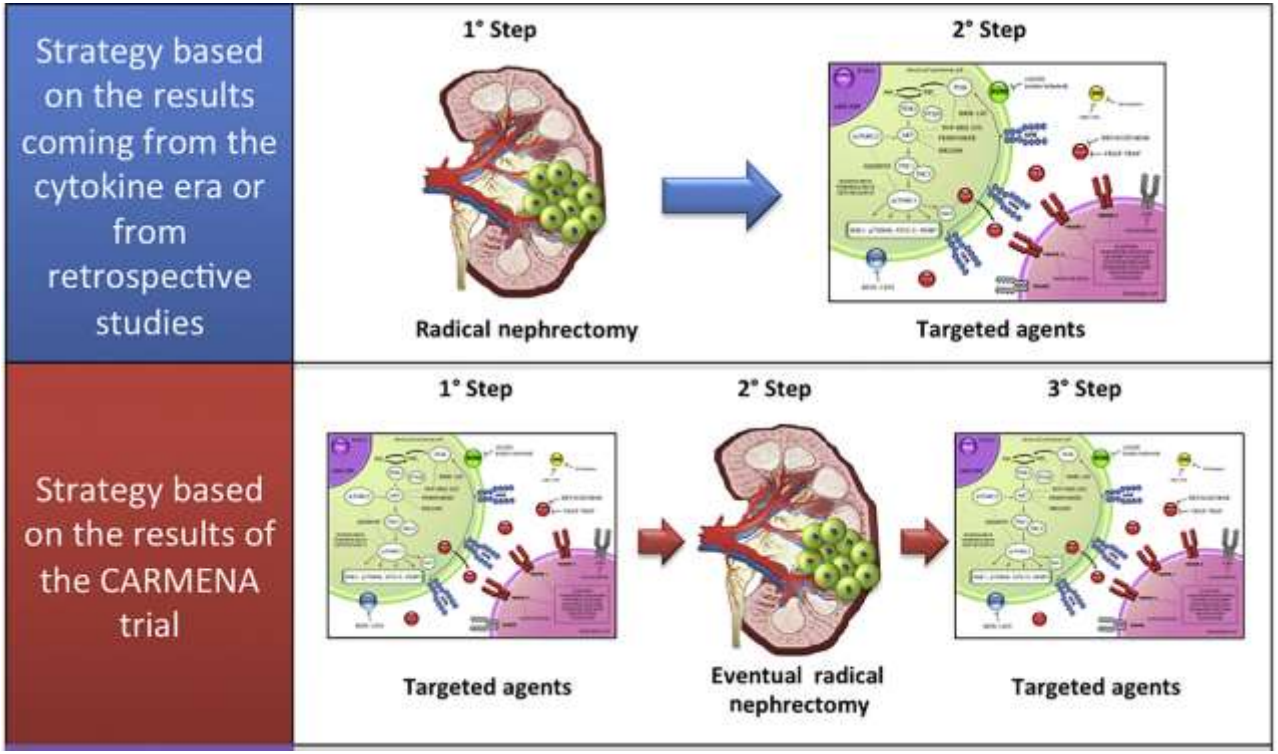
Probably CARMENA data already obsolete

Strategy based on the results coming from the cytokine era or from retrospective studies



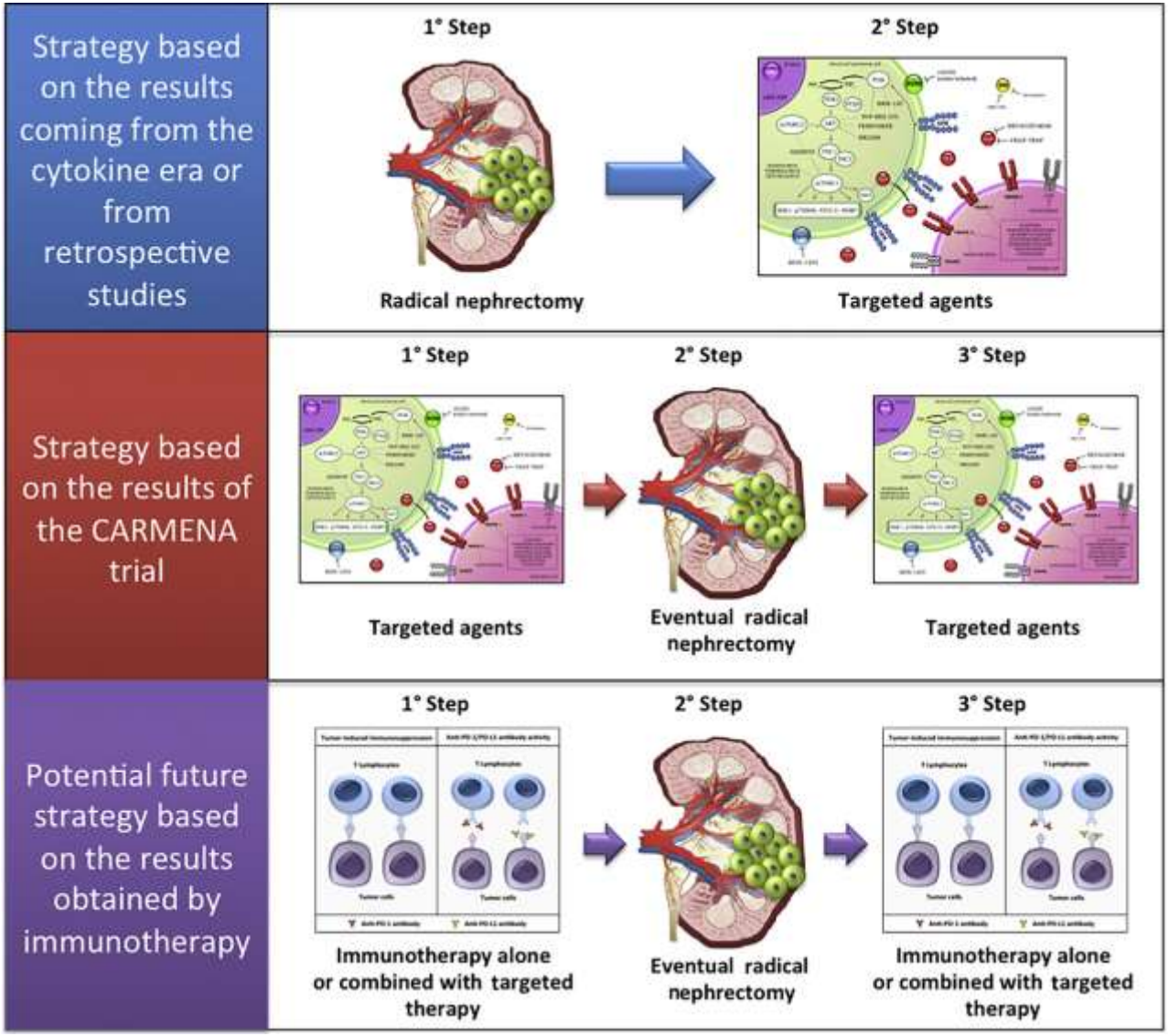
Santoni M, Montironi R, Battelli N, Massari F. European Urology 2018

