Prostate Cancer Update ASCO/ESMO REVIEW October 14, 2022

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UPDATES IN CANCER THERAPIES:
AN ASCO | ESMO REVIEW
Hilton Aventura Miami | Aventura, FL
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Agenda

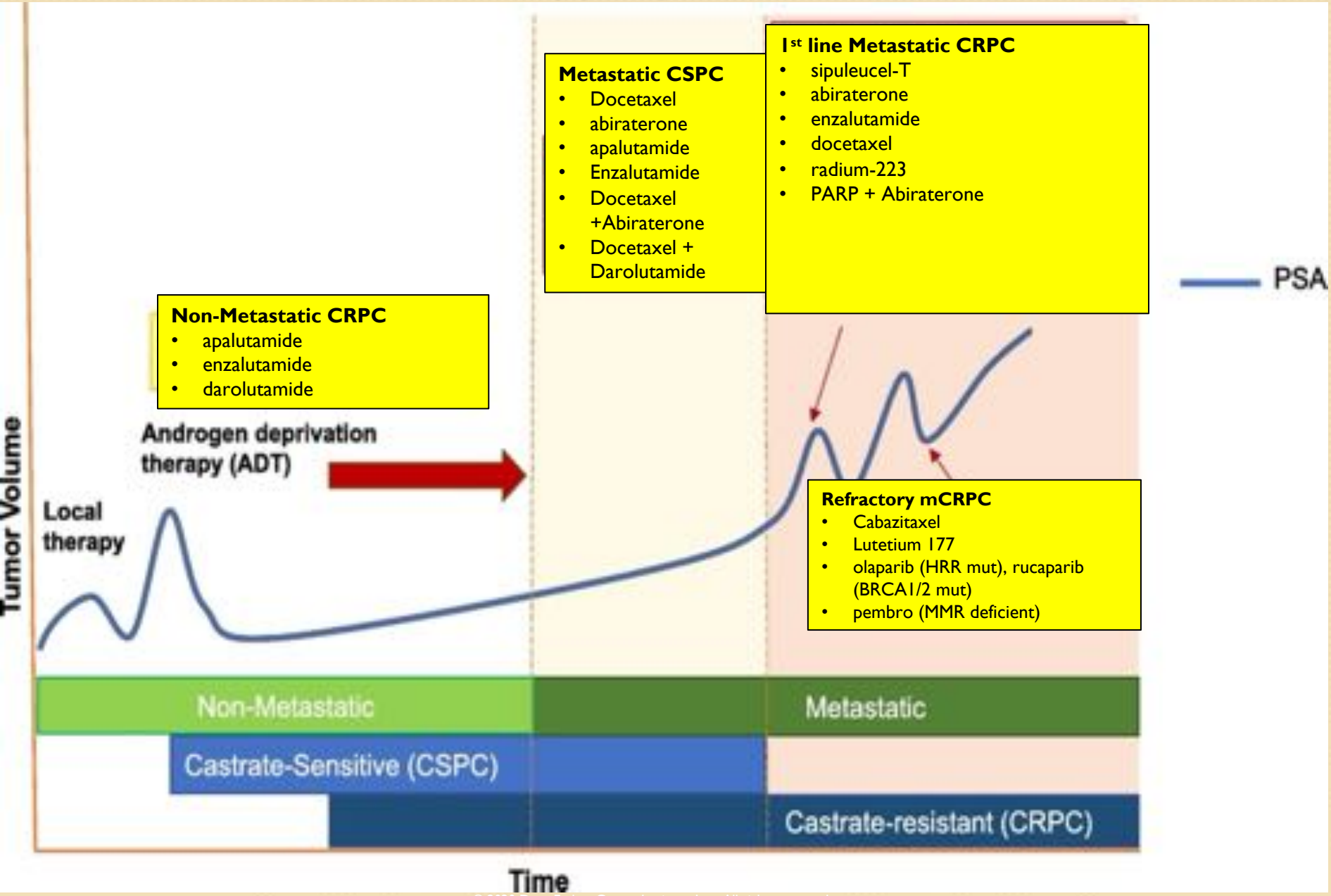
1. Oligometastatic Castrate Sensitive Prostate CA
   - STOMP, Oriole Trial (ASCO 2022)

2. Nonmetastatic Castrate Sensitive Prostate CA
   - PRESTO Study (ESMO 2022)

3. Metastatic castrate sensitive Prostate CA
   - ARASENS Update (ASCO 2022)

4. Metastatic castrate resistant Prostate CA
   - PROpel Update (ESMO 2022)
   - VISION Update, TheraP (ASCO 2022)

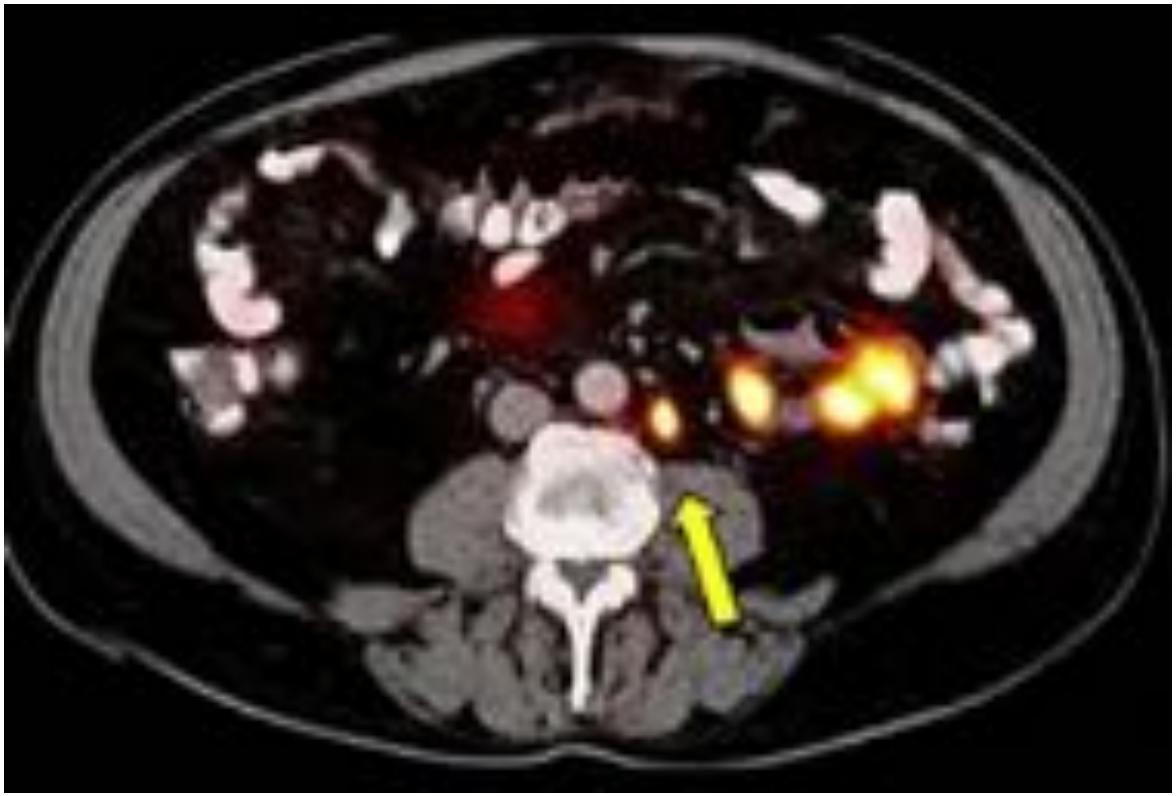
Systemic therapy of prostate cancer 2022



Alkhudair NA. *Saudi Pharm J.* 2019 Mar;27(3):368-372.

1. Oligometastatic Prostate Cancer

- Clinical Problem
- Are we over treating patients with ADT?
- ADT side effects for patients



ASCO 2022: Poster 5025
Pooled analysis STOMP + Oriole study

- Phase II STOMP and ORIOLE trials to examine long term outcomes of MDT in patients with oligometastatic castration sensitive prostate cancer

- In pooled analysis, evaluated ability of a high-risk (HiRi) mutational signatures to provide prognostic and predictive information

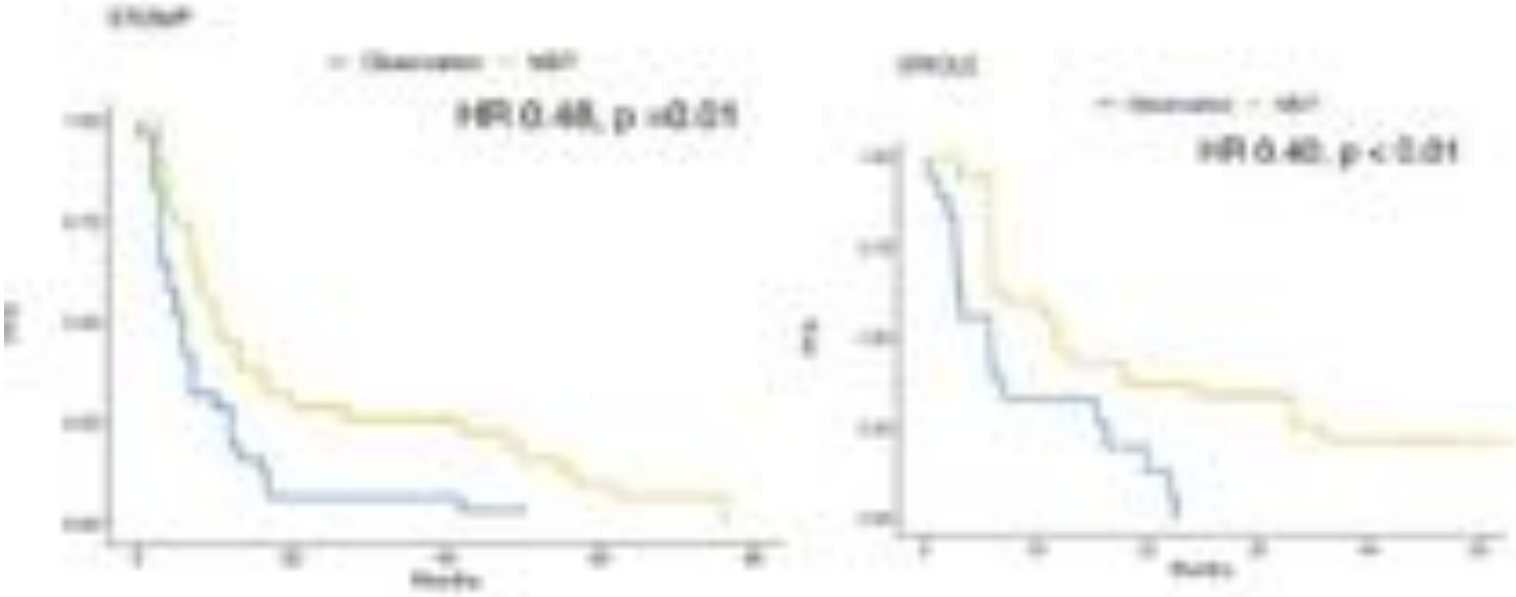
ASCO 2022: Poster 5025

- omCSPC (defined as less than 3 lesions) enrolled on STOMP (n = 62) and ORIOLE (n = 54).
- Patients were randomized to MDT or observation.
- Primary endpoint was progression-free survival (PFS) defined as either PSA progression, initiation of androgen deprivation, or death.

ASCO 2022: Poster 5025 (Primary Endpoint)

Results

Median PFS was prolonged with MDT (11.9 months) compared to observation (5.9 months) with a pooled HR of 0.44 (95% CI, 0.29 – 0.66, p-value < 0.001).

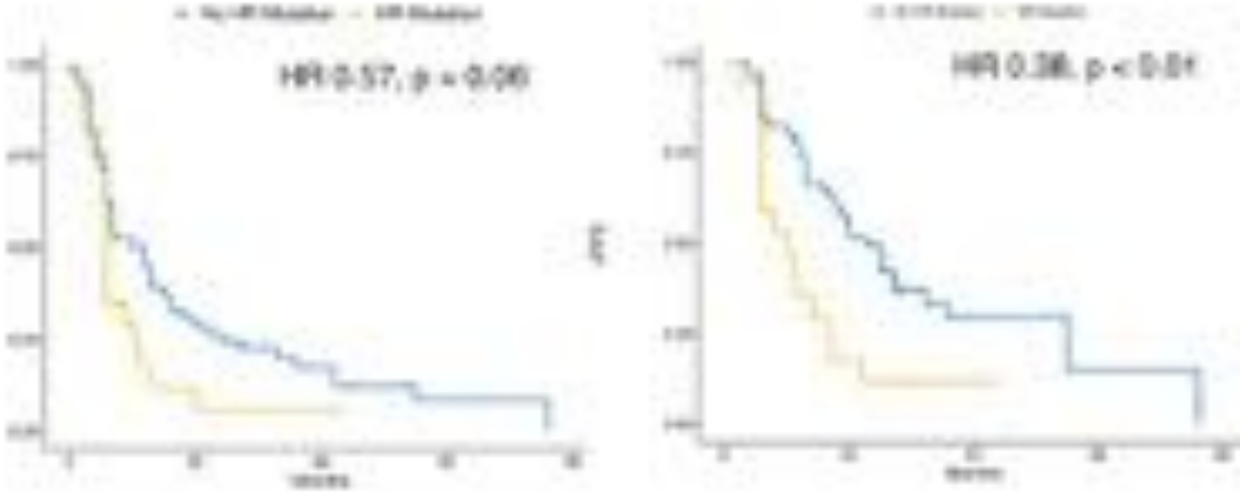


ASCO 2022: Poster 5025

- Secondary endpoint was radiographic PFS (rPFS) defined as radiographic progression or death.
- Identify a high risk mutational signature defined as pathogenic mutations
- ATM, BRCA1/2, Rb1, pTEN, and TP53 evaluated using next generation sequencing (NGS).

ASCO 2022: Poster 5025 (Secondary Endpoint/Radiographic)

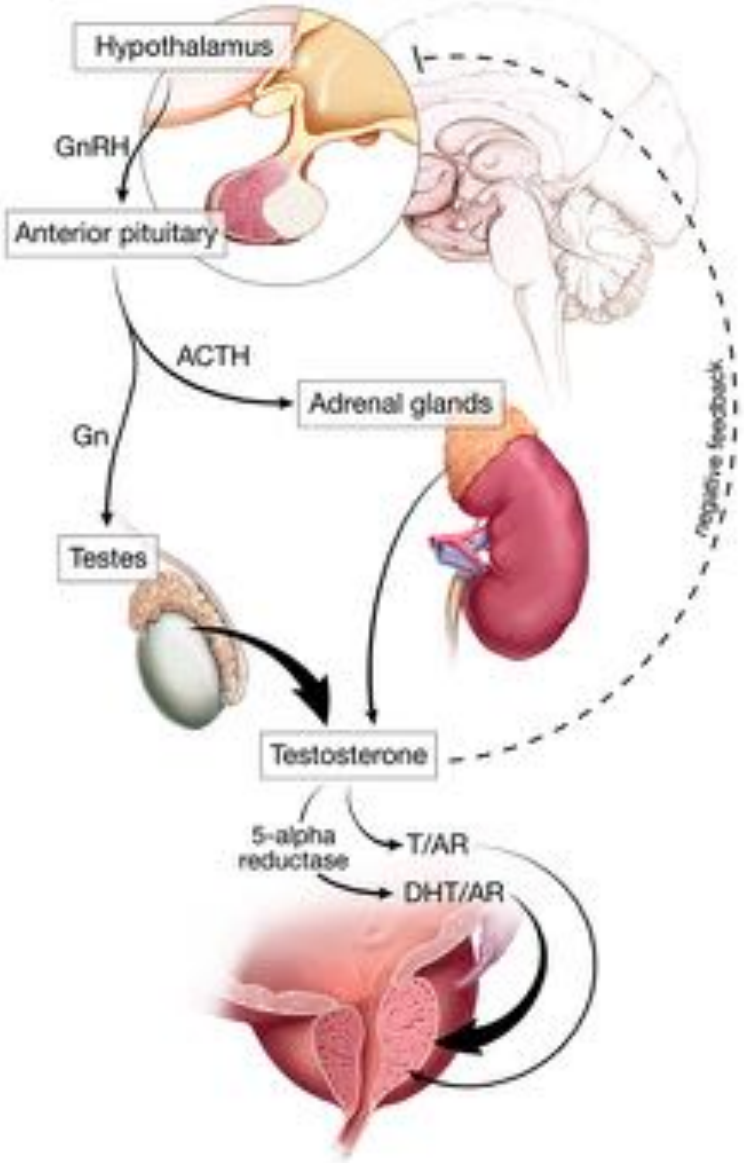
HiRi mutation was prognostic for PFS -- in those without a HiRi mutation median PFS was 11.9 months compared to 5.9 months in those with a HiRi mutation (HR of 1.74, p = 0.06). HiRi mutation was also prognostic for rPFS -- those without a high-risk mutation experienced median rPFS of 22.6 months compared to 10.0 months in those with a high-risk mutation (HR 2.62, p <0.01).



