PRACTICE UPDATE ON PROSTATE CANCER

Winston Tan MD MSeD FACP

Professor of medicine

Genitourinary Oncology

Mayo Clinic Florida

Vice President FLASCO

Very low:
- T1c
- Gleason score ≤6/Gleason grade group 1
- PSA <10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core
- PSA density <0.15 ng/mL/g

Low:
- T1-T2a
- Gleason score ≤6/ Gleason grade group 1
- PSA <10 ng/mL

Intermediate:[f]
- T2b-T2c or
- Gleason score 3+4=7/ Gleason grade group 2 or
- Gleason score 4+3=7/ Gleason grade group 3 or
- PSA 10–20 ng/mL

High:[f]
- T3a or
- Gleason score 8/ Gleason grade group 4 or
- Gleason score 9–10/ Gleason grade group 5
- PSA >20 ng/mL

Locally Advanced:

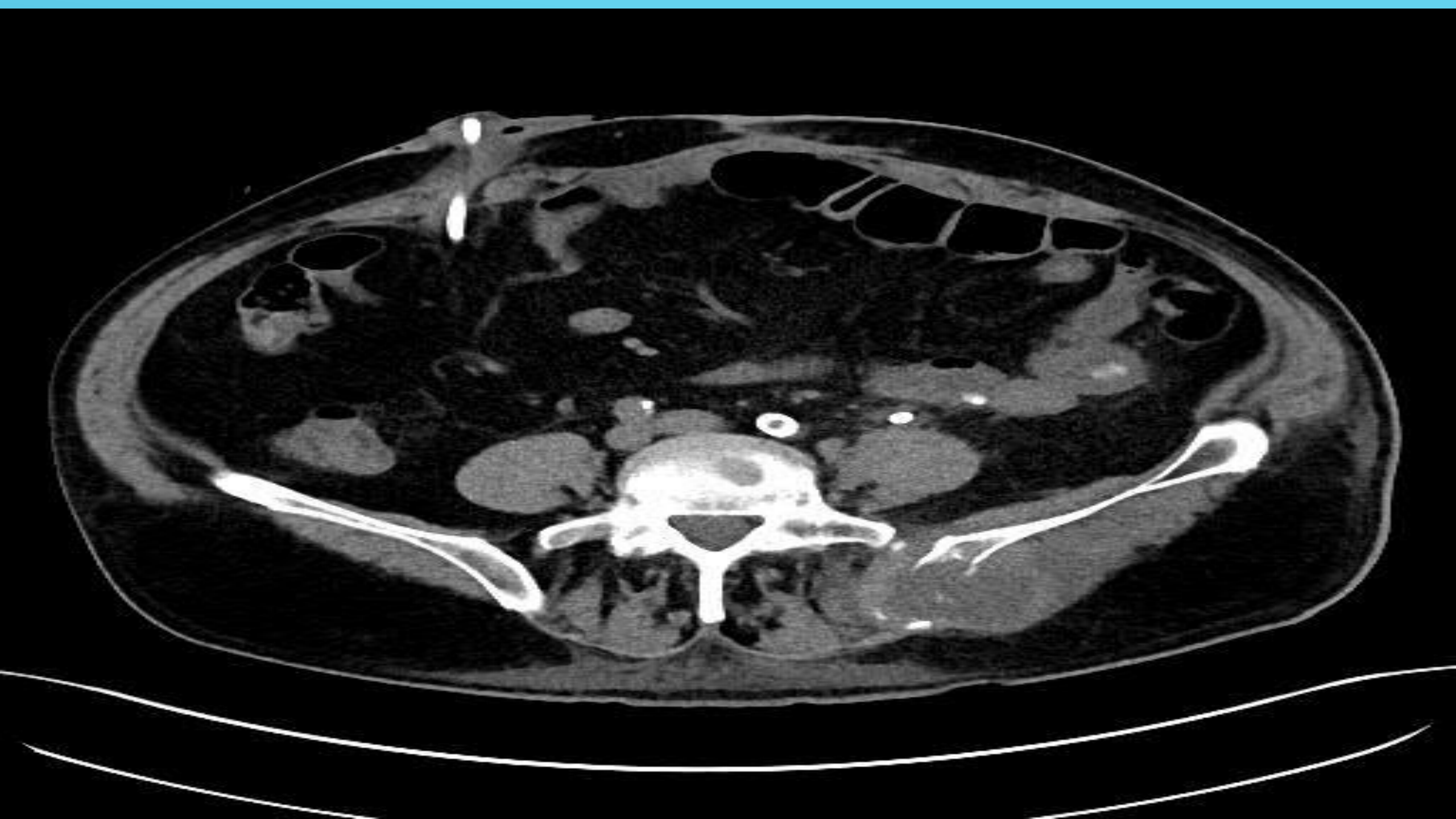
Very high:
- T3b-T4 or
- Primary Gleason pattern 5/ Gleason grade group 5 or
- >4 cores with Gleason score 8–10/ Gleason grade group 4 or 5