Probably CARMENA data already obsolete



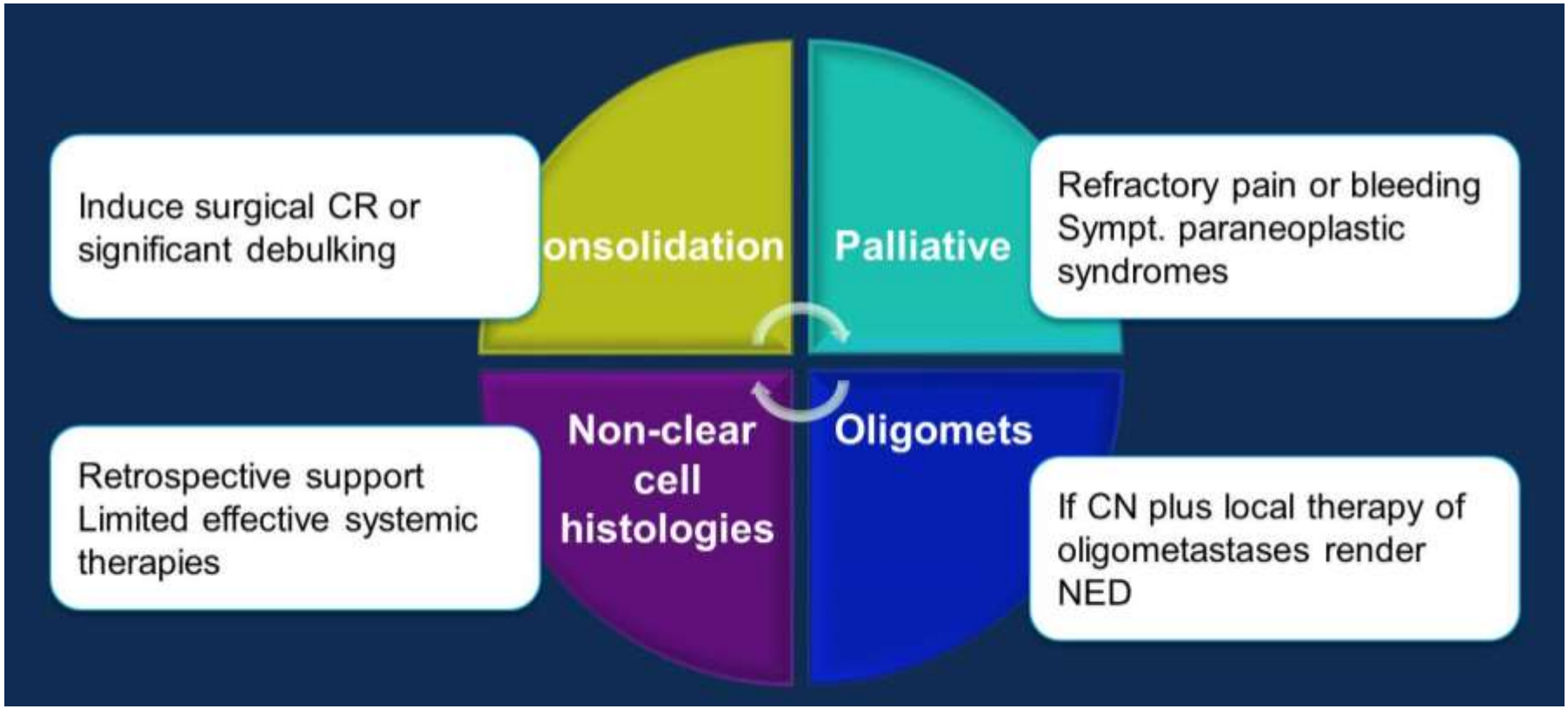
Santoni M, Montironi R, Battelli N, Massari F. European Urology 2018

Probably CARMENA data already obsolete



Santoni M, Montironi R, Battelli N, Massari F. European Urology 2018

Probably CN should be considered a standard of care for patients with mRCC if:



Modified By Lauren Harshman at 2019 Genitourinary Cancers Symposium

ASCO NEWS IN KIDNEY CANCER

1. UPDATE ON CARMENA

2. UPDATE ON KEYNOTE 426

UPDATE ON KEYNOTE-426

Pembrolizumab plus Axitinib as First-Line Therapy for mRCC: Outcomes in the Combined IMDC Intermediate/Poor Risk and Sarcomatoid Subgroups of KEYNOTE-426

Brian I. Rini,[1] Elizabeth R. Plimack,[2] Viktor Stus,[3] Rustem Gafanov,[4] Robert Hawkins,[5] Dmitry Nosov,[6] Frédéric Pouliot,[7] Denis Soulières,[8] Bohuslav Melichar,[9] Ihor Vynnychenko,[10] Sergio J. Azevedo,[11] Delphine Borchiellini,[12] Raymond S. McDermott,[13] Jens Bedke,[14] Satoshi Tamada,[15] Shuyan Wan,[16] Scot Ebbinghaus,[16] Rodolfo F. Perini,[16] Mei Chen,[16] Michael B. Atkins,[17] Thomas Powles[18]

[1]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipro, Ukraine; [4]Russian Scientific Center of Roentgenoradiology, Moscow, Russia; [5]The Christie NHS Foundation Trust, Manchester, UK; [6]Central Clinical Hospital with Outpatient Clinic, Moscow, Russia; [7]CHU de Québec and Université Laval, Quebec City, QC, Canada; [8]Centre Hospitalier de l'Universitaire de Montréal, Montréal, QC, Canada; [9]Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic; [10]Sumy State University, Sumy Regional Oncology Center, Sumy, Ukraine; [11]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [12]Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; [13]Adelaide and Meath Hospital and University College Dublin, Dublin, Ireland; [14]Department of Urology, Eberhard-Karls University Tübingen, Tübingen, Germany; [15]Osaka City University Hospital, Osaka, Japan; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Georgetown–Lombardi Comprehensive Cancer Center, Washington, D.C., USA; [18]Barts Health and the Royal Free NHS Trusts, Barts Cancer Institute, and Queen Mary University of London, London, UK

Presented By Brian Rini at 2019 ASCO Annual Meeting

KEYNOTE-426

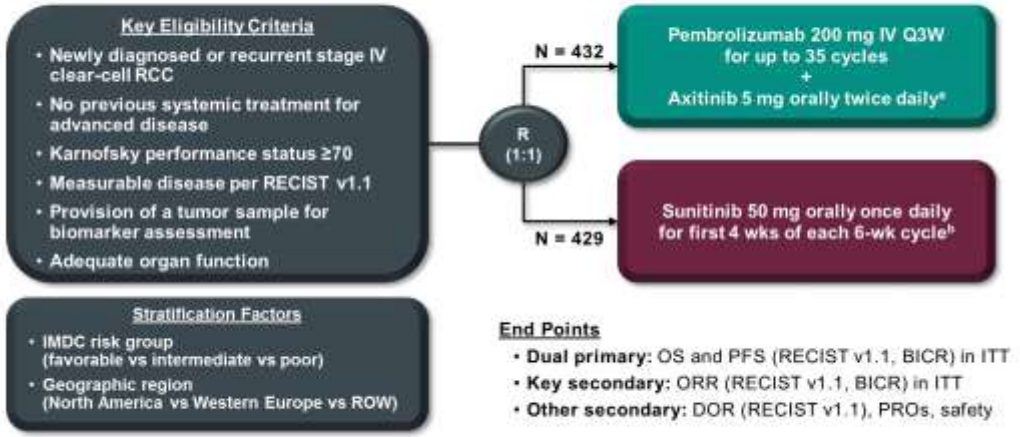
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

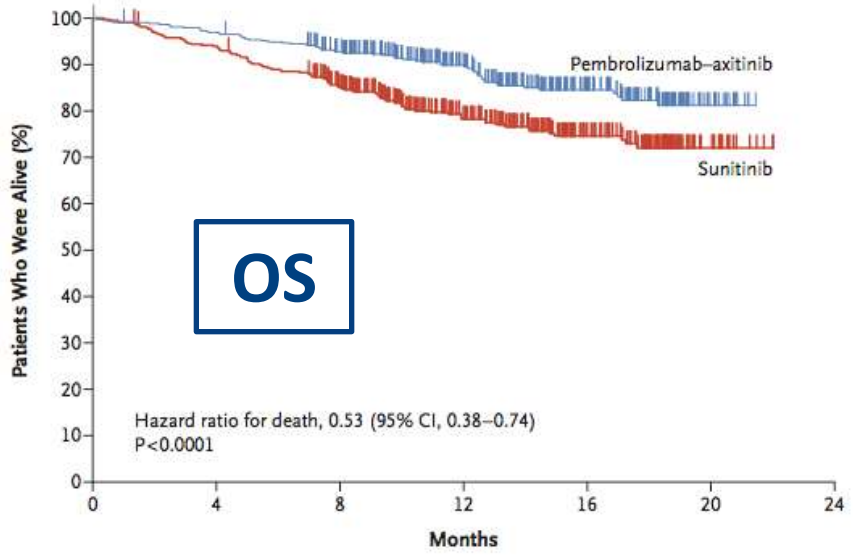
Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