My Practice based on Poster 5025

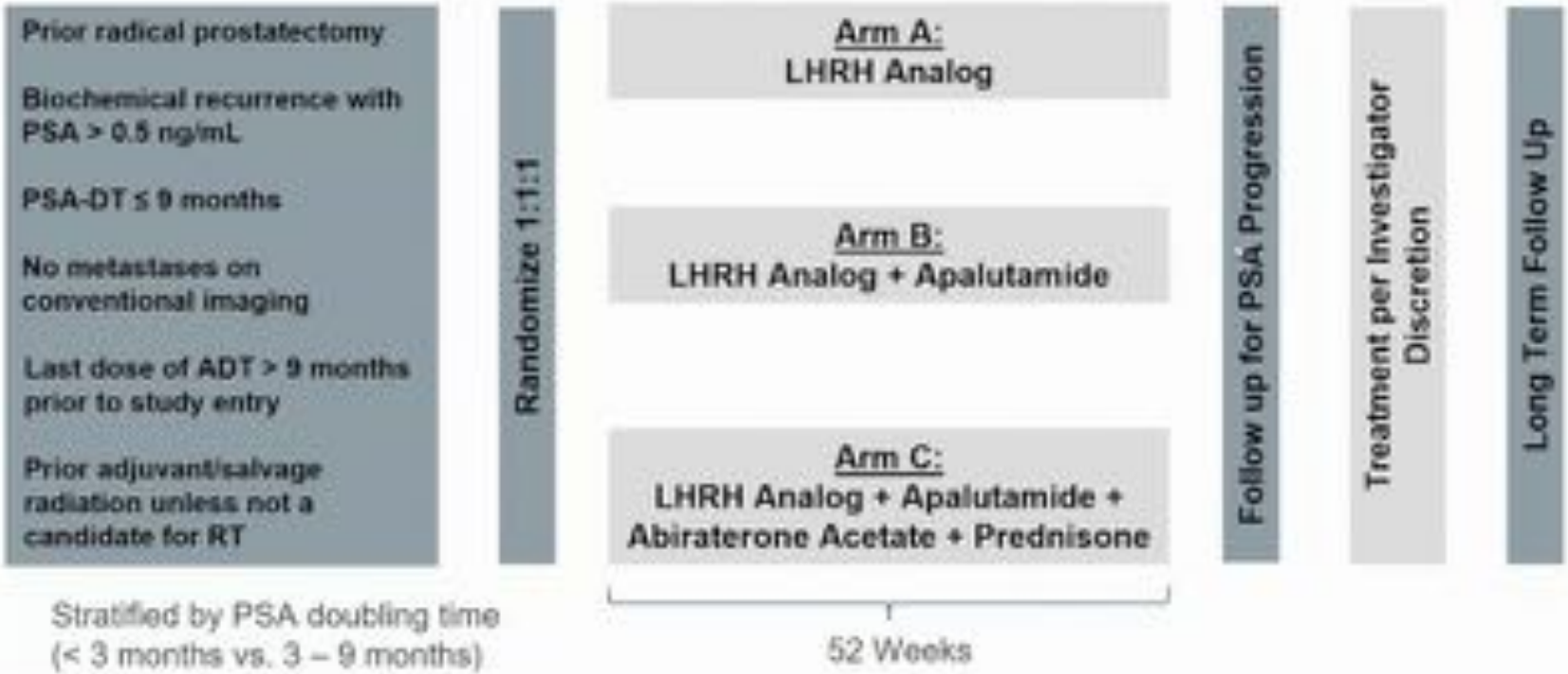
- Next generation sequencing for all metastatic prostate cancer patients (liquid and tissue).
- Prioritize MDT for patients with 3 or fewer lesions if they do NOT have homologous recombination repair deficiency (rPFS 22.6 months vs 10 months)
- Keeps patients off of ADT and the side effects associated with treatment

2. Nonmetastatic prostate cancer



- **<u>Clinical Problem</u>**
- Watch and worry after radical prostatectomy
- Increased PSA
- Patient Anxiety
- Testosterone Suppression with associated side effects
- Life Long Treatment?

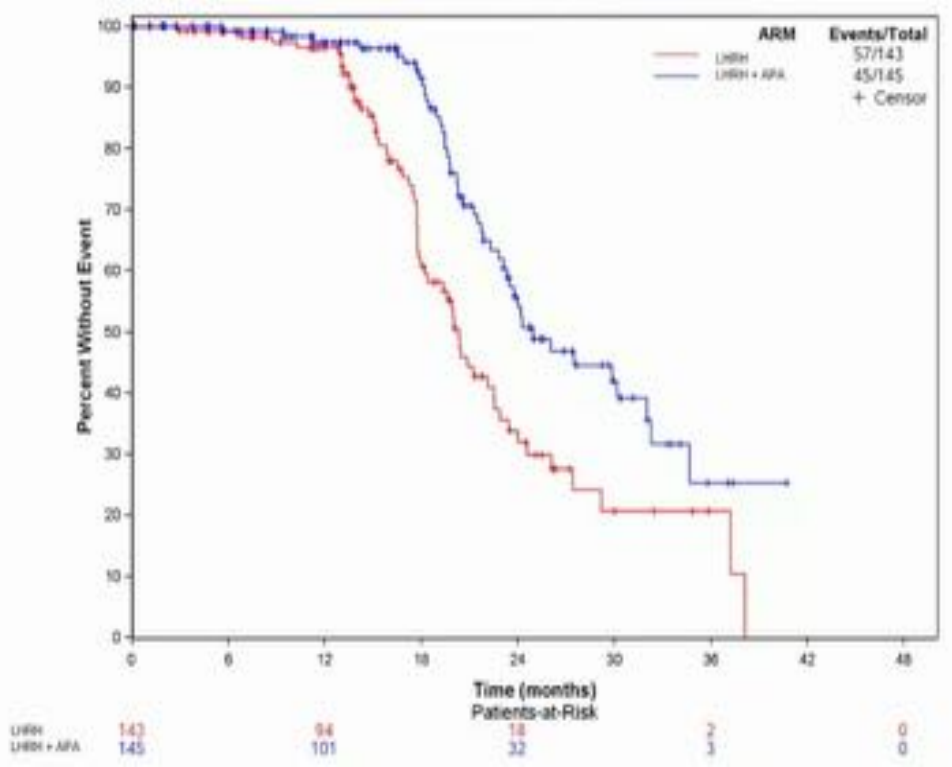
PRESTO design



Cohort Groups

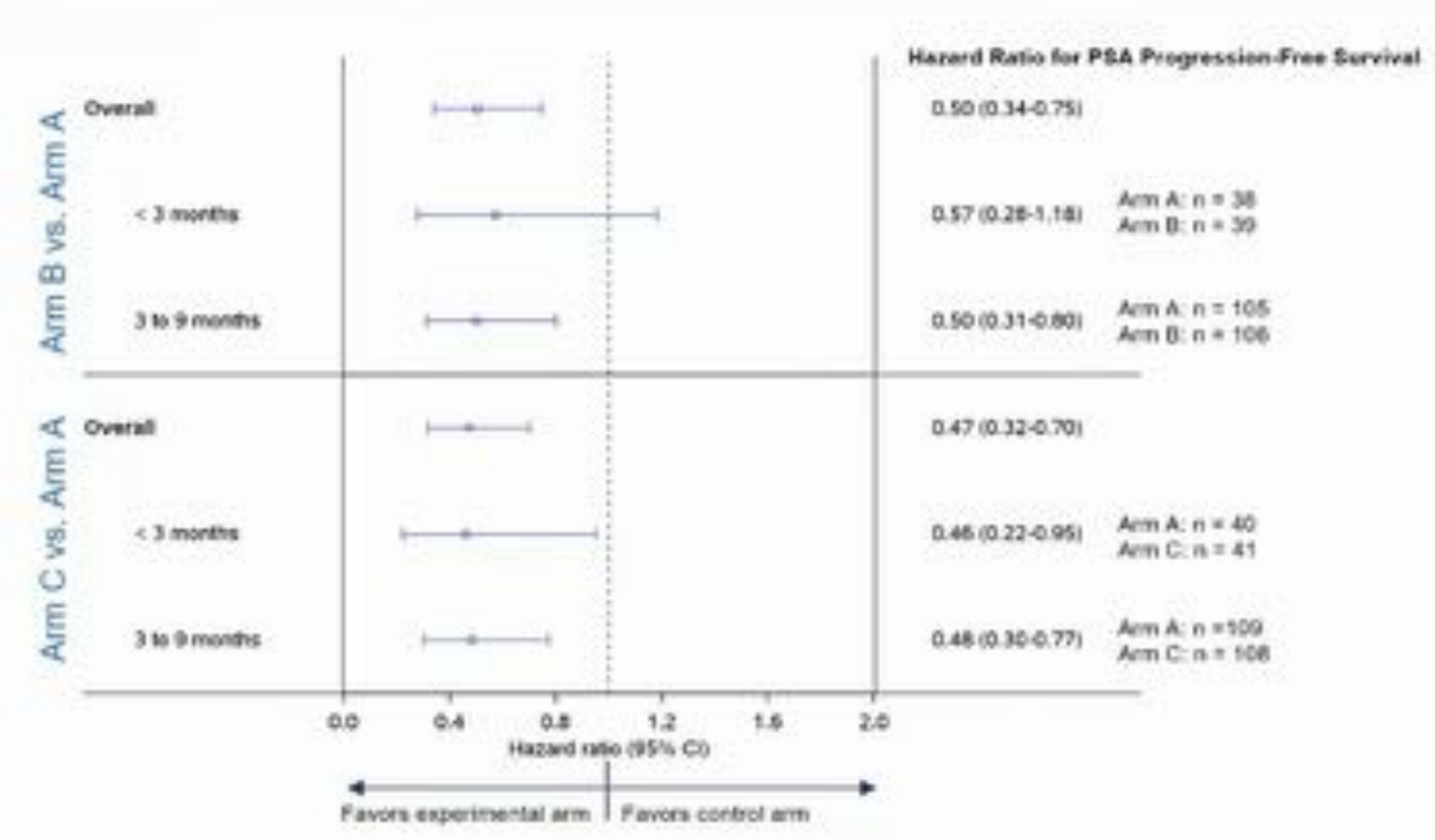
	Arm A (n = 166)	Arm B (n = 168)	Arm C (n = 169)	Overall Study Cohort (N = 503)
Median PSA at study entry, ng/mL (Q1, Q3)	1.73 (1.01, 3.20)	1.80 (0.97, 3.58)	1.77 (0.95, 4.21)	1.77 (0.97,3.57)
PSA doubling time strata (%)				
< 3 months	43 (25.9)	43 (25.6)	44 (26.0)	130 (25.8)
3 – 9 months	123 (74.1)	125 (74.4)	125 (74.0)	373 (74.2)
Median time interval between radical prostatectomy and study entry, years (Q1, Q3)	4.6 (2.8, 7.3)	4.7 (2.8, 6.5)	4.0 (2.8, 6.8)	4.4 (2.8, 6.8)
Prior radiation, N (%)	147 (88.6)	142 (84.5)	137 (81.1)	426 (84.7)
Prior androgen deprivation therapy, N (%)	71 (42.8)	75 (44.6)	67 (39.6)	213 (42.35)

PRESTO Study



- Median follow-up 21.5 months
- both experimental arms significantly prolonged biochemical progression-free survival compared to the control arm
- median 24.9 months for ADT + apalutamide vs 20.3 months for ADT, HR 0.52 (95% CI 0.35–0.77):

PRESTO Study



Most common adverse effect was hypertesion

Summary of Adverse Events

	Arm A ADT (n=160)	Arm B ADT + APA (n=163)	Arm C ADT + APA + AAP (n=161)
Adverse Events (AE)	n (%)	n (%)	n (%)
Any AE	145 (90.6)	148 (90.8)	155 (96.3)
Grade 3 or 4 AE	30 (18.8)	41 (25.2)	61 (37.9)
Any Serious AE	13 (8.1)	14 (8.6)	28 (17.4)
AE leading to treatment discontinuation	0 (0.0)	3 (1.8)	5 (3.1)

PRESTO Study

- Median time to testosterone recovery was 4.0, 3.9 and 4.8 months in ADT, ADT + apalutamide, and ADT + apalutamide + abiraterone acetate plus prednisone arms, respectively.
- Study Limitations
  - A. PSA-based rather than metastasis-free survival endpoints
  - B. Metabolic imaging (PSMA PET) were not used at screening (M0 biochemically recurrent CSPC population maybe seen with PSMA PET)
  - C. Metastasis-directed therapy in oligometastatic CSPC in conjunction with ADT remains to be defined.

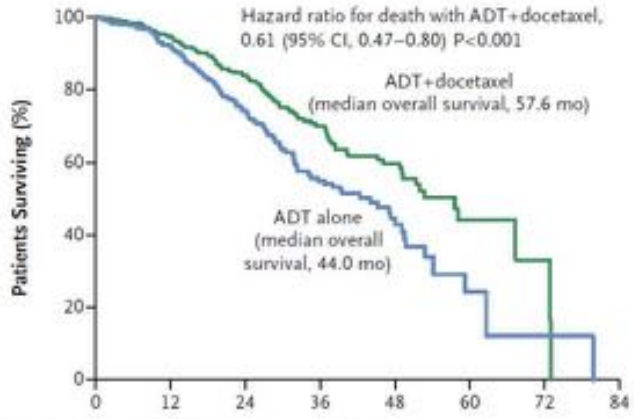
My Practice based on PRESTO

- Not practice changing at this time.
- I am intrigued with 1 year fixed treatment with ADT and Androgen pathway inhibitor.
- Patient's testosterone level recovered.