Metastatic:
Any T, N1 or
Any T, Any N, M1

MOLECULAR IMAGING

Biochemical Recurrence of Prostate Cancer

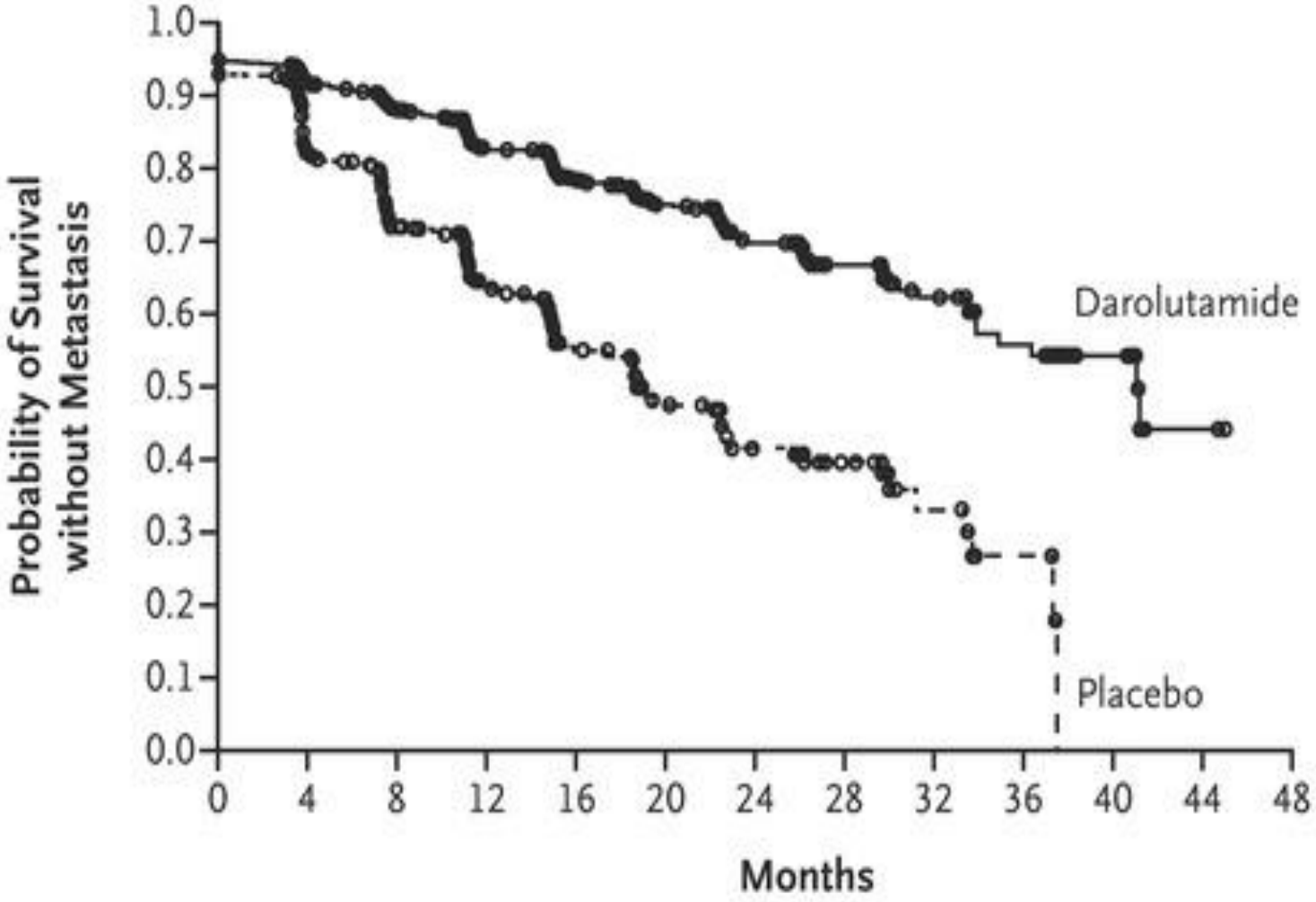
- •FDA approval of PET Tracers:
- –C-11 Choline (2012)
- –F-18 Fluciclovine (2016)



NON-METASTATIC DISEASE

- Metastasis free survival
- Prevention of metastasis

A Kaplan–Meier Analysis of Metastasis-free Survival



	Median Metastasis-free Survival (95% CI) *mo*
Darolutamide	40.4 (34.3–NR)
Placebo	18.4 (15.5–22.3)