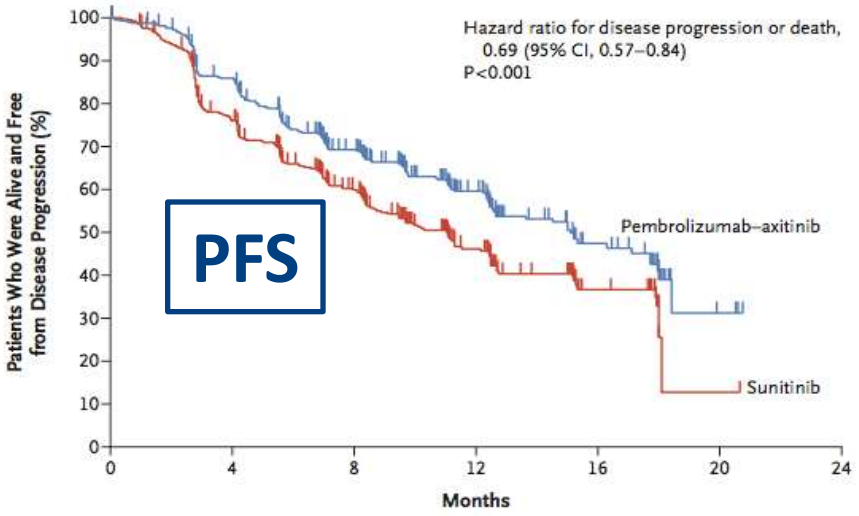
B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

KEYNOTE-426 Study Design



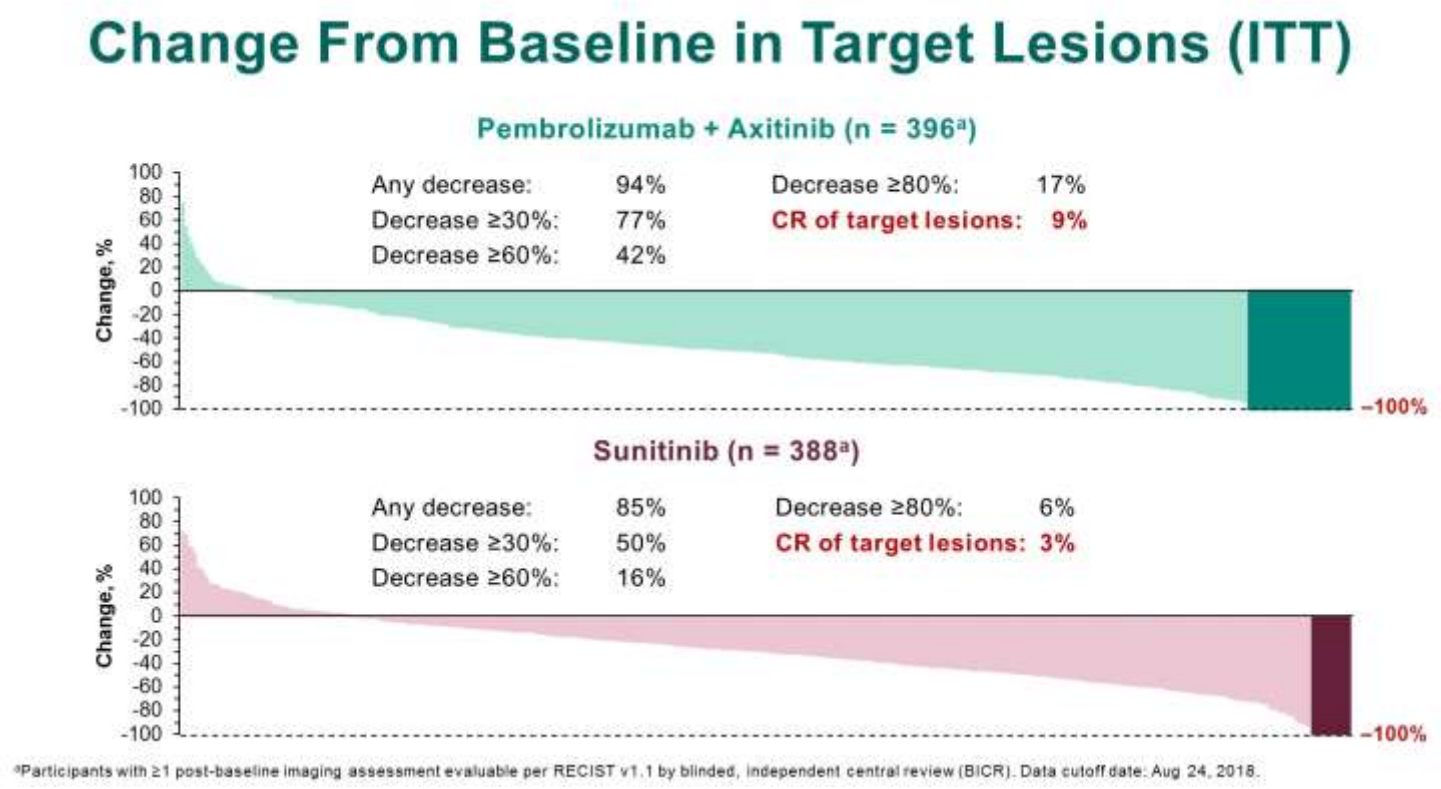
[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity. BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world. KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).





Rini et al NEJM 2019; 380(12):1116-1127

UPDATE ON KEYNOTE-426



Percentage of tumor shrinkage was substantially greater with pembrolizumab plus axitinib vs sunitinib

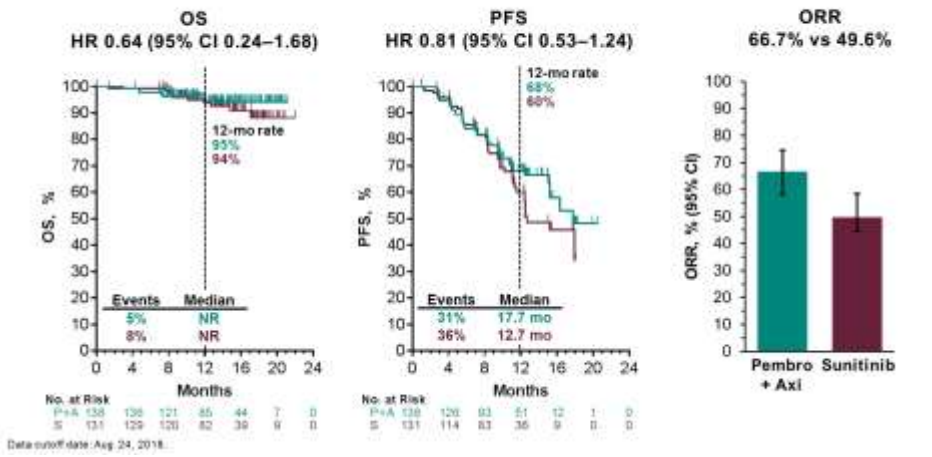
- 60% reduction in target lesions: 42% vs 16%
- 80% reduction in target lesions: 17% vs 6%
- Complete response in all target lesions: 9% vs 3%