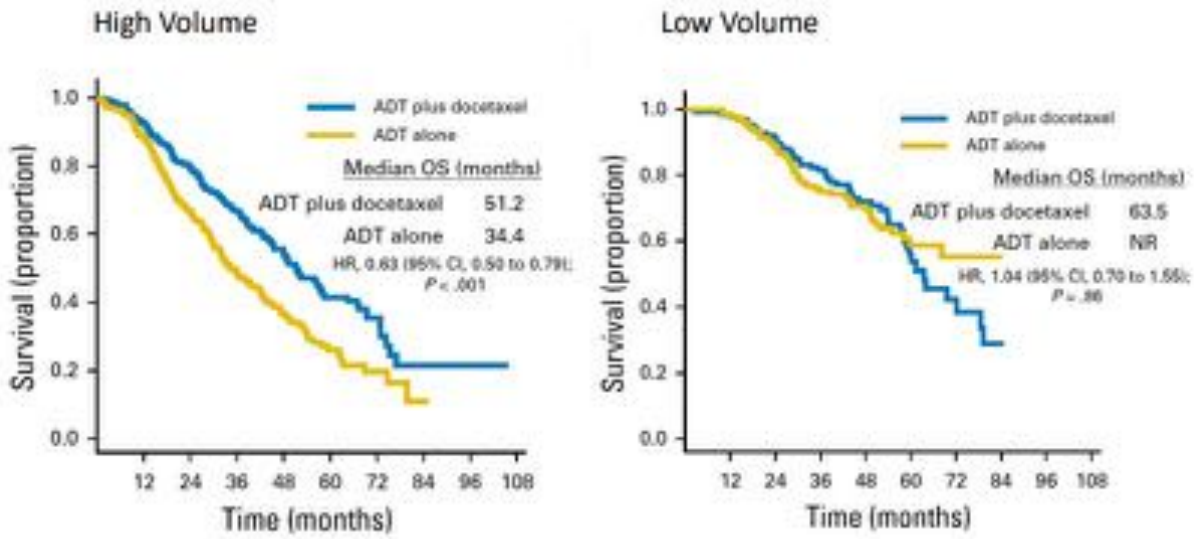
3. Metastatic Hormone Sensitive Prostate Cancer

- Clinical Problem
- Triplet vs Doublet Treatment
- Heterogenous Group (Synchronous vs Metachronous)

Historical Data: CHAARTED Study



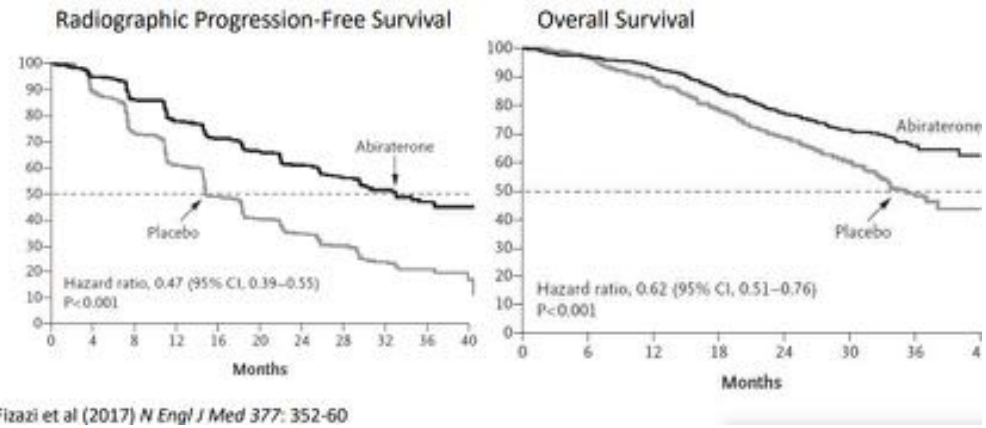
Sweeney et al (2015) *N Engl J Med 373*: 737-46



Kyriakopoulos et al (2018) *J Clin Oncol 36*: 1080-0187

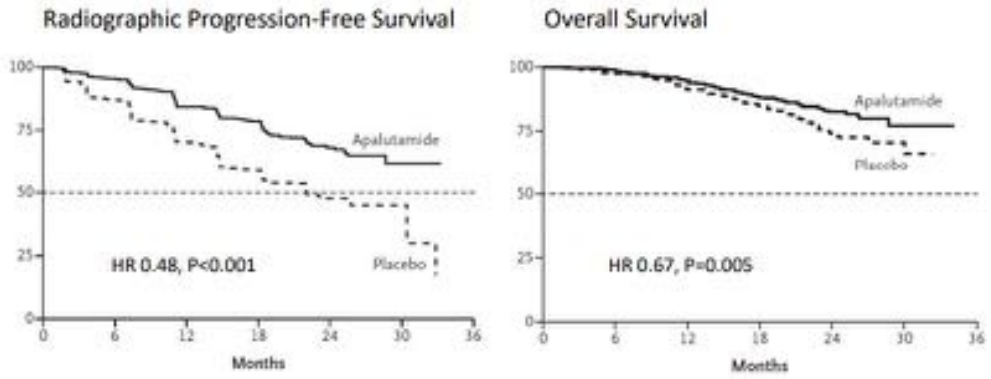
Androgen Pathway Inhibitors

LATITUDE: Abiraterone Acetate for mHSPC



Fizazi et al (2017) *N Engl J Med 377*: 352-60

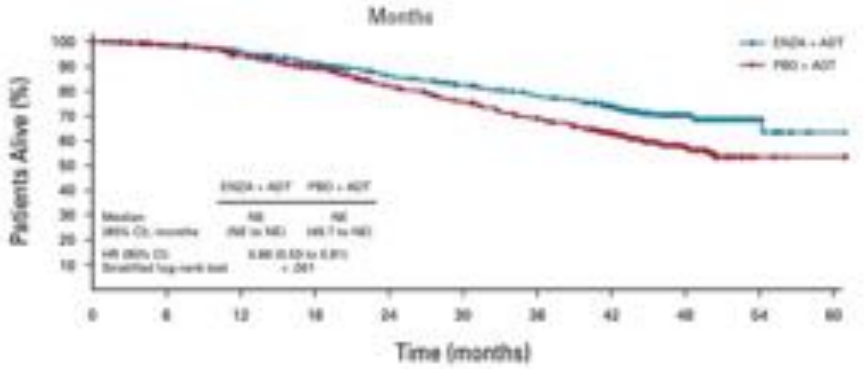
TITAN: Apalutamide for mHSPC



Chi et al (2019) *N Engl J Med 381*: 13-24

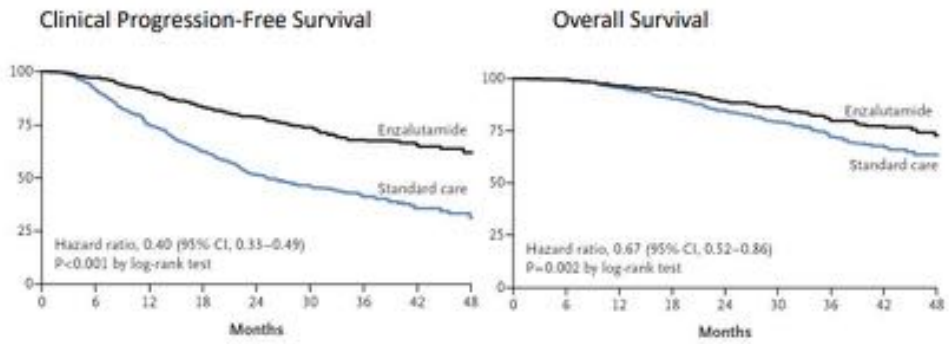
ARCHES and ENZAMET

OS



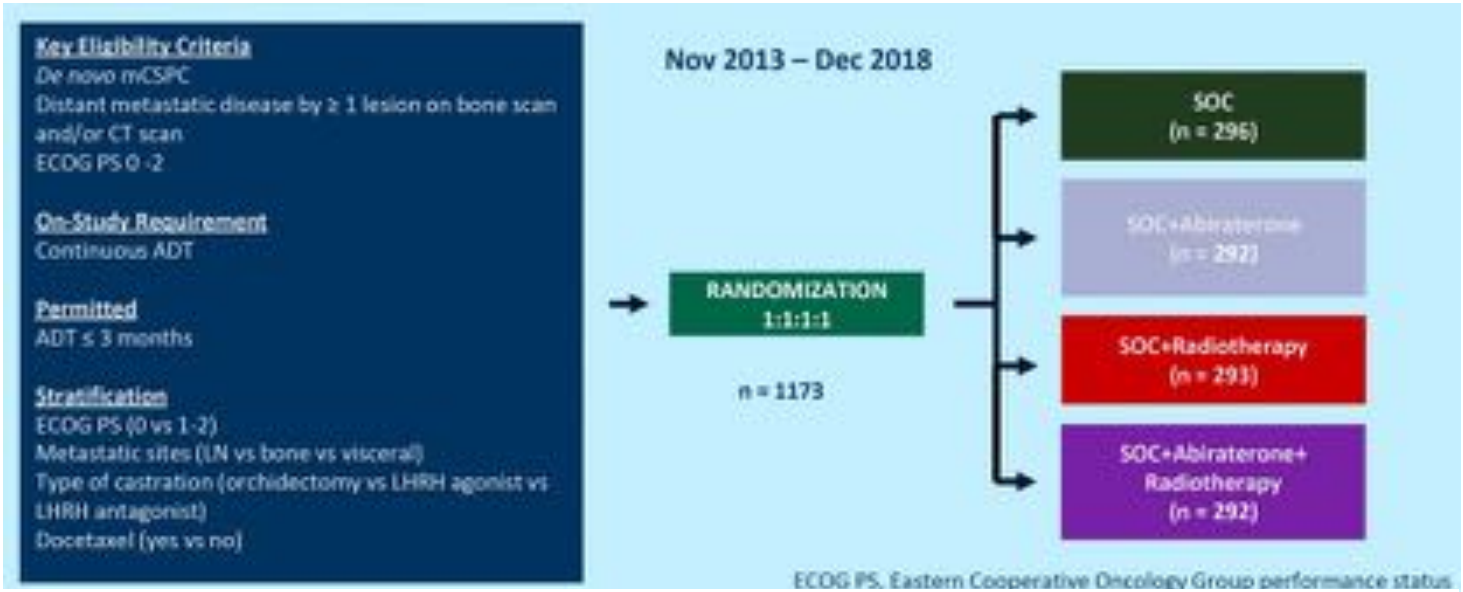
Armstrong et al (2019) *J Clin Oncol 37:* 2974-2986; Armstrong et al (2022) *J Clin Oncol* DOI: 10.1200/JCO.22.00193

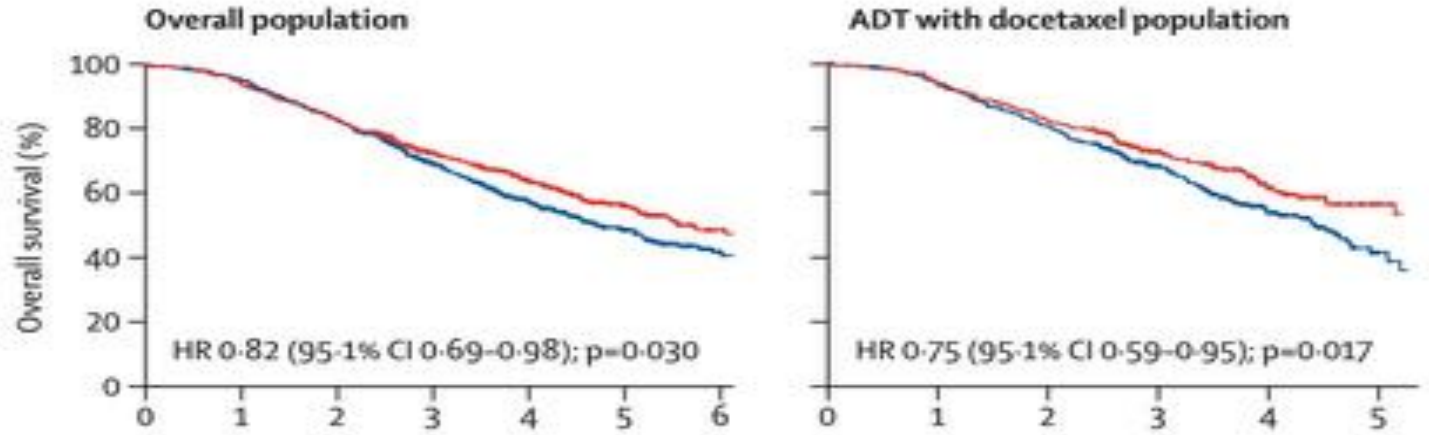
ENZAMET: Enzalutamide for mHSPC



Davis et al (2019) *N Engl J Med 381*: 121-131

PEACE -1





Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

ARASENS Study

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Alvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

March 24, 2022

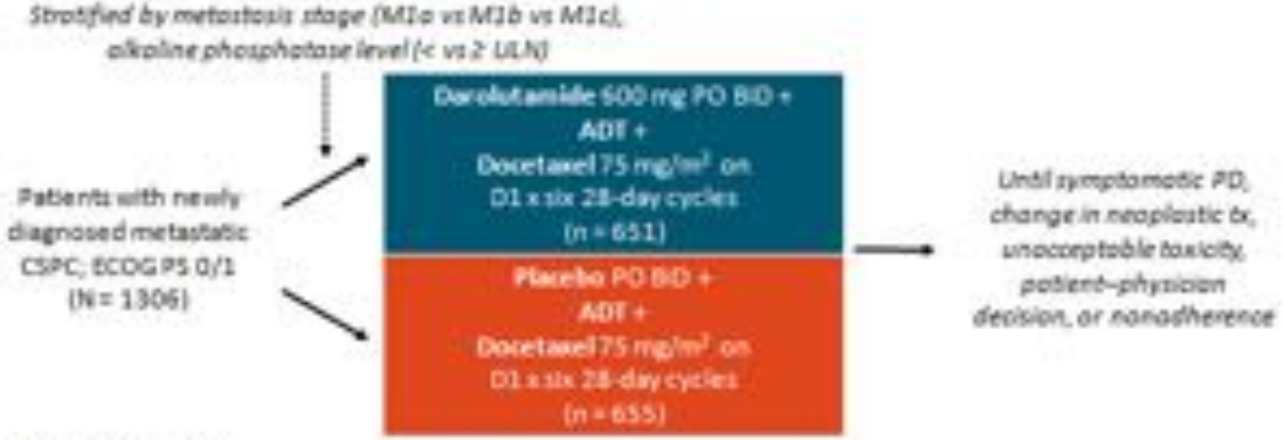
N Engl J Med 2022; 386:1132-1142

DOI: 10.1056/NEJMoa2119115

ARASENS

ARASENS: Darolutamide vs Placebo in Combination With ADT + Docetaxel in mCSPC

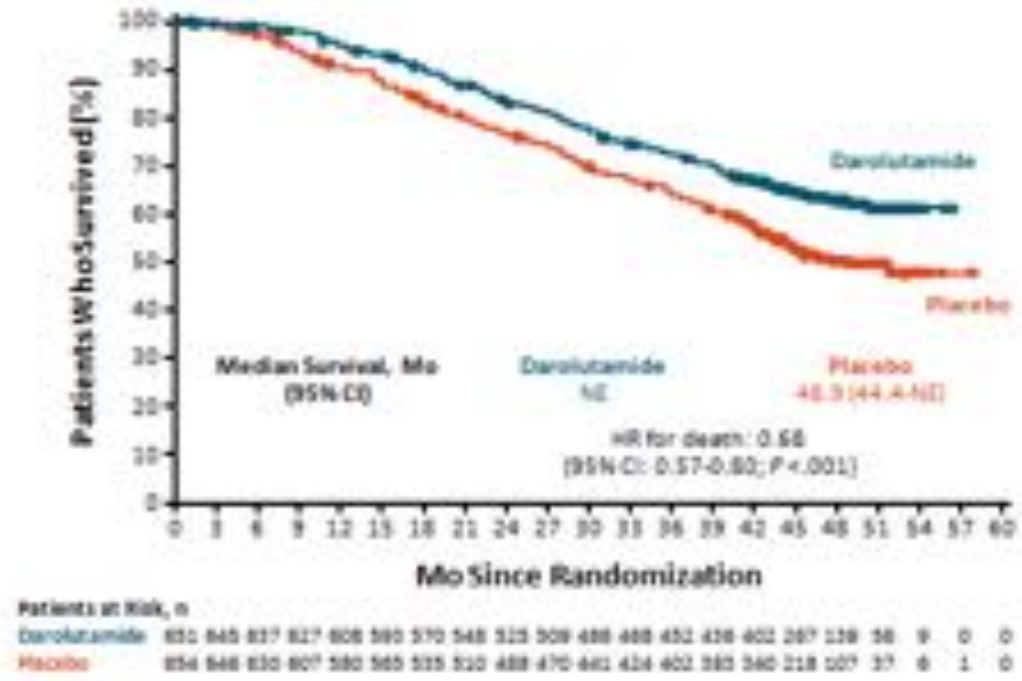
- International, randomized, double-blind phase III trial in 286 sites across 23 countries



- **Primary endpoint:** OS
- **Secondary endpoints tested hierarchically in this order:** time to CRPC, time to pain progression, SSE-free survival, time to first SSE, time to initiation of subsequent anticancer therapy, time to worsening of physical symptoms, time to first opioid use, safety

Overall Survival

ARASENS: OS (Primary Endpoint)



- Addition of darolutamide to ADT + docetaxel significantly reduced risk of death by 32.5% vs placebo (P <.001)
  - 75.6% of patients in placebo arm received subsequent life-prolonging systemic tx
- OS benefit observed across most subgroups
  - HR (95%) for those stratified by metastatic stage at initial dx: M1, 0.707 (0.590-0.848); M0, 0.605 (0.348-1.052)