Modified By Brian Rini at 2019 ASCO Annual Meeting

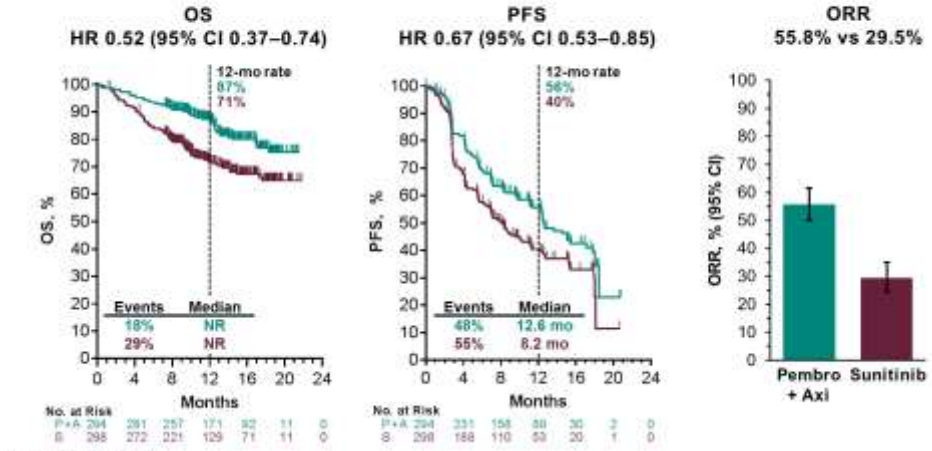
UPDATE ON KEYNOTE-426

OS, PFS and ORR benefit of pembro+axitinib observed across key subgroups

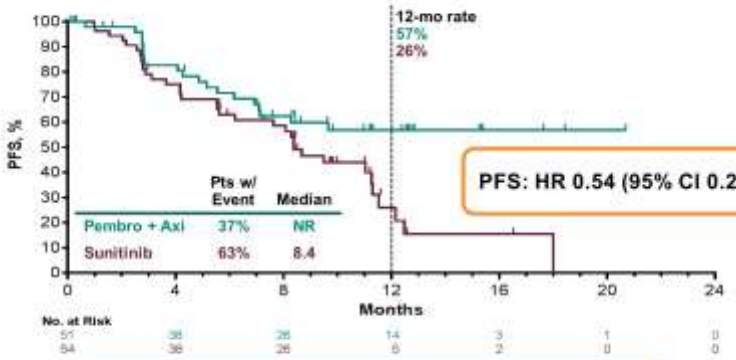
IMDC Favorable Risk: OS, PFS, and ORR



IMDC Intermediate/Poor Risk: OS, PFS, and ORR



PFS: Presence of Sarcomatoid Features[a]



PFS: HR 0.54 (95% CI 0.29–1.00)

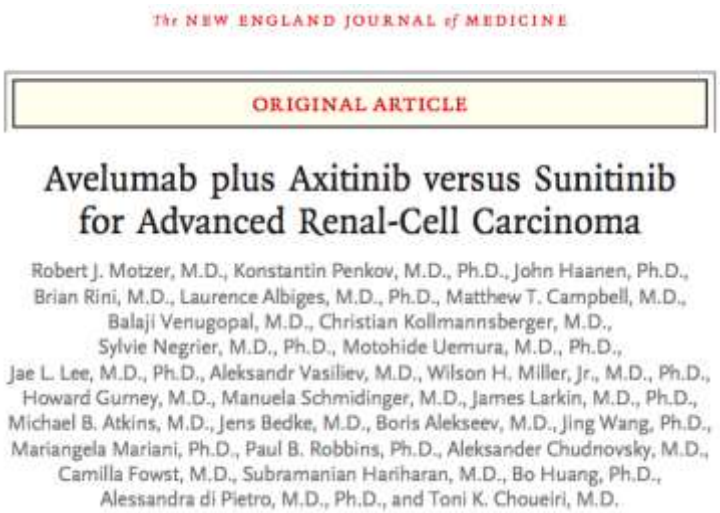
OS: HR 0.58 (95% CI 0.21–1.59); median NR in either arm[b]

[a]Among the 370 participants with known status assessed by local pathology review and as indicated on the eCRF. [b]Pts who died: 16% in the pembro + axi arm, 20% in the sunitinib arm.
Data cutoff date: Aug 24, 2018.

Modified By Brian Rini at 2019 ASCO Annual Meeting

NEW TREATMENT OPTIONS IN I LINE

JAVELIN RENAL 101[1]

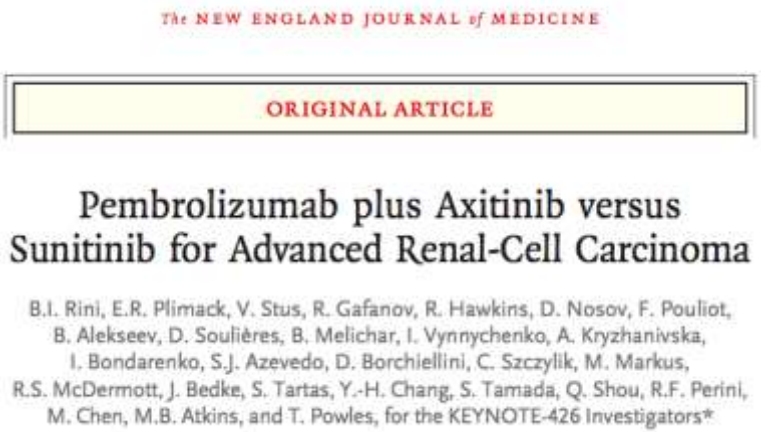

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M.D., Laurence Albiges, M.D., Ph.D., Matthew T. Campbell, M.D., Balaji Venugopal, M.D., Christian Kollmannsberger, M.D., Sylvie Negrier, M.D., Ph.D., Motohide Uemura, M.D., Ph.D., Jae L. Lee, M.D., Ph.D., Aleksandr Vasiliev, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Howard Gurney, M.D., Manuela Schmidinger, M.D., James Larkin, M.D., Ph.D., Michael B. Atkins, M.D., Jens Bedke, M.D., Boris Alekseev, M.D., Jing Wang, Ph.D., Mariangela Mariani, Ph.D., Paul B. Robbins, Ph.D., Aleksander Chudnovsky, M.D., Camilla Fowst, M.D., Subramanian Hariharan, M.D., Bo Huang, Ph.D., Alessandra di Pietro, M.D., Ph.D., and Toni K. Choueiri, M.D.

KEYNOTE 426[2]

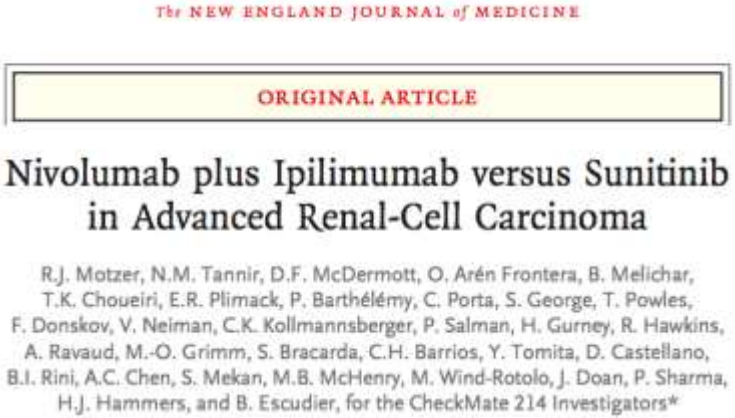

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

CHECKMATE 214[3]


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

1. Motzer et al NEJM 2019;380(12):1103-1115
2. Rini et al NEJM 2019; 380(12):1116-1127
3. Motzer et al NEJM 2018;378:1277-90

NEW TREATMENT OPTIONS IN I LINE

Table 1. Comparisons among Trials of Combination Therapy vs. Sunitinib for Patients with Metastatic Renal-Cell Carcinoma.*

Variable	Trial of Pembrolizumab plus Axitinib vs. Sunitinib[5] (N=861)	Trial of Avelumab plus Axitinib vs. Sunitinib[4] (N=886)	Trial of Nivolumab plus Ipilimumab vs. Sunitinib[3] (N=1096)
IMDC prognostic risk (% of patients)†			
Favorable	31.2	21.4	23
Intermediate	56.2	61.8	61
Poor	12.6	16.2	17
Quantifiable tumor PD-L1 expression ≥1% (% of patients)	60.5	63.2	24
Overall survival			
Hazard ratio for death	0.53	0.78	0.68
CI	95% CI, 0.38–0.74	95% CI, 0.55–1.08	99.8% CI, 0.49–0.95
P value	<0.0001	0.14	<0.001
Median progression-free survival (mo)			
Combination therapy group	15.1	13.8	12.4
Sunitinib group	11.1	8.4	12.3
Objective response in combination-therapy group (% of patients)	59.3	51.4	39.0
Complete response in combination-therapy group (% of patients)	5.8	3.4	10.2
Median follow-up (mo)	12.8	11.6	25.2

Escudier B NEJM 2019;380(12):1176-78

UROTHELIAL CANCER

ASCO NEWS IN UROTHELIAL CANCER

1. CALGB 90601

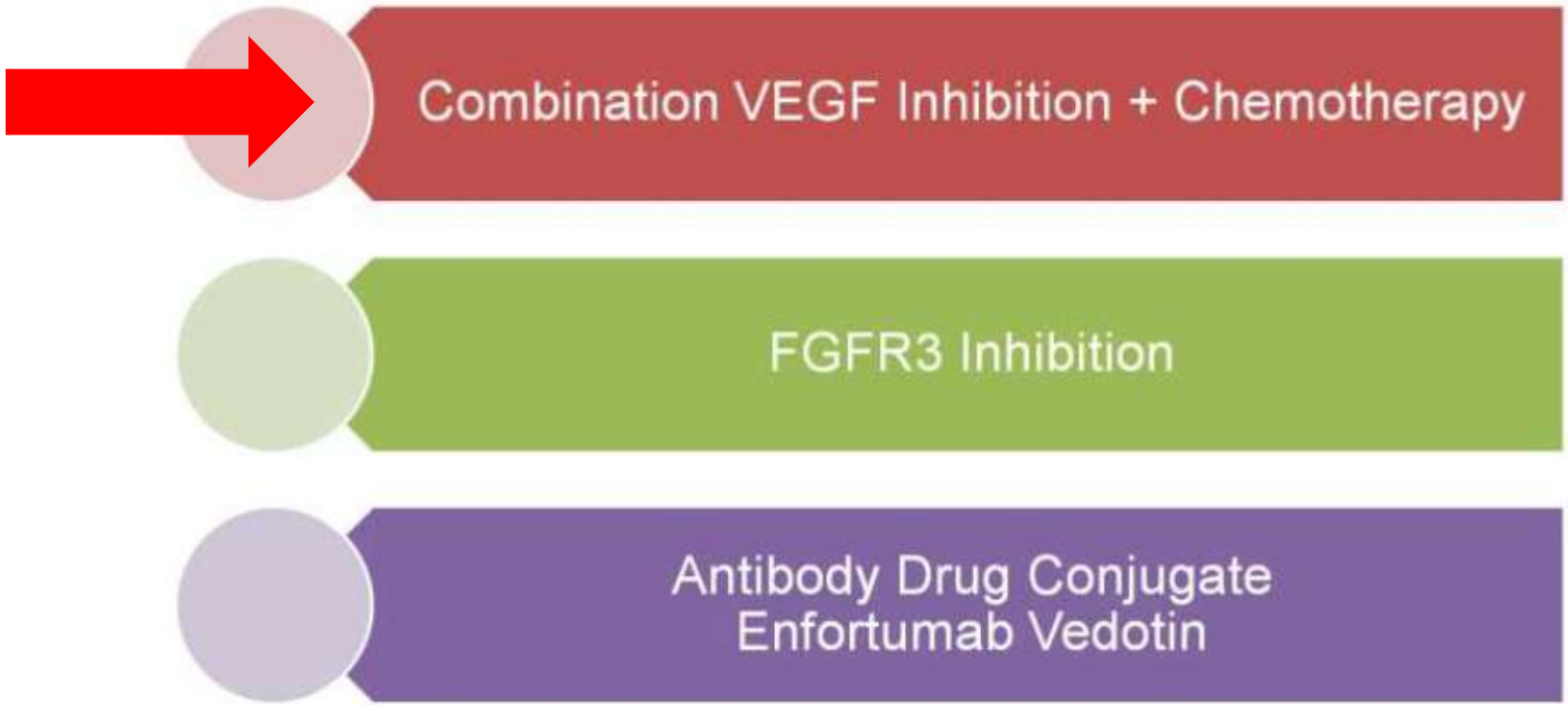
2. EV-201

ASCO NEWS IN UROTHELIAL CANCER

1. CALGB 90601

2. EV-201

EMERGING THERAPEUTIC STRATEGIES IN mUC



Modified By Elizabeth Plimack at 2018 ASCO Annual Meeting

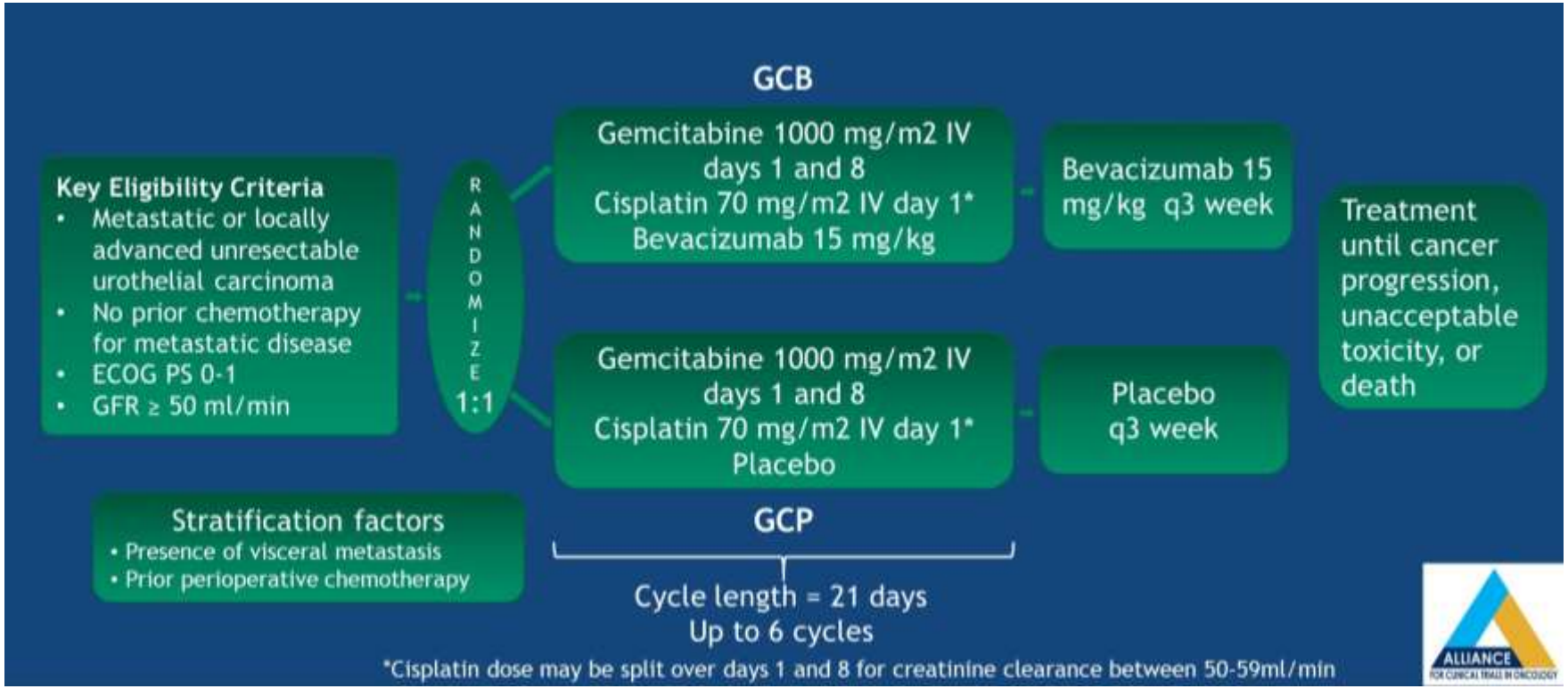
CALGB 90601

CALGB 90601 (Alliance): Randomized, double blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma.

Jonathan E. Rosenberg, Karla V. Ballman, Susan Halabi, Colleen Watt, Olwen M. Hahn, Preston D. Steen, Robert Dreicer, Thomas W. Flaig, Walter M. Stadler, Christopher Sweeney, Amir Mortazavi, Michael J. Morris on behalf of Alliance and NCTN Investigators