Adverse Events

Selected Grade 3/4 AE, n (%)	Darolutamide + ADT + Docetaxel (n = 652)	Placebo + ADT + Docetaxel (n = 650)
Neutropenia	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT	18 (2.8)	11 (1.7)
Increased AST	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
UTI	13 (2.0)	12 (1.8)

Safety Outcome, n (%)	Darolutamide + ADT + Docetaxel (n = 652)	Placebo + ADT + Docetaxel (n = 650)
Any AE	649 (99.5)	642 (98.8)
Serious AE	292 (44.8)	275 (42.3)
AE leading to permanent d/c of trial agent		
• Darolutamide or placebo	88 (13.5)	69 (10.6)
• Docetaxel	52 (8.0)	67 (10.3)

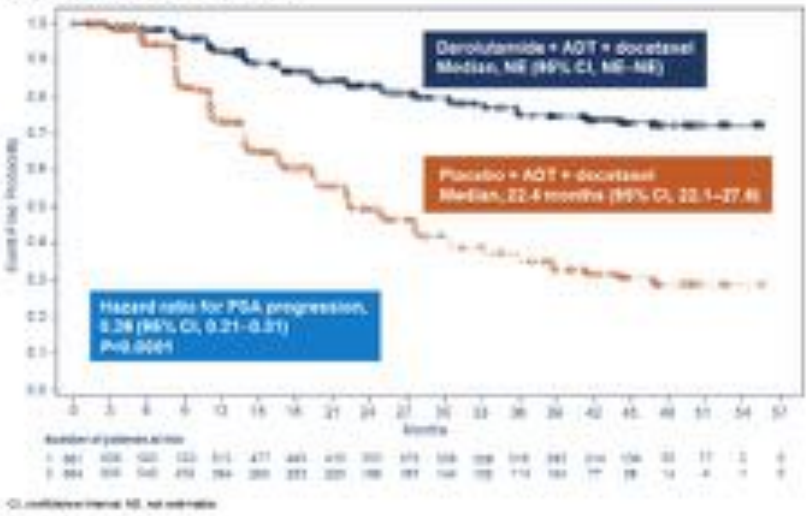
Smith. NEJM. March 2023

ARASENS Update ASCO 2022

RESULTS (cont'd)

- Darolutamide significantly prolonged time to PSA progression versus placebo (HR 0.26; 95% CI 0.21–0.31; P <0.0001) (**Figure 1**)

Figure 1. Time to PSA progression

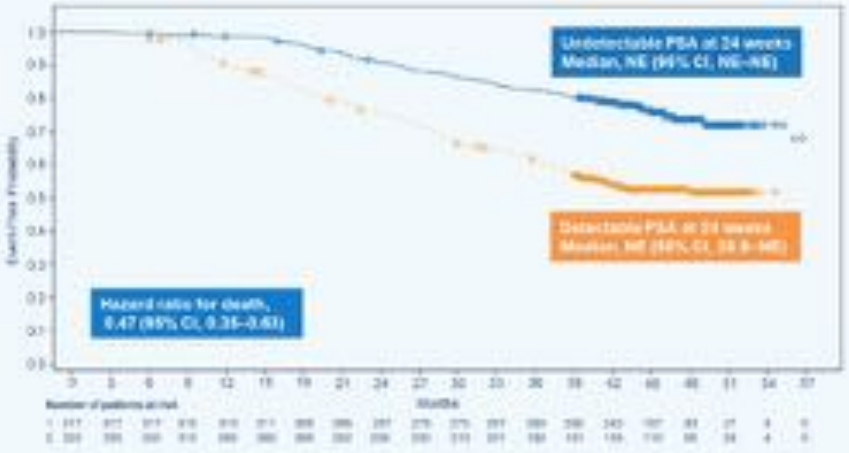


- Incidences of adverse events (AEs) were generally similar in patients achieving and not achieving undetectable PSA and by treatment groups, with a higher rate of drug discontinuations due to AEs among patients who did not achieve undetectable PSA at any time (**Table 2**)

Overall survival was improved for patients who achieved undetectable PSA

- Among darolutamide-treated patients, achievement of undetectable PSA at 24 and 36 weeks was associated with improved OS; risk reductions of death were 53% and 63%, respectively, by stratified Cox regression

Darolutamide + ADT + docetaxel



Saad et al. ASCO 2022 J Clin Oncol 40, 2022 (suppl 16; abstr 5078)

ARASENS Conclusion

- Darolutamide, Docetaxel, and ADT significantly increased OS vs placebo + ADT + docetaxel in patients with metastatic castrate sensitive prostate cancer
- Median OS: NE vs 48.9 mo (HR: 0.68; 95% CI: 0.57-0.80; *P* <.001)
- Every patient with metastatic hormone sensitive prostate adenocarcinoma should receive androgen pathway inhibitor with ADT at a bare minimum.
- Consider Darolutamide, Docetaxel, and ADT as new standard of care for mCSPC with high risk and/or high volume disease.
- Triplet vs Double treatment for all patients?

Prostate Cancer Classification

High Volume

- Visceral
- Greater than 3 bone lesions with 1 extra-axial

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

High Risk

Gleason 8-10

At least 3 bone lesion

Measurable visceral lesions

All patients

- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria

www.stampedetrial.org

Synchronous vs Metachronous Prostate Cancer

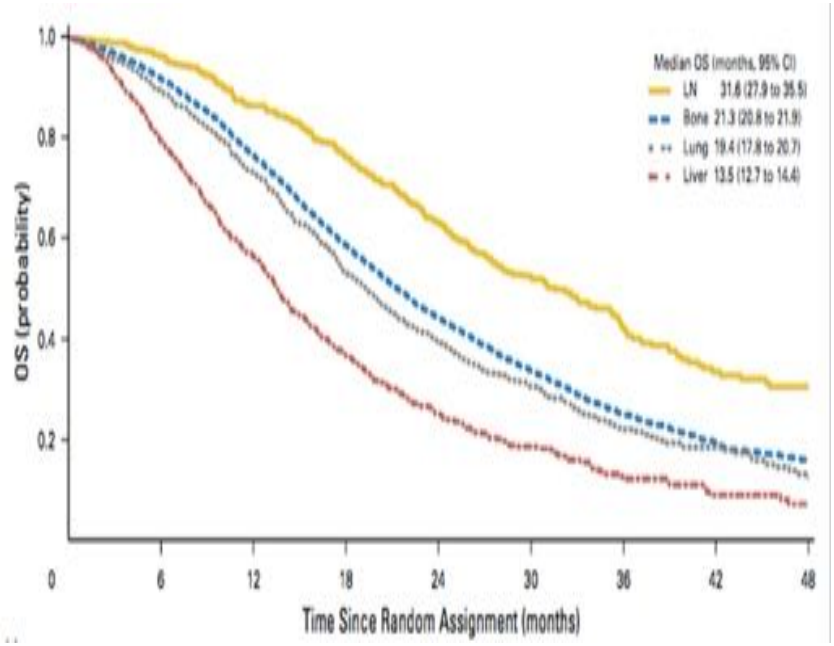
Synchronous

- Patients diagnosed with a primary prostate cancer and metastases simultaneously

Metachronous

- Patients diagnosed with nonmetastatic disease at initial diagnosis and develop metastases during follow up

Staging in prognostication



ADT Alone (using CHAARTED and GETUG)	Median OS
Relapsed Low Volume	~8 y
Relapsed High Volume	4.5
De Novo Low Volume	4.5
De Novo High Volume	3

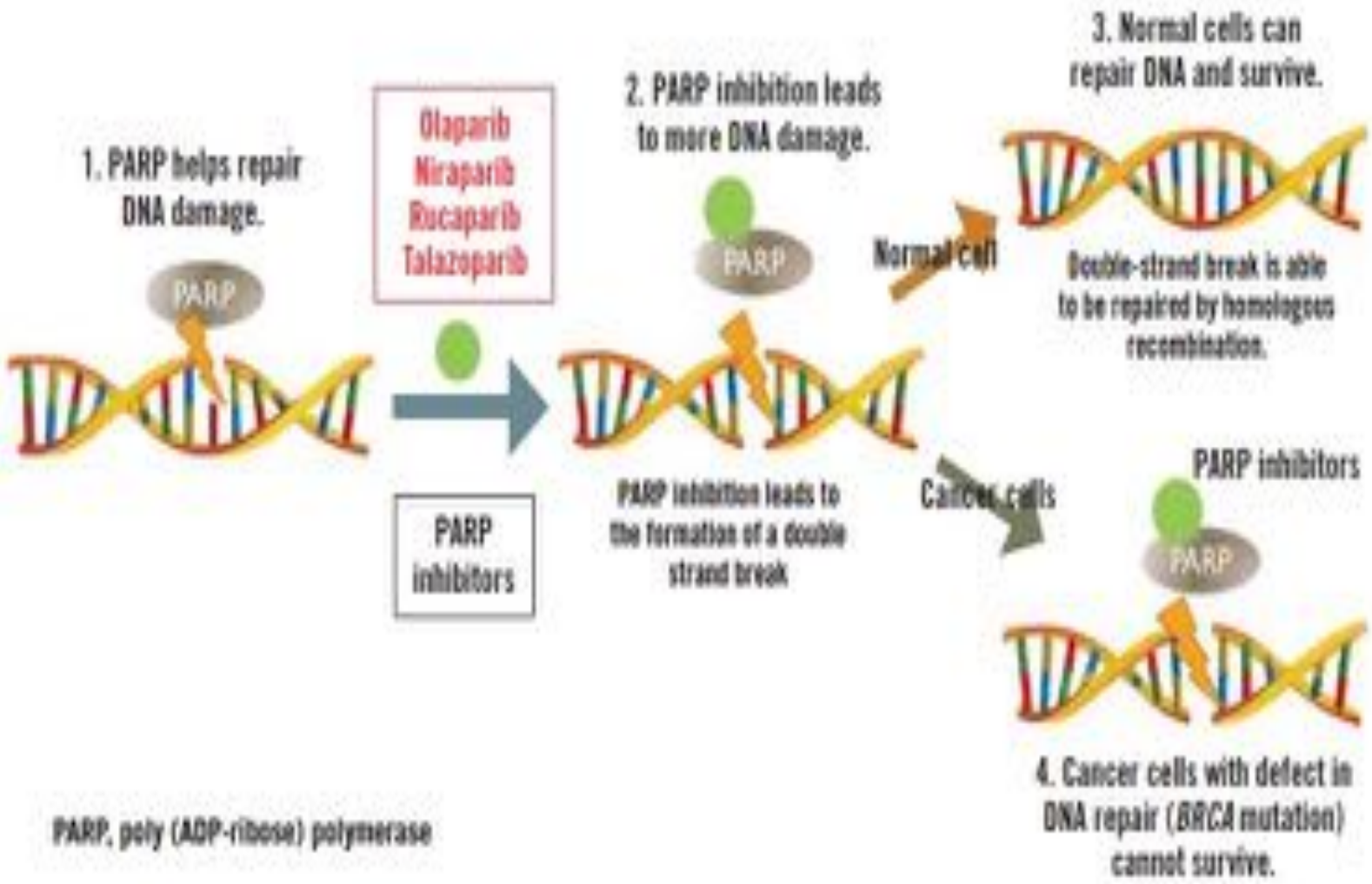
Halabi, JCO, 2016; Gravis Eur Urol 2018; Kyriakopoulos JCO 2018

My Practice

Synchronous High Volume **Darolutamide, Docetaxel, and ADT**	**Metachronous High Volume** **Darolutamide, Docetaxel, and ADT**
Synchronous Low Volume **Consider Darolutamide, Docetaxel, and ADT for p53, RB1, PTEN mutation**	**Metachronous Low Volume** **Androgen Pathway Inhibitor and ADT**

4. Metastatic Castrate Resistant Prostate Cancer

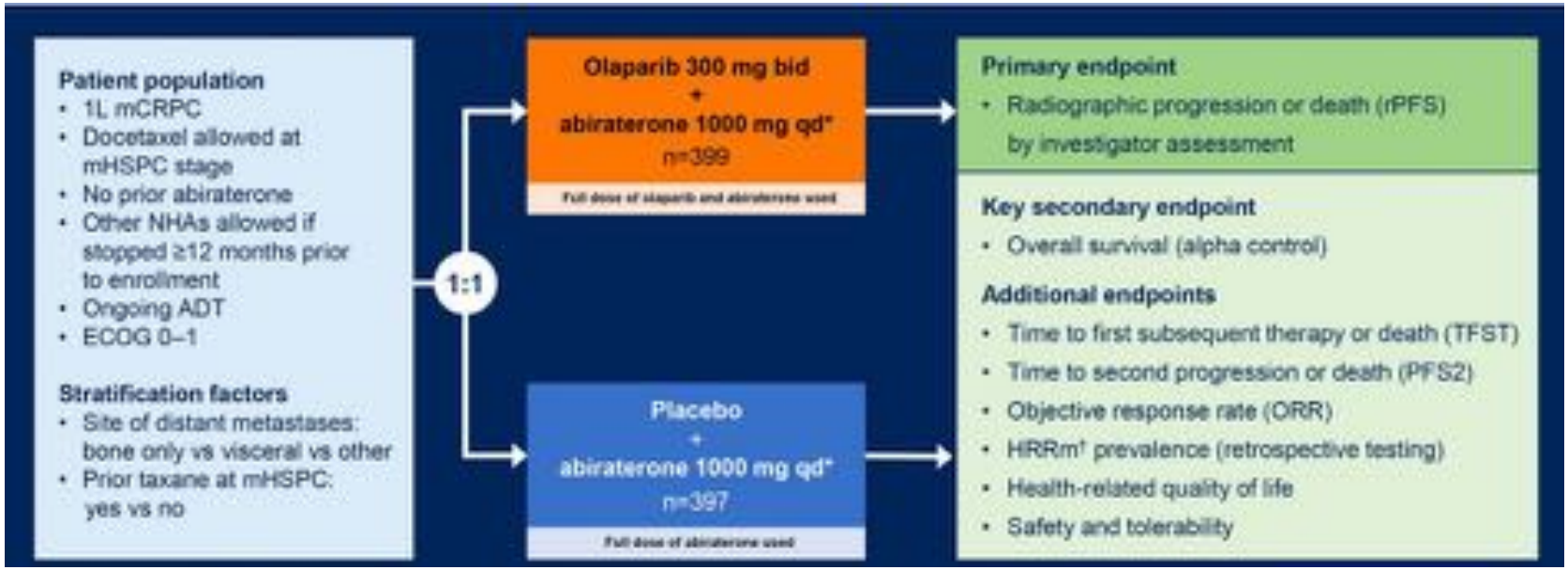
- **Clinical Problem**
- When do you use PARP inhibitors?
- Which patients should we prioritize for PARP inhibitors?