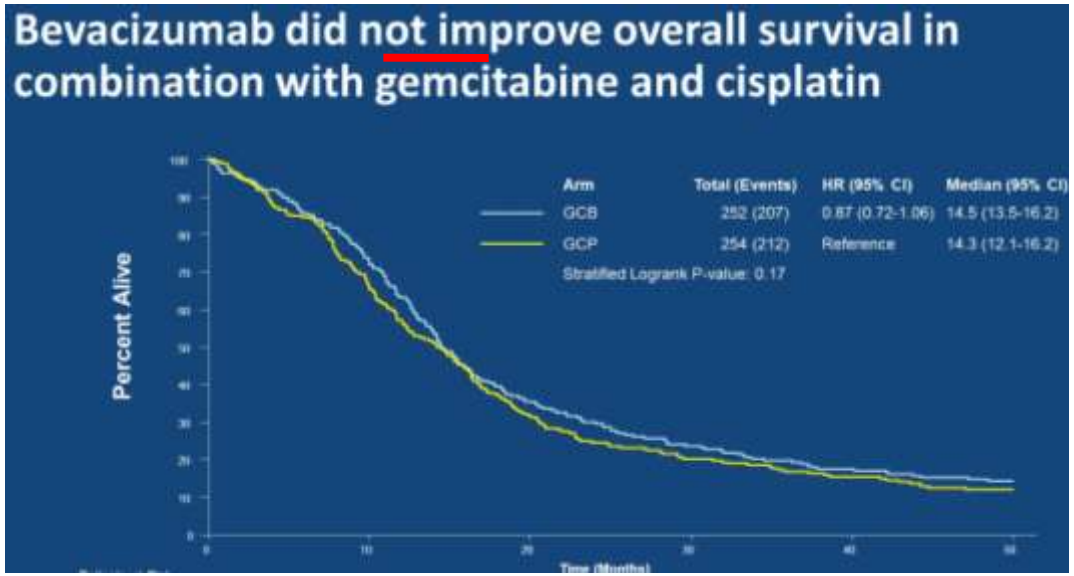
Presented By Jonathan Rosenberg at 2019 ASCO Annual Meeting

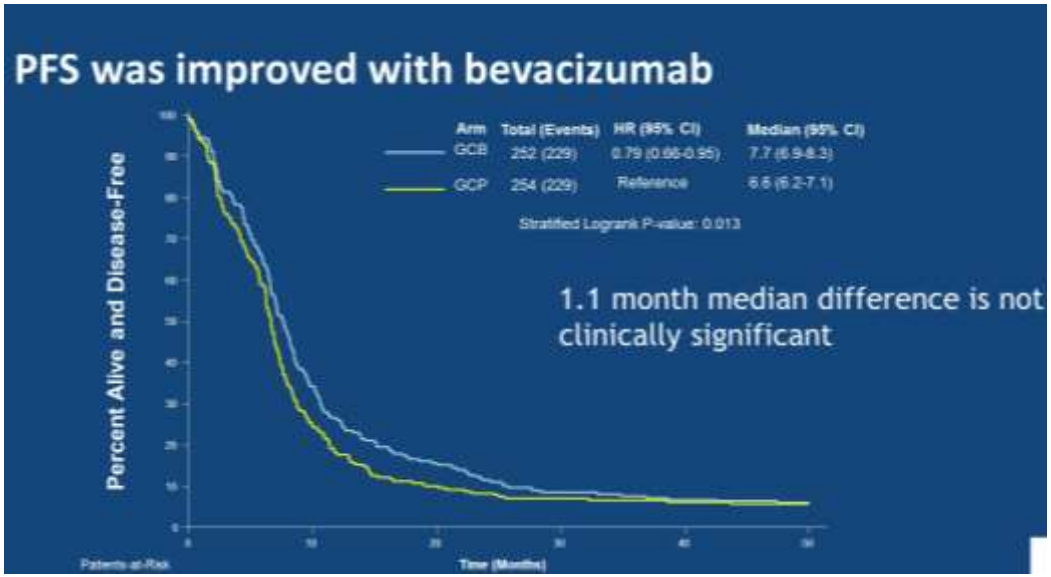
CALGB 90601 – Study Design



Presented By Jonathan Rosenberg at 2019 ASCO Annual Meeting

CALGB 90601 - Results





Presented By Jonathan Rosenberg at 2019 ASCO Annual Meeting

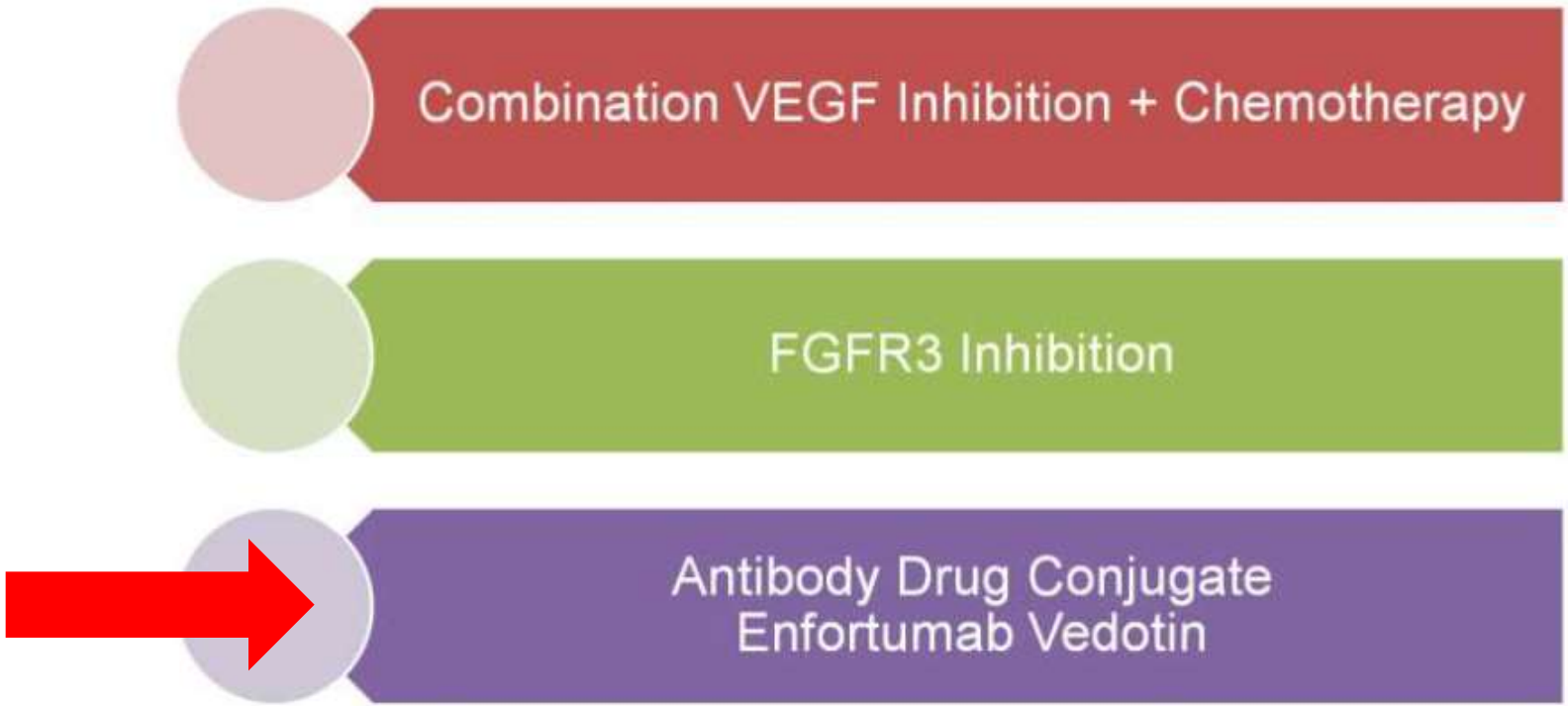
THERAPEUTIC ALGORITHM IN CISPLATIN ELIGIBLE

ASCO NEWS IN UROTHELIAL CANCER

1. CALGB 90601

2. EV-201

EMERGING THERAPEUTIC STRATEGIES IN mUC



Modified By Elizabeth Plimack at 2018 ASCO Annual Meeting

EV-201

EV-201: Results of Enfortumab Vedotin Monotherapy for Locally Advanced or Metastatic Urothelial Cancer Previously Treated with Platinum and Immune Checkpoint Inhibitors (NCT03219333)

Daniel P. Petrylak, Arjun V. Balar, Peter H. O'Donnell, Bradley A. McGregor, Elisabeth I. Heath, Evan Y. Yu, Matthew D. Galsky, Noah M. Hahn, Elaina M. Gartner, Juan M. Pinelli, Shang-Ying Liang, Amal Melhem-Bertrandt, and Jonathan E. Rosenberg

Presented By Daniel Petrylak at 2019 ASCO Annual Meeting

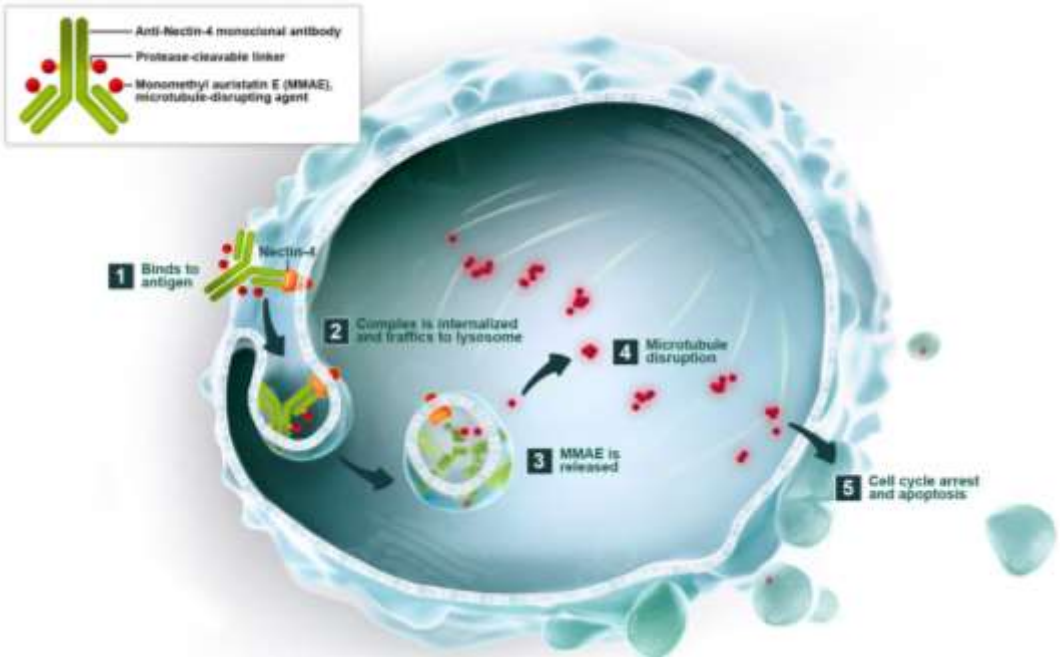
EV-201

ENFORTUMAB VEDOTIN: antibody-drug conjugated composed of

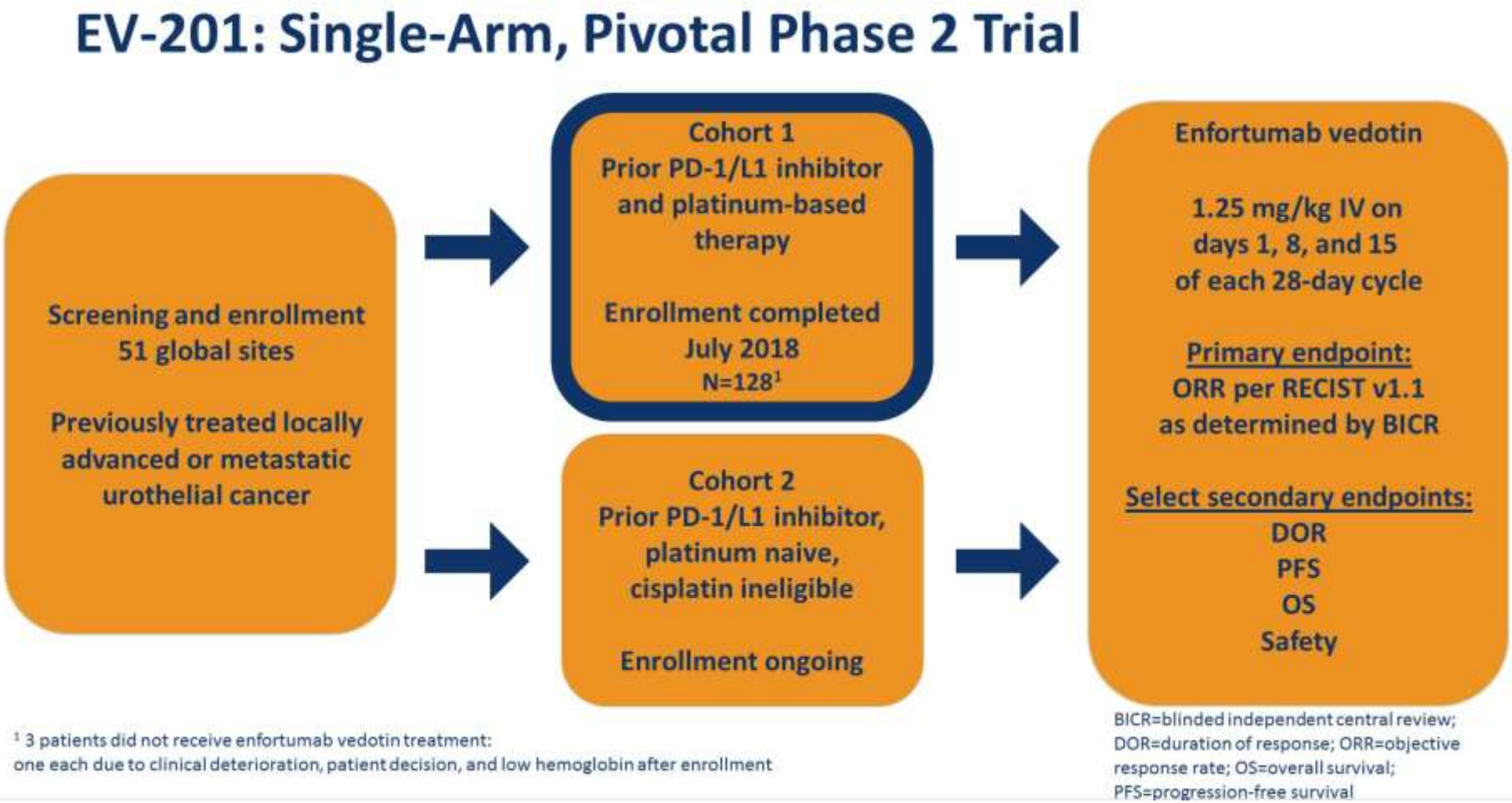
- **anti-Nectin 4** monoclonal antibody

  +

- **monomethyl auristatin E (MMAE)** → microtubule-disrupting agent



EV-201 – Study Design



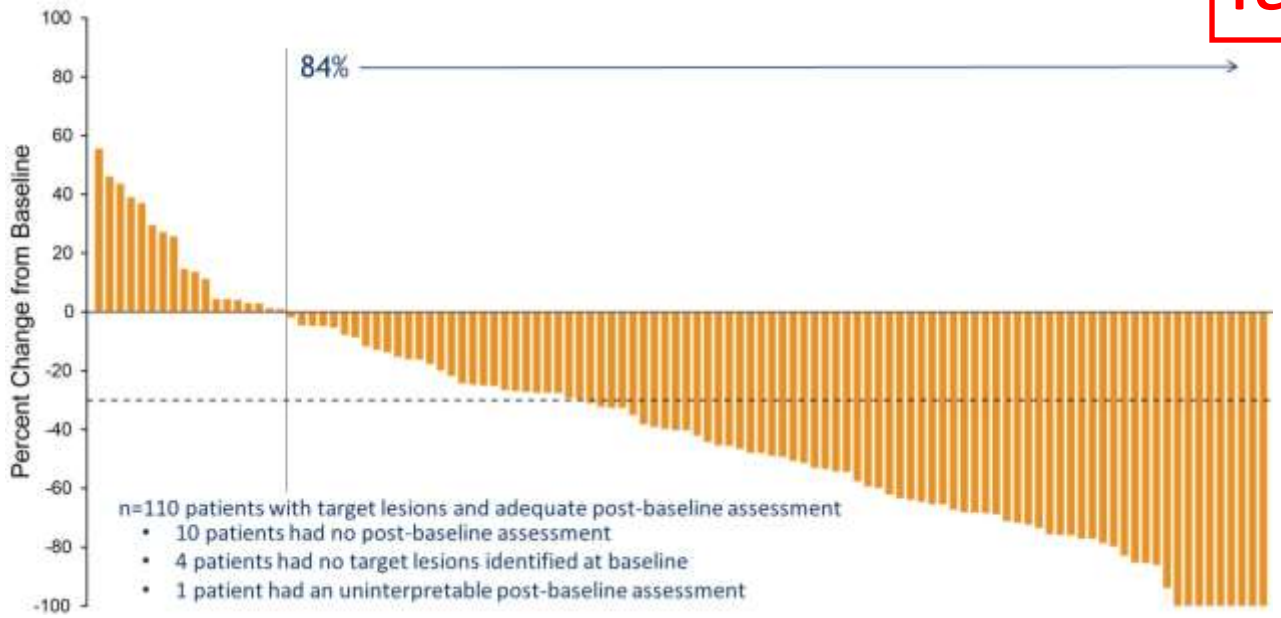
Presented By Daniel Petrylak at 2019 ASCO Annual Meeting