Jacob et al. UCC December 2020,Volume 09, Issue 04

PROpel Study

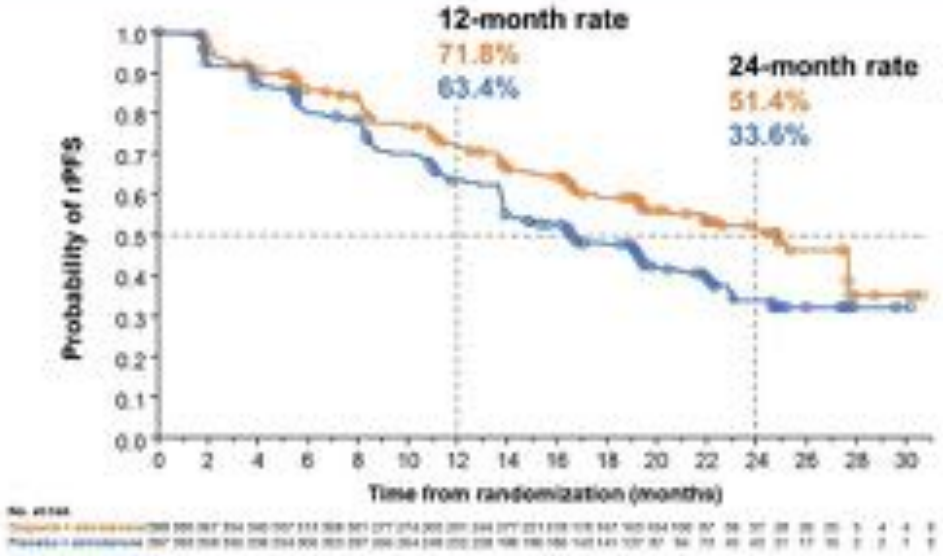
PROpel Study



Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel study

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

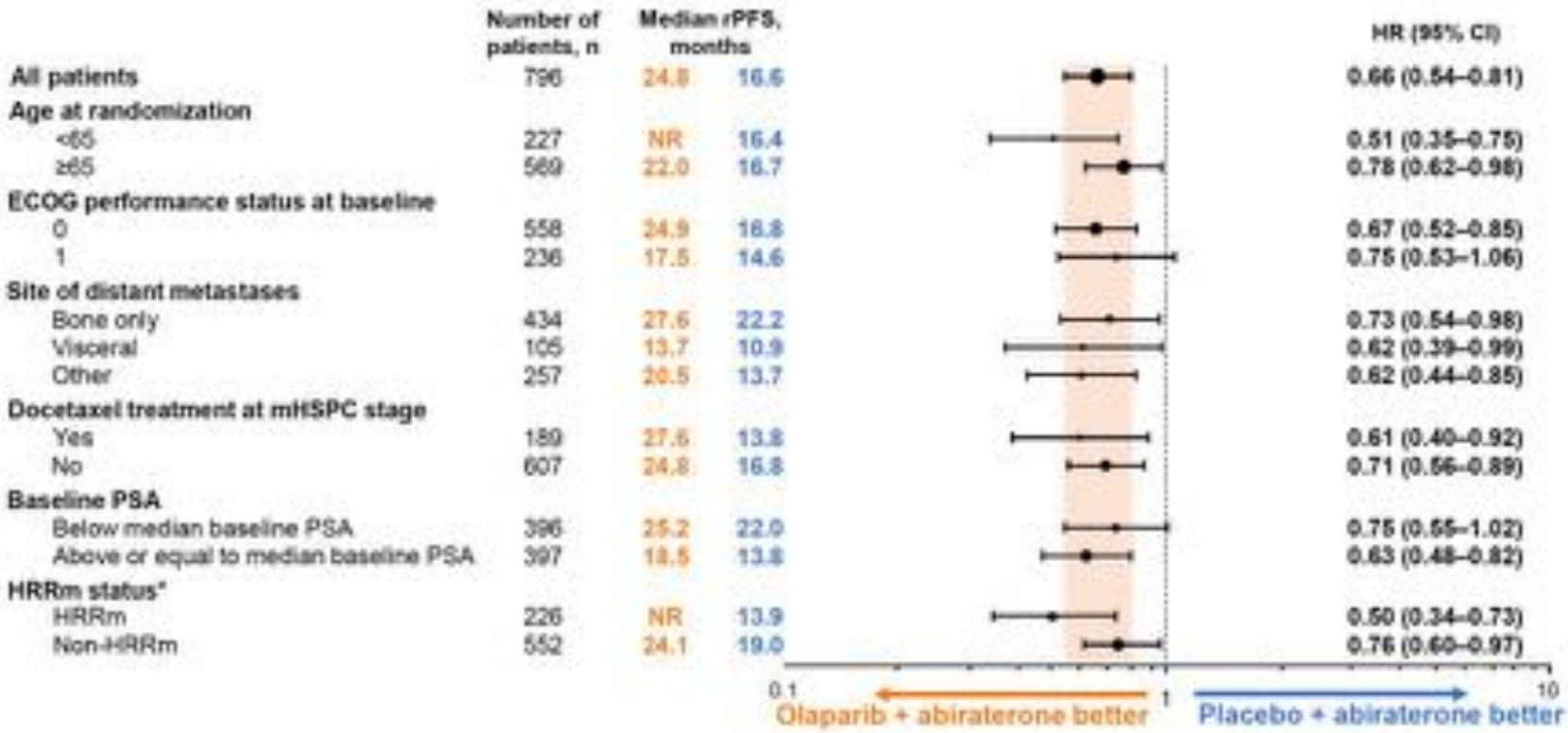
Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel Study

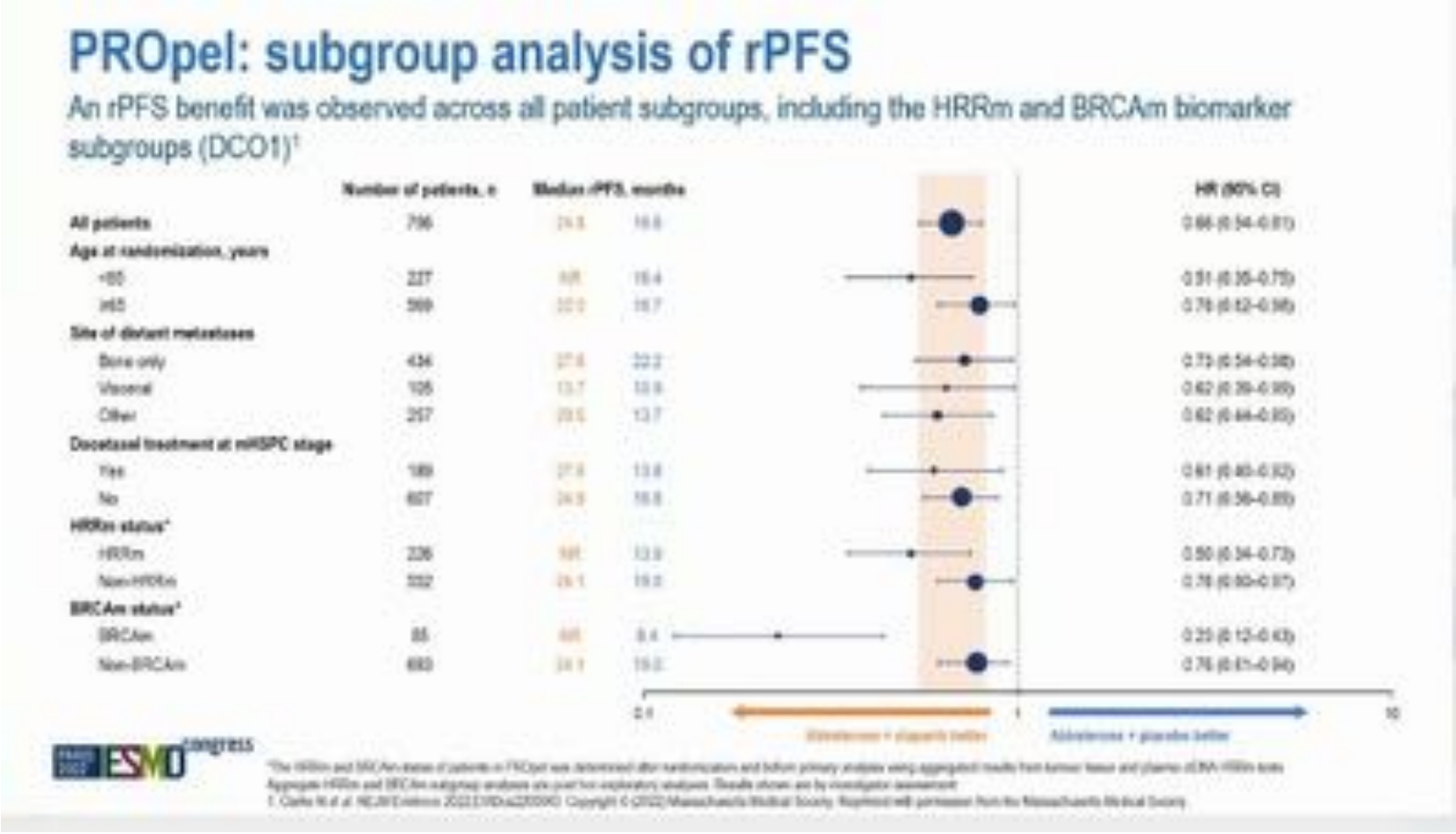


Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel Study

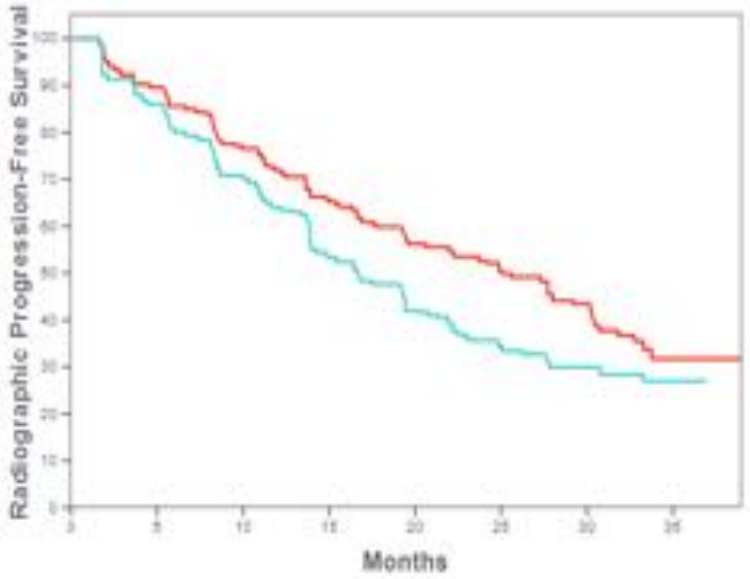
Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

ESMO 2022 Update



ITT Population

Radiographic progression-free survival by investigator assessment in ITT population

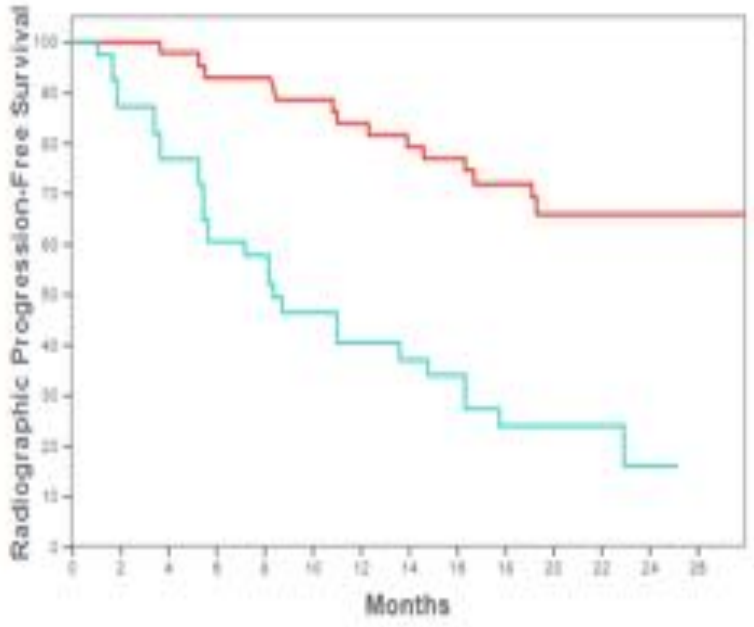


Curves	N	Median (95% CI)
Abiraterone + Olaparib	399	25
Placebo + Abiraterone	397	16.4

	HR (95% CI)
Abiraterone + Olaparib vs Placebo + Abiraterone	0.67 (0.56 - 0.81)

ESMO 2022 BRCA mutation group

Radiographic progression-free survival: BRCA mutation subgroup: Investigator assessment

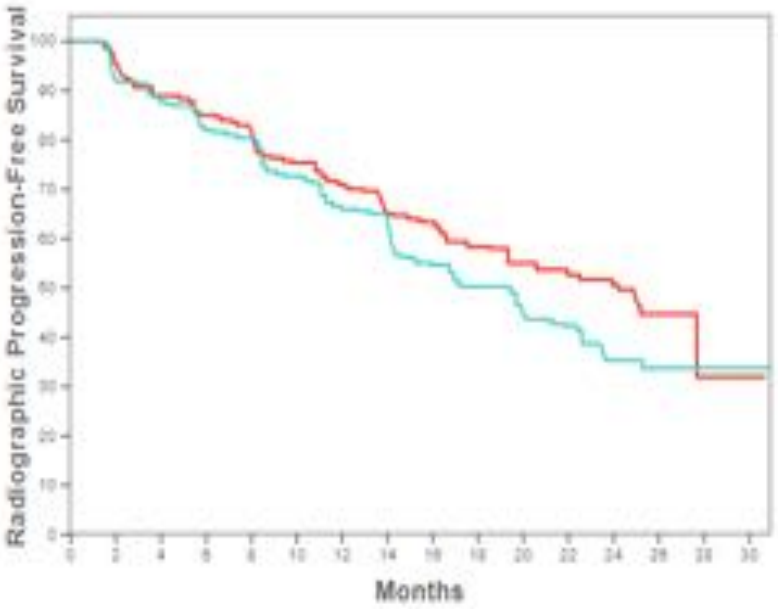


Curves	N	Median (95% CI)
Abiraterone + Olaparib	47	-
Placebo + Abiraterone	38	8.4

	HR (95% CI)
Abiraterone + Olaparib vs Placebo + Abiraterone	0.23 (0.12 - 0.43)

ESMO 2022 PROpel Non BRCA group

Radiographic progression-free survival: Non-BRCA mutation subgroup: Investigator assessment

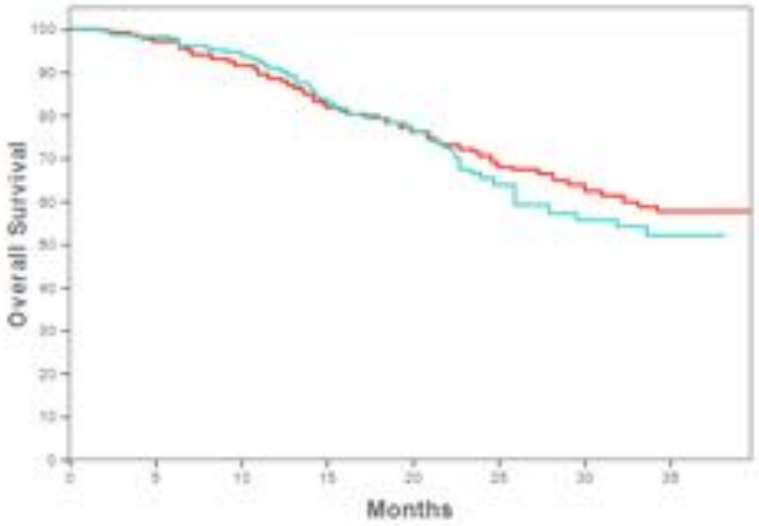


Curves	N	Median (95% CI)
Abiraterone + Olaparib	343	24.1
Placebo + Abiraterone	350	19

	HR (95% CI)
Abiraterone + Olaparib vs Placebo + Abiraterone	0.76 (0.61 - 0.94)

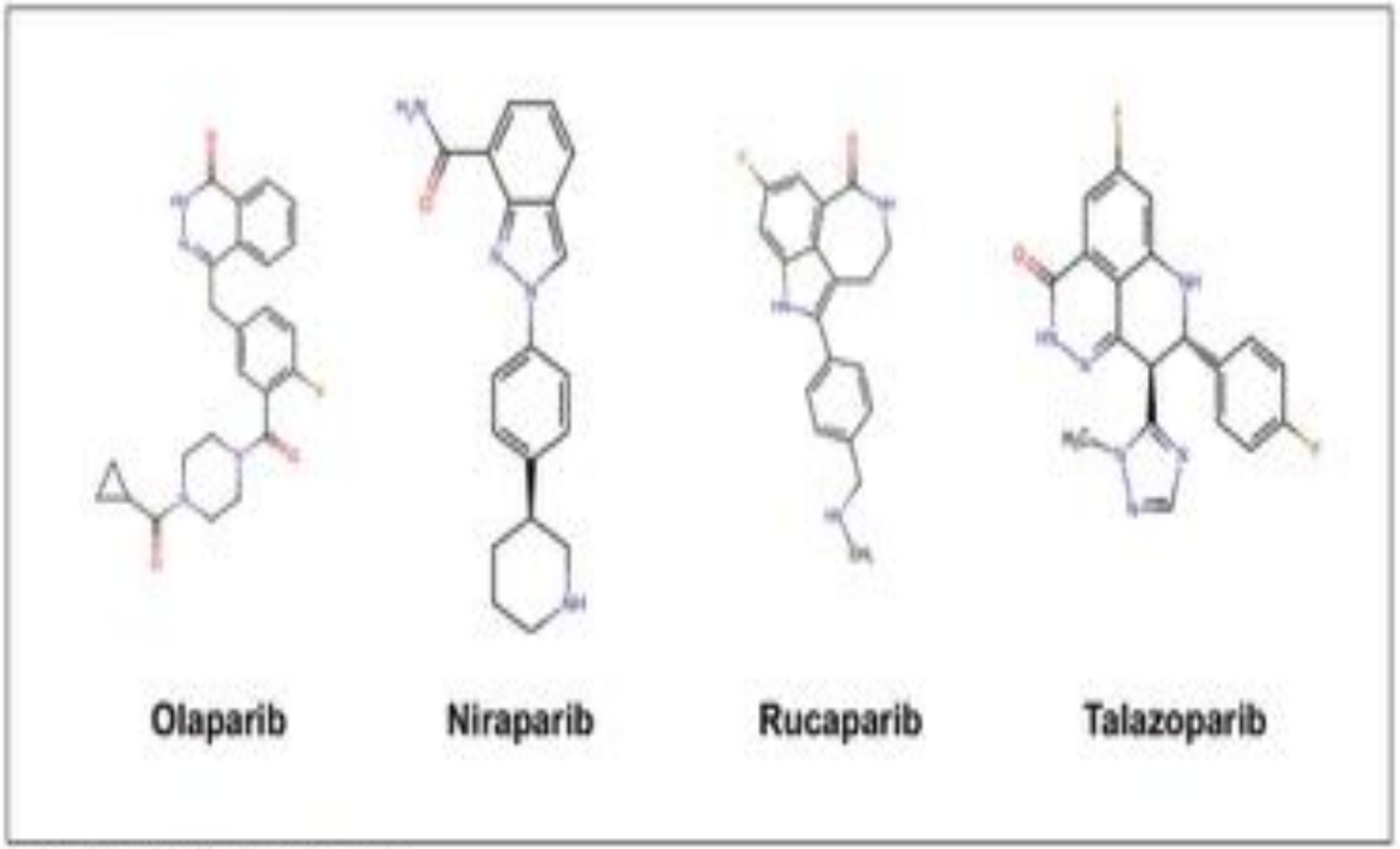
PROpel ESMO 2022 Update

Overall survival: Updated results: Data cut-off 2, 40.1% maturity



Curves	N
Abiraterone + Olaparib	399
Placebo + Abiraterone	397

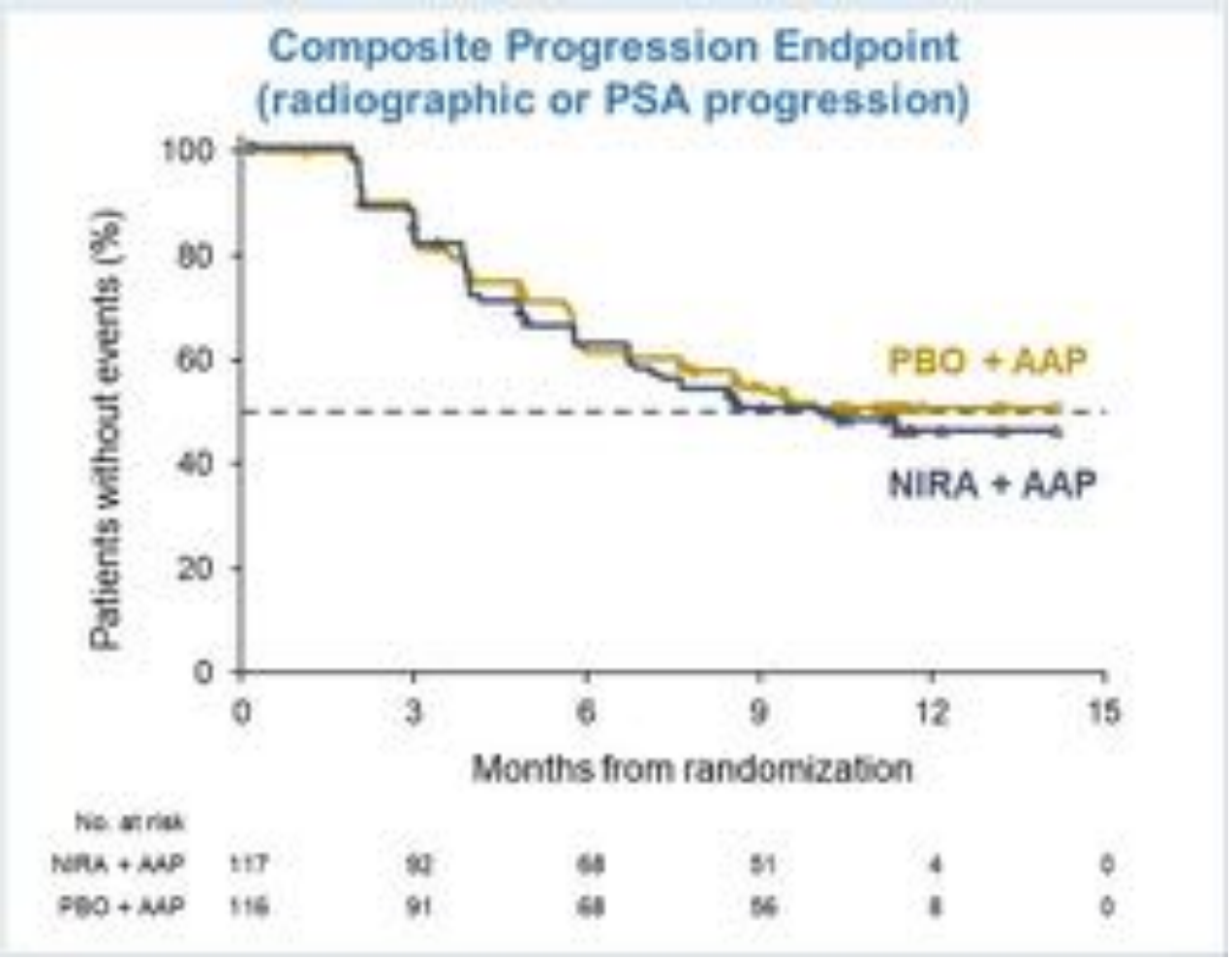
	HR (95% CI)	P-value
Abiraterone + Olaparib vs Placebo + Abiraterone	0.83 (0.66 - 1.03)	0.11



PARP, poly (ADP-ribose) polymerase

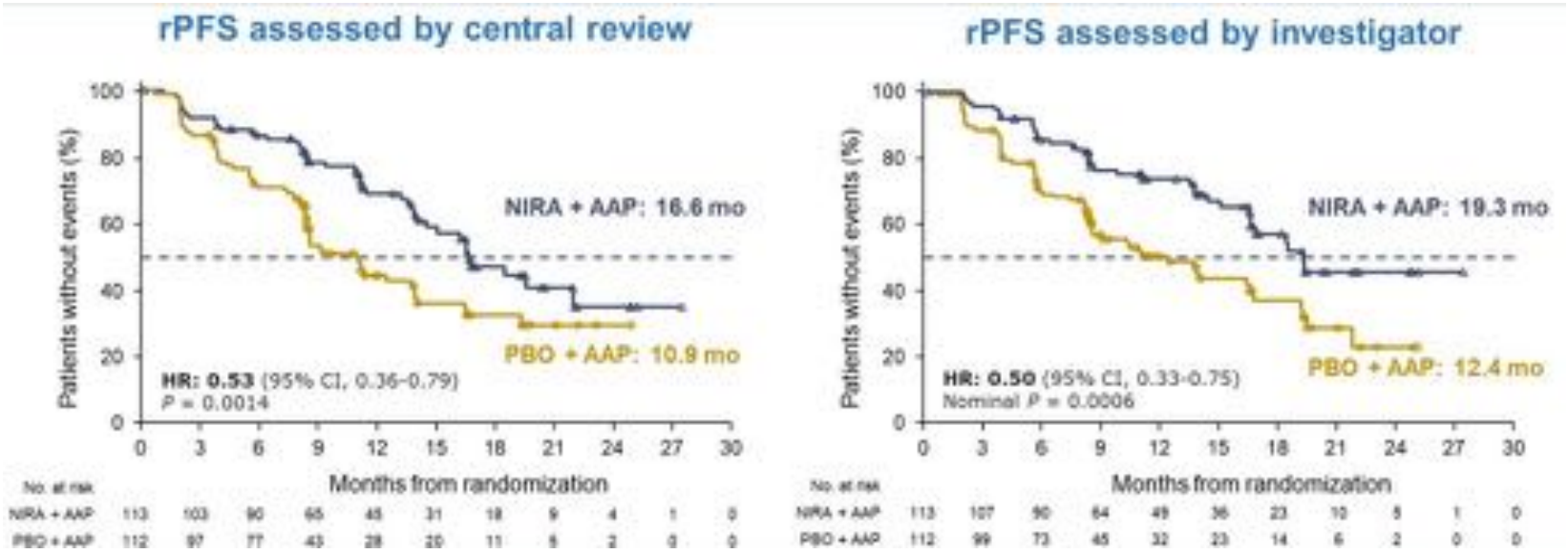
Jacob et al. UCC December 2020, Volume 09, Issue 04

MAGNITUDE study (HRR-)



Chi *et al* Journal of Clinical Oncology *40, no. 6_suppl (February 20, 2022) 12-12.*

Magnitude study



Chi et al Journal of Clinical Oncology *40, no. 6_suppl (February 20, 2022) 12-12.*

Talazoparib/Enzalutamide Combo Meets rPFS End Point in Untreated Metastatic CRPC

October 4, 2022

Take Home

- **TALAPRO-2**

  Enzalutamide and Talazaparib Positive for HRR (+) and HRR (-). Announced October 4, 2022.

  Paper not released yet.

- **PROpel**
  - rPFS benefit for olaparib + Abi/Pred vs placebo + Abi/Pred in overall population
  - (24.8 vs 16.6 mo; HR: 0.66; *P* <.0001)
  - Patients were not stratified by HRR status
- **MAGNITUDE Study**
  - rPFS benefit for niraparib + Abi/Pred vs placebo + Abi/Pred
  - Patients with HRR alterations (16.5 vs 13.7 mo; HR: 0.53; *P* = .0014)
  - No benefit in HRRmut -ve cohort

My practice

- Practice changing
  - I consider Olaparib + Abiraterone + ADT for patients with metastatic castrate resistant prostate cancer with BRCA1 and BRCA2 mutation the new standard of care

- Will await data for Enzalutamide + Rucaparib (CASPAR trial) for unselected patients since there appears to be discordance with MAGNITUDE and PROpel for unselected patients

Prostate Cancer Treatment Sequencing?

- **Clinical Problem**
- What is the best treatment after patients receive Docetaxel, Androgen pathway inhibitor, and ADT?
- Lutetium 177, Cabizitaxel, or PARP inhibitor?

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[ddd,ggg,hhh]

No prior docetaxel/no prior novel hormone therapy[ii]

- Preferred regimens
  - Abiraterone[1,jjj] (category 1[kkk])
  - Docetaxel[YY,lll] (category 1)
  - Enzalutamide[1] (category 1)
- Useful in certain circumstances
  - Radium-223[mmm] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[YY,nnnn] (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[l]

Prior novel hormone therapy/No prior docetaxel[ii,ooo]

- Preferred regimens
  - Docetaxel (category 1)[YY]
  - Sipuleucel-T[YY,nnnn]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[YY,lll]
  - Olaparib for HRRm (category 1)[ppp]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[YY]
  - Radium-223[mmm] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[ppp]
- Other recommended regimens
  - Abiraterone[1,jjj]
  - Abiraterone + dexamethasone[jjj,YY]
  - Enzalutamide[1]
  - Other secondary hormone therapy[l]

Prior docetaxel/no prior novel hormone therapy[ii]

- Preferred regimens
  - Abiraterone[1,jjj] (category 1)
  - Cabazitaxel[YY]
  - Enzalutamide[1] (category 1)
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[YY,lll]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[YY]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[YY]
  - Radium-223[mmm] for symptomatic bone metastases (category 1)
- Other recommended regimens
  - Sipuleucel-T[YY,nnnn]
  - Other secondary hormone therapy[l]

Prior docetaxel and prior novel hormone therapy[ii,ooo]

- Useful in certain circumstances
  - Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases (category 1)[sss]

(The following systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - Cabazitaxel[YY] (category 1[kkk])
  - Docetaxel rechallenge[YY]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[YY,lll]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[YY]
  - Olaparib for HRRm (category 1[kkk])[ppp]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[YY]
  - Radium-223[mmm] for symptomatic bone metastases (category 1[kkk])
  - Rucaparib for BRCAm[ppp]
- Other recommended regimens
  - Abiraterone[1,jjj]
  - Enzalutamide[1]
  - Other secondary hormone therapy[l]

See Footnotes for Systemic Therapy M1 CRPC (PROST-F 4 of 4)

VISION Study

Lutetium 177 FDA approval March 23, 2022

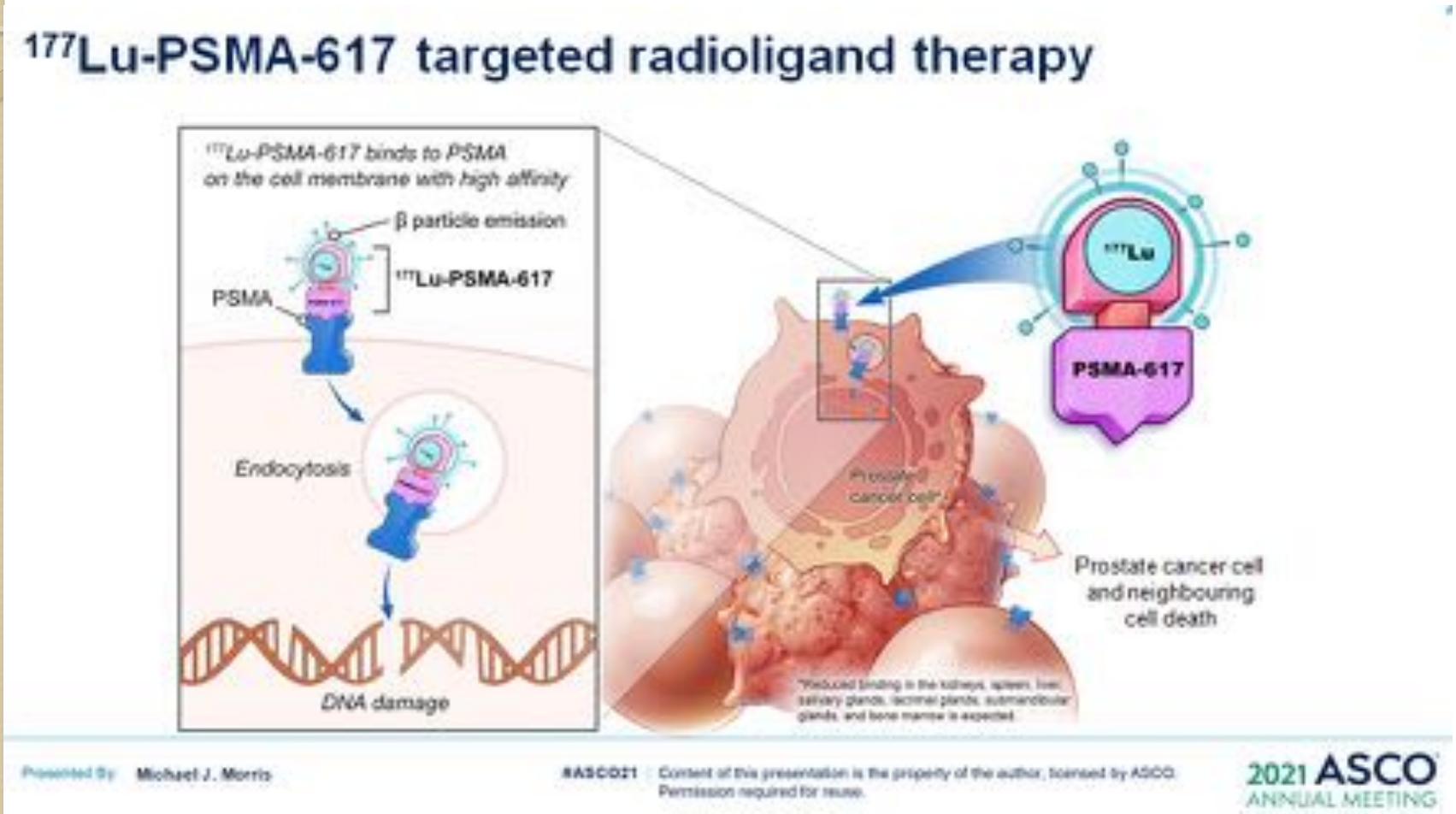
ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