EV-201 – Results

ORR per RECIST v 1.1 assessed by BICR	Patients (N=125) n (%)
Confirmed objective response rate	55 (44)
95% confidence interval[1]	(35.1, 53.2)
Best overall response per RECIST v. 1.1, n (%)	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable[2]	12 (10)

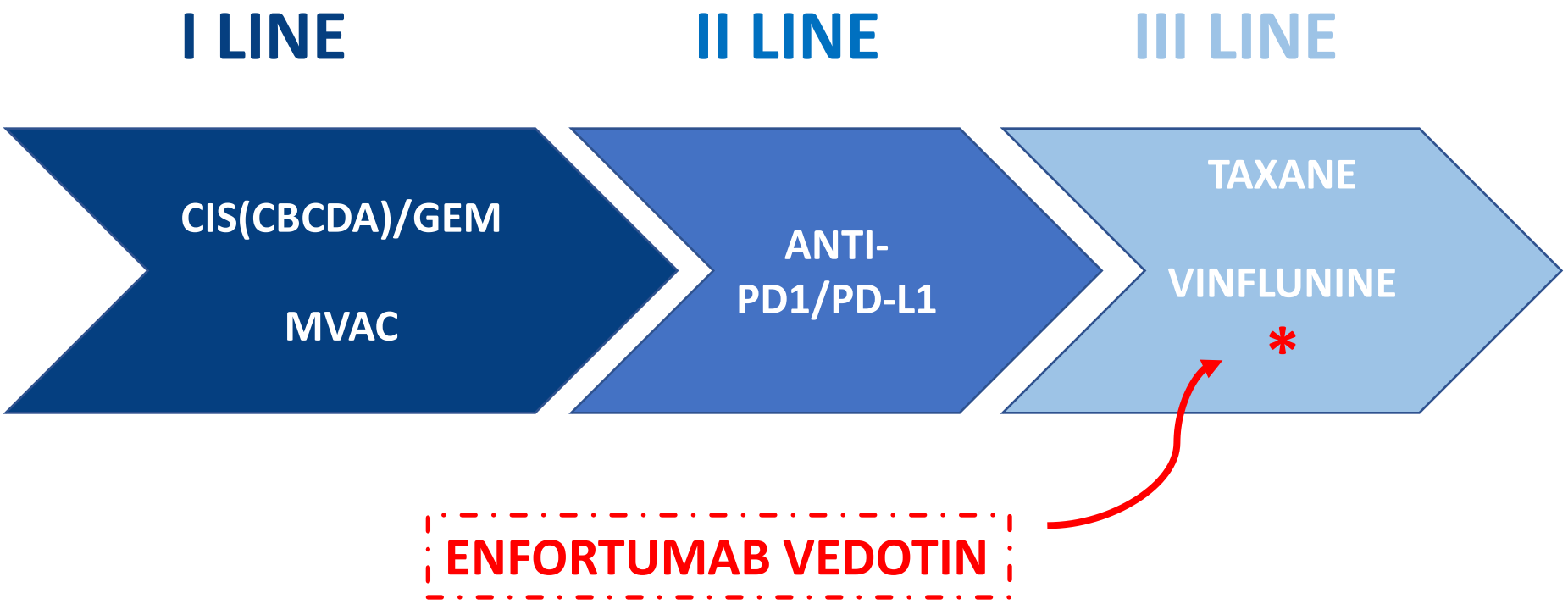
44% RR

7.6 months median duration of response



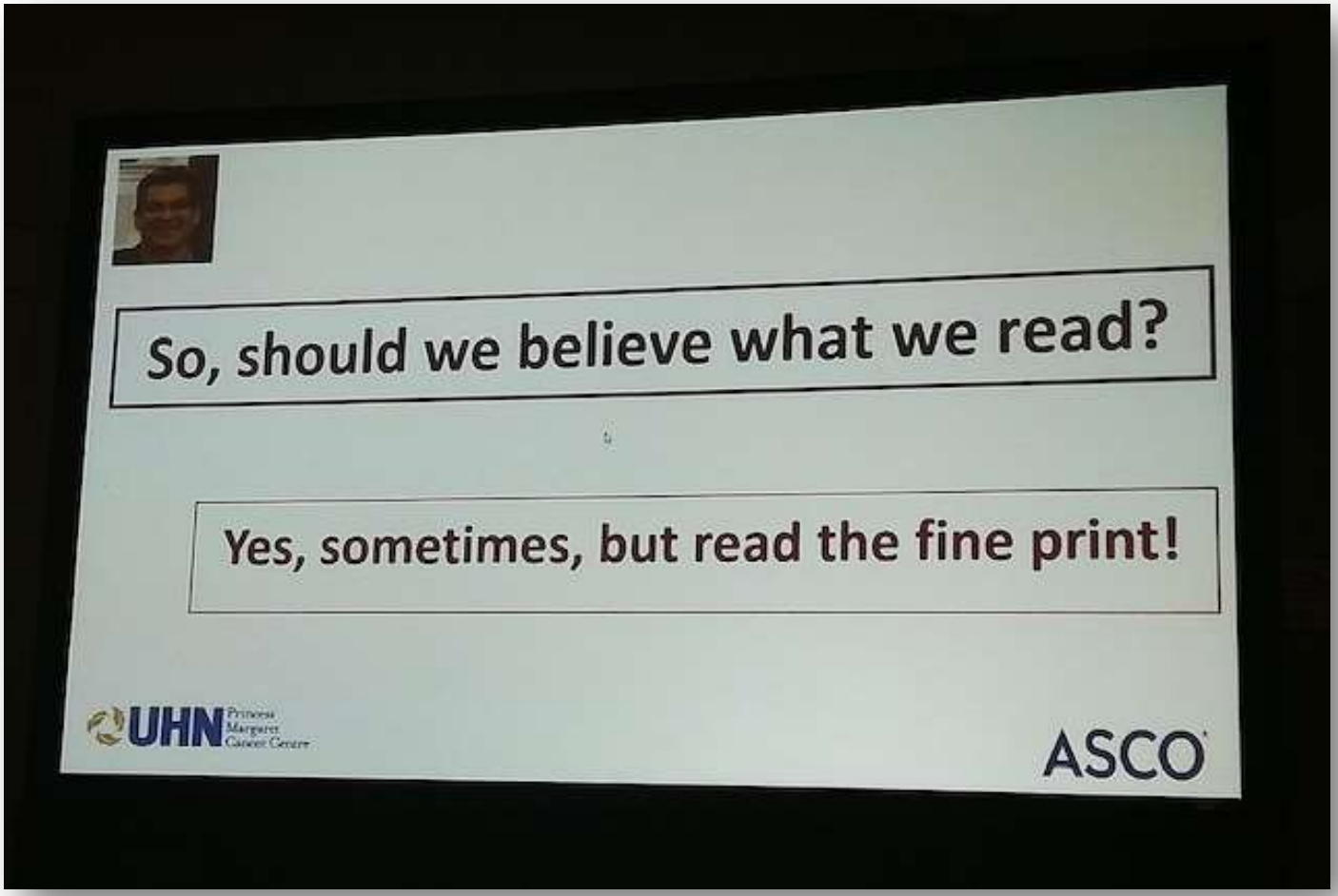
Modified By Daniel Petrylak at 2019 ASCO Annual Meeting

EMERGING THERAPEUTIC STRATEGIES IN mUC:



Ongoing:

- EV-201 Cohort 2: enrolling cisplatin-ineligible patients without prior platinum (NCT03219333)
- EV-301: randomized phase 3 trial of EV vs SOC post-platinum and a PD-1/PD-L1 inhibitor (NCT03474107)
- EV-103: EV in combination with pembrolizumab and/or chemotherapy (NCT03288545)



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