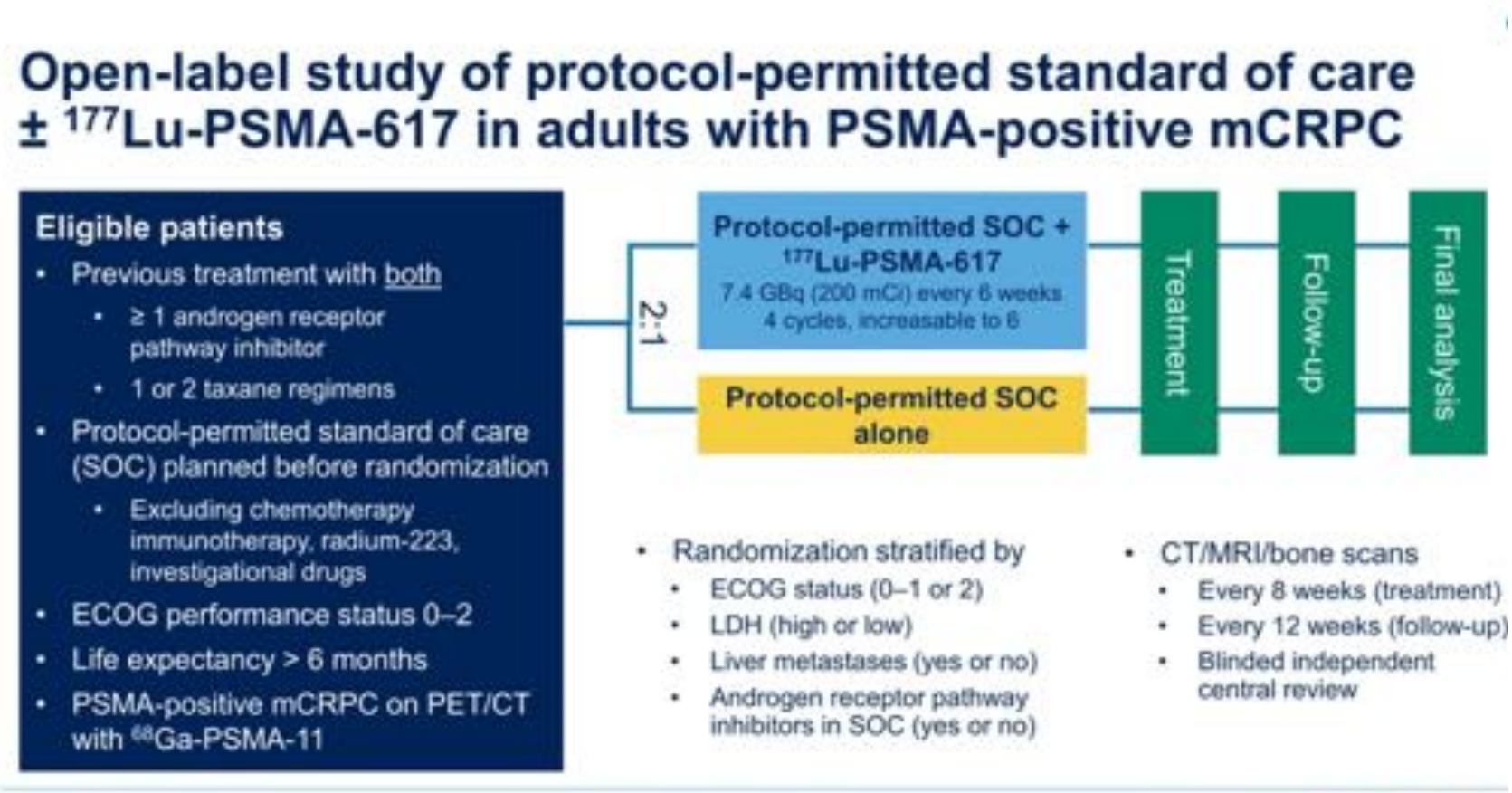
Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators*

September 16, 2021
N Engl J Med 2021; 385:1091-1103
DOI: 10.1056/NEJMoa2107322
Chinese Translation 中文翻译

Mechanism of Action



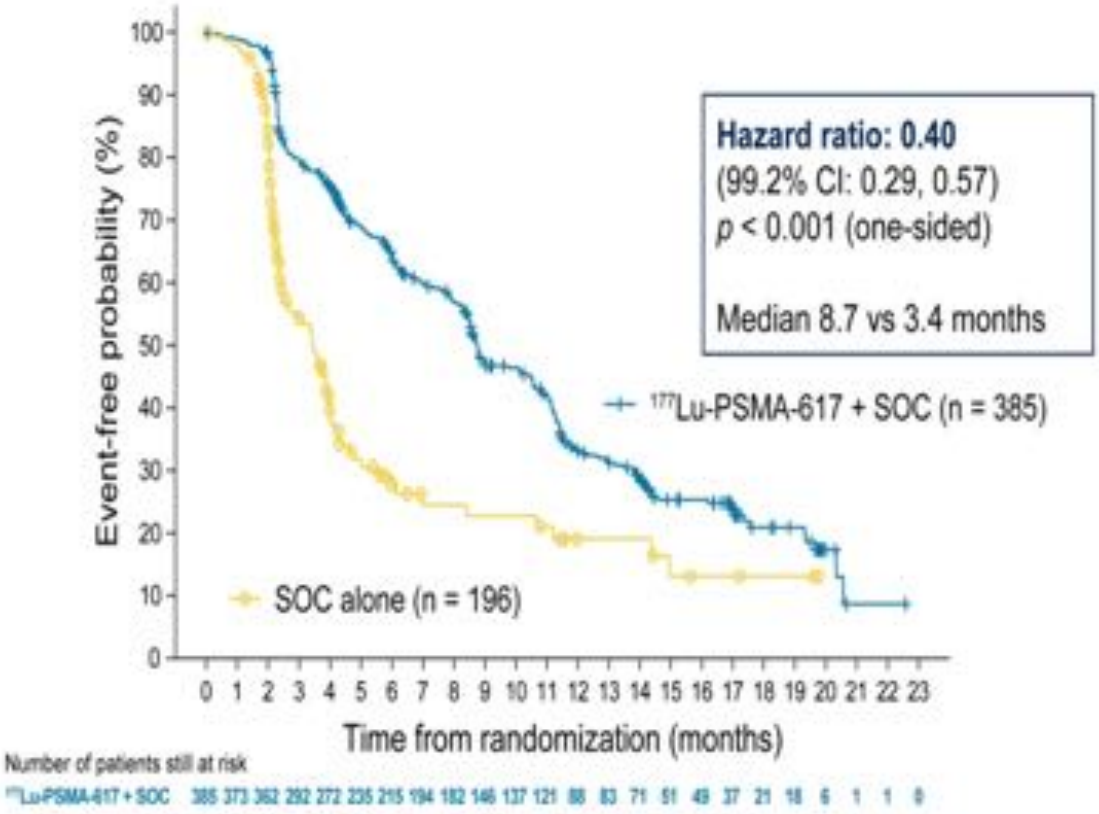
VISION Study



Primary endpoints: ^{177}Lu-PSMA-617 improved rPFS

Primary analysis

rPFS analysis set (n = 581)

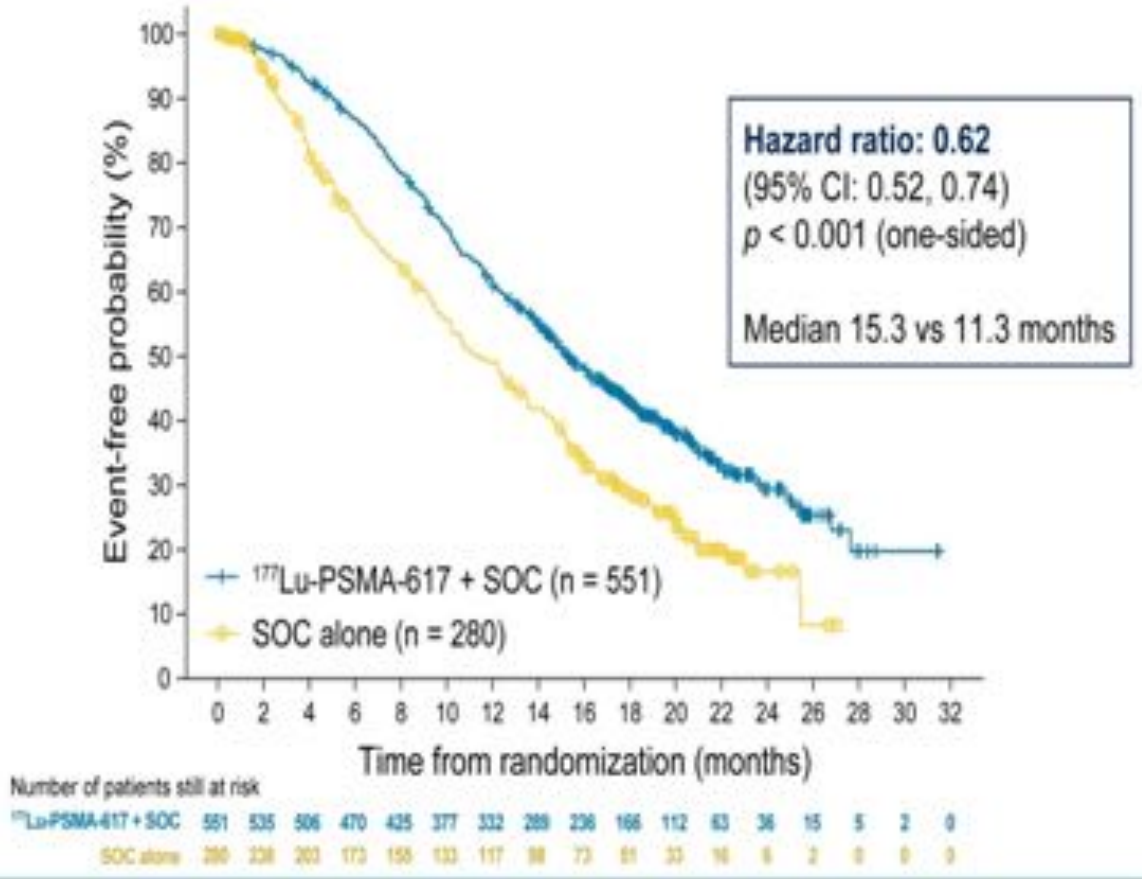


Morris MJ, ASCO 2021

Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients (N = 831)



Morris MJ, ASCO 2021

Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

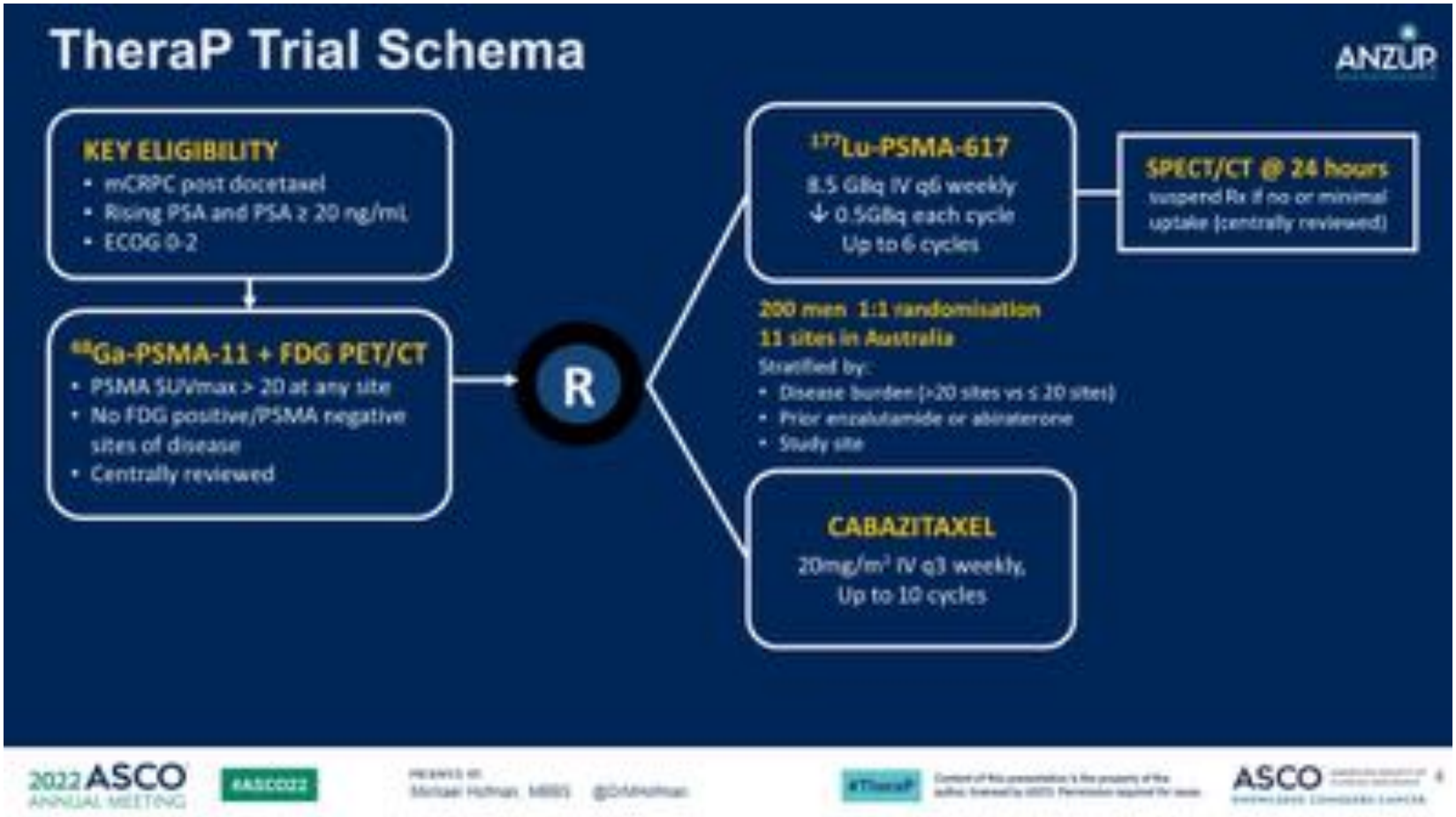
Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

Morris MJ, ASCO 2021

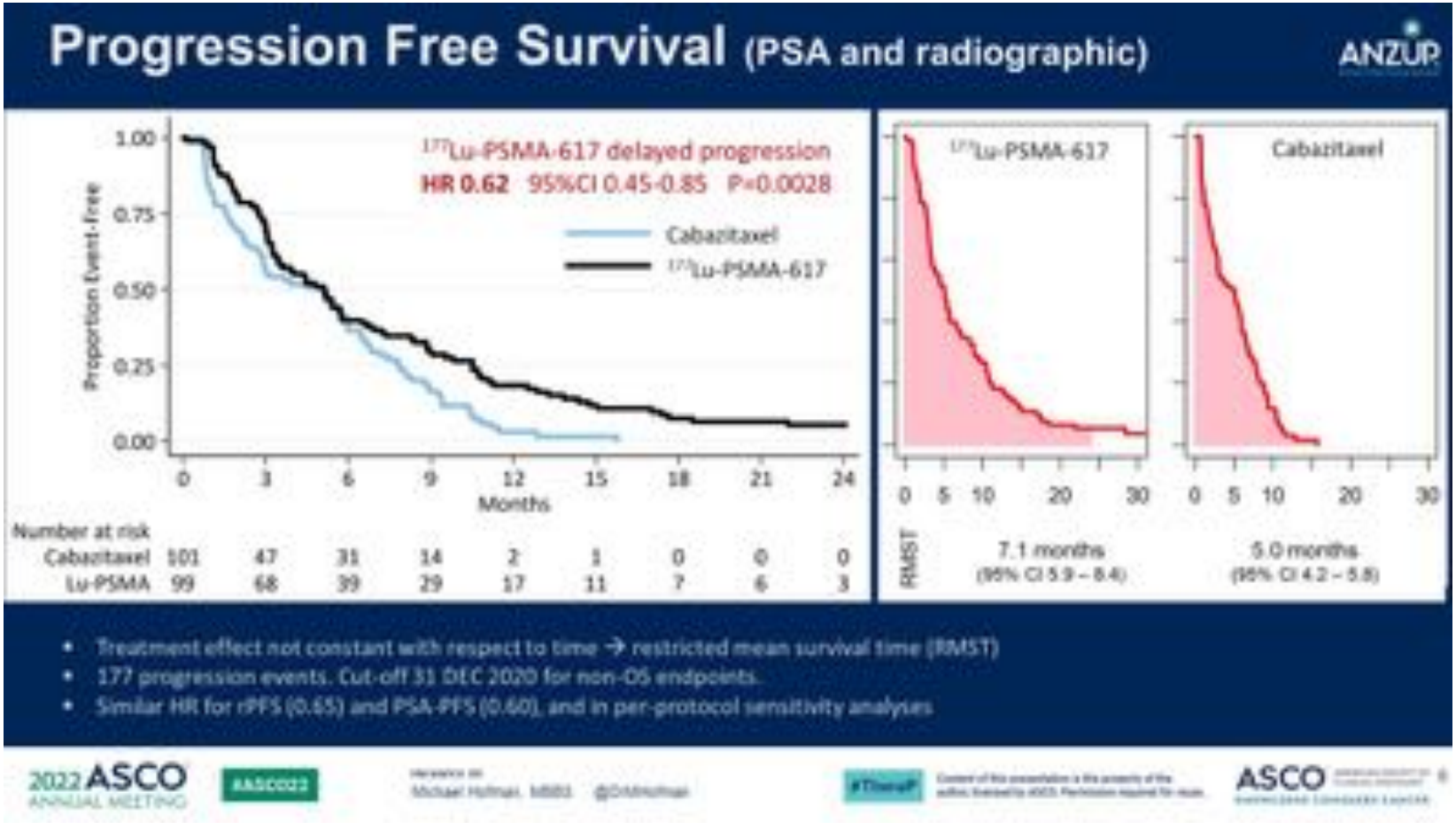
VISION study

- ^{177}Lu-PSMA-617 significantly prolonged vs standard care
- Imaging-based progression-free survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40;)
- Overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62;)
- Clinical Question: ^{177}Lu-PSMA-617 vs Cabizitaxel?

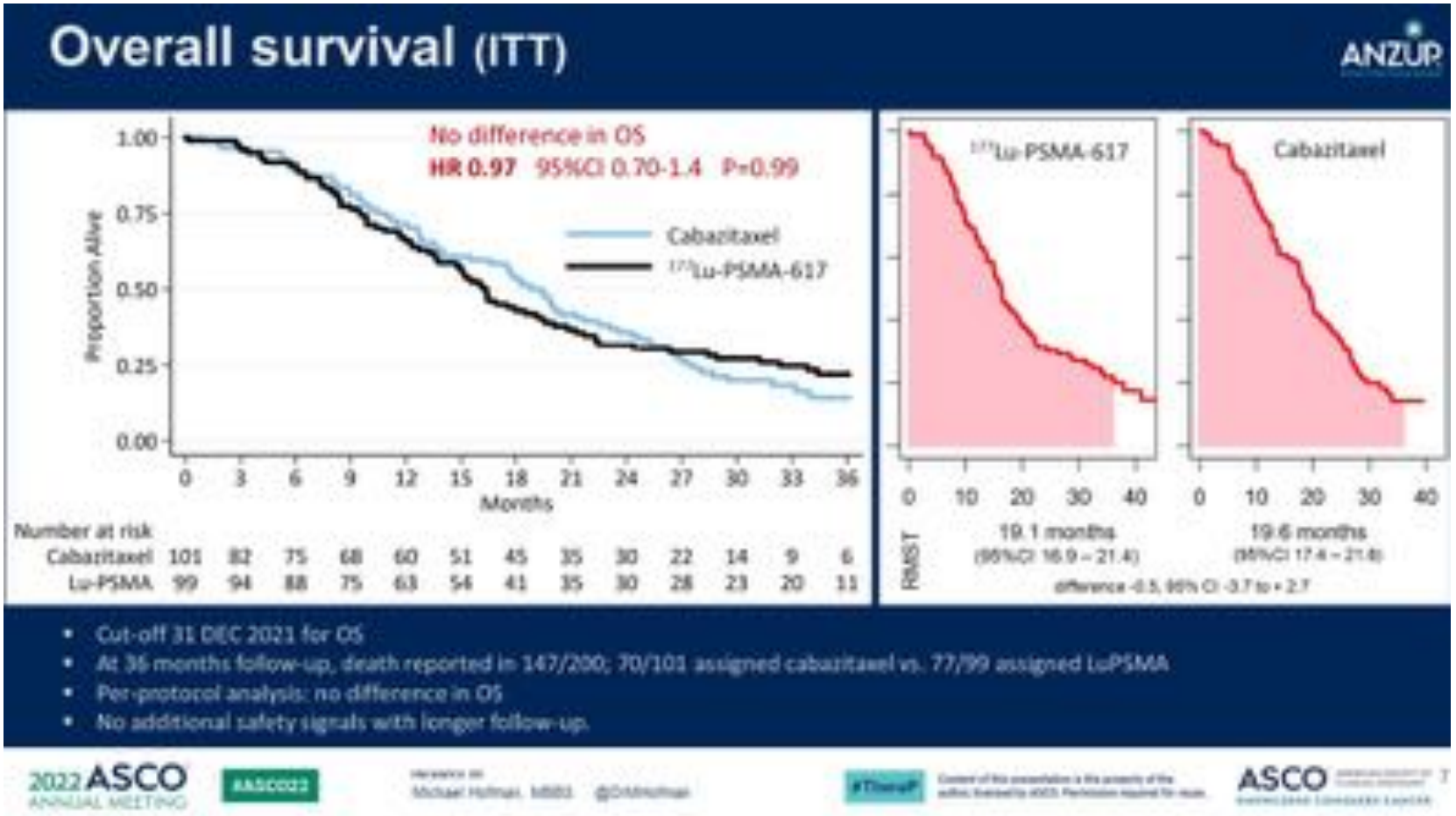
TheraP Trial Study Design



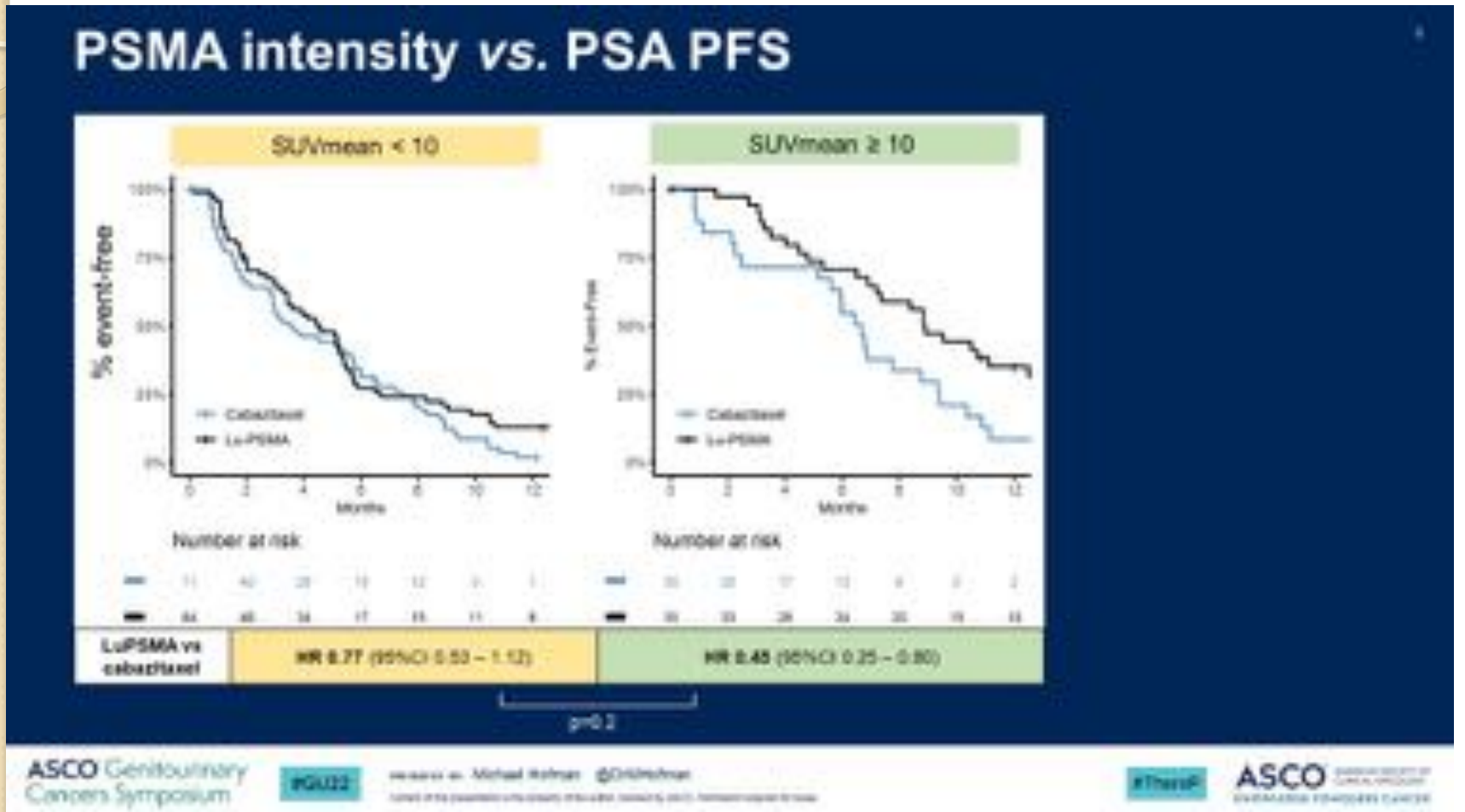
TheraP


Progression Free Survival (PSA and radiographic)
ANZUP
177Lu-PSMA-617 delayed progression
HR 0.62 95%CI 0.45-0.85 P=0.0028
Cabazitaxel
177Lu-PSMA-617
Proportion Event-Free
1.00
0.75
0.50
0.25
0.00
0 3 6 9 12 15 18 21 24
Months
Number at risk
Cabazitaxel 101 47 31 14 2 1 0 0 0
Lu-PSMA 99 68 39 29 17 11 7 6 3
177Lu-PSMA-617
Cabazitaxel
RMST
0 5 10 20 30
7.1 months
(95% CI 5.9 – 8.4)
5.0 months
(95% CI 4.2 – 5.8)
• Treatment effect not constant with respect to time → restricted mean survival time (RMST)
• 177 progression events. Cut-off 31 DEC 2020 for non-OS endpoints.
• Similar HR for rPFS (0.65) and PSA-PFS (0.60), and in per-protocol sensitivity analyses
2022 ASCO ANNUAL MEETING
#ASCO22
#TheraP
ASCO

TheraP

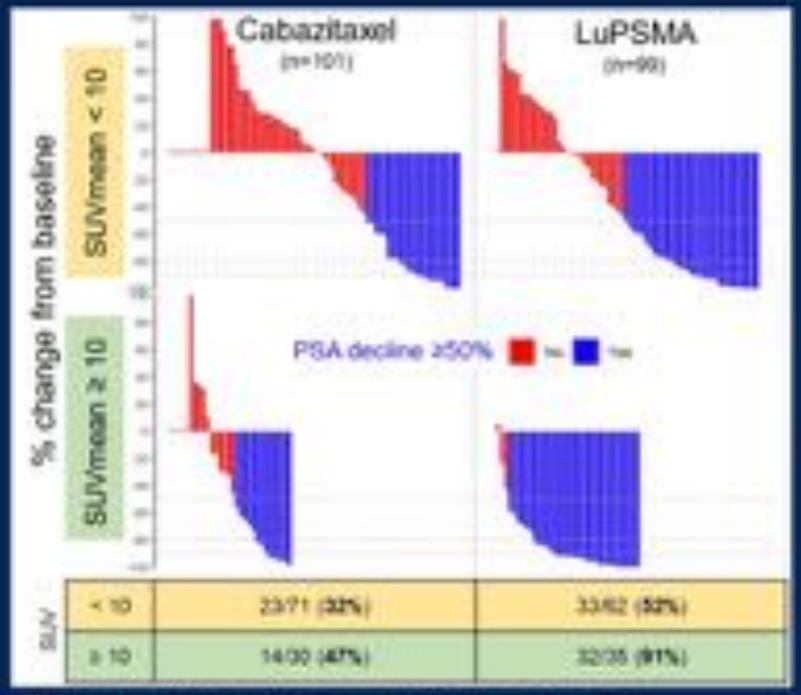

Overall survival (ITT)
ANZUP
No difference in OS
HR 0.97 95%CI 0.70-1.4 P=0.99
Cabazitaxel
177Lu-PSMA-617
Proportion Alive
1.00
0.75
0.50
0.25
0.00
0 3 6 9 12 15 18 21 24 27 30 33 36
Months
Number at risk
Cabazitaxel 101 82 75 68 60 51 45 35 30 22 14 9 6
Lu-PSMA 99 94 88 75 63 54 41 35 30 28 23 20 11
177Lu-PSMA-617
Cabazitaxel
0 10 20 30 40
RMST
19.1 months
19.6 months
• Cut-off 31 DEC 2021 for OS
• At 36 months follow-up, death reported in 147/200; 70/101 assigned cabazitaxel vs. 77/99 assigned LuPSMA
• Per-protocol analysis: no difference in OS
• No additional safety signals with longer follow-up.
2022 ASCO
ANNUAL MEETING
ASCO

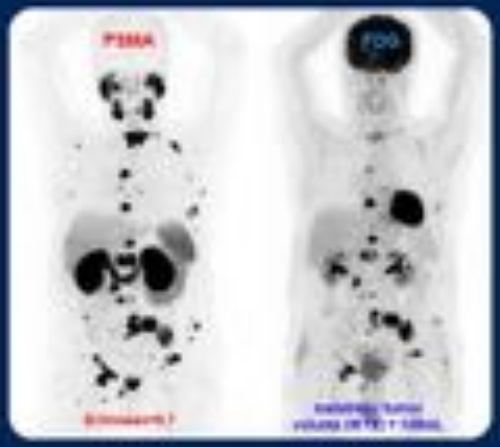
ASCO 2022: TheraP Study



ASCO 2022: TheraP Study

Discussion: PSMA as predictive biomarker[1] (PSA50-RR)





Odds of PSA50-RR to LuPSMA vs cabazitaxel

	OR (95% CI)
PSMA SUVmean < 10	2.2 (1.1 – 4.5)
PSMA SUVmean ≥ 10	12.2 (3.4 - 59)

P=0.03

Further analysis to be performed including OS

2022 ASCO ANNUAL MEETING #ASCO22

#TheraP

My practice 3rd Line Treatment

- Every patient should have a somatic and germline mutational studies to look for HRR deficiencies
- Patients with BRCA2 mutations, I would favor Olaparib (2nd line as well) and Rucaparib before Lutetium 177 and Cabizitaxel
- Patients without mutations, I would consider Lutetium 177 vs Cabizitaxel based on PSMA PET avid disease ie SUV greater than 10
- Also consider, CARD inclusion criteria. Progression less than 12 months on novel androgen pathway inhibitor

Norton Cancer Institute

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