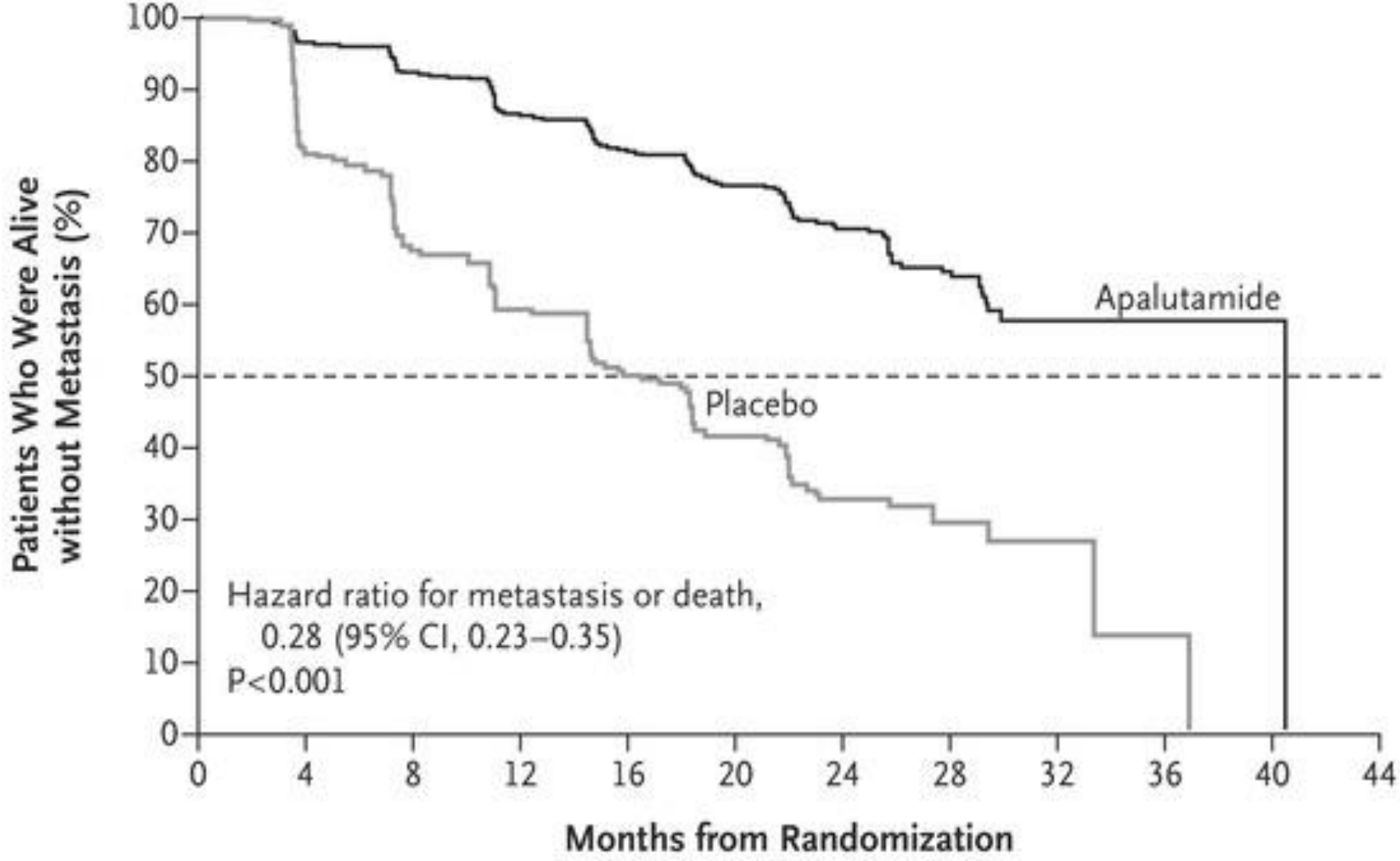
Hazard ratio, 0.41 (95% CI, 0.34–0.50)
P<0.001

No. at Risk

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

B Subgroup Analysis of Metastasis-free Survival

A Kaplan–Meier Estimates of Metastasis-free Survival



No. at Risk												
Apalutamide	806	713	652	514	398	282	180	96	36	16	3	0
Placebo	401	291	220	153	91	58	34	13	5	1	0	0

PROSPER

- In 1401 men, ENZA significantly prolonged median MFS (36.6 mo vs 14.7 mo [*P* < .0001]), time to first use of new antineoplastic therapy (39.6 mo vs 17.7 mo [*P* < .0001]) and time to PSA progression (37.2 mo vs 3.9 mo [*P* < .0001]) compared to PBO (Table). In the first interim analysis of OS there was a trend in favor of ENZA (hazard ratio [HR] = 0.80; *P* = .1519). Median duration of treatment was 18.4 mo vs 11.1 mo for ENZA vs PBO.
- Adverse events (AEs) were higher with ENZA vs PBO (any grade: 87% vs 77%; grade ≥ 3: 31% vs 23%; serious: 24% vs 18%); 10% with ENZA discontinued treatment due to AE vs 8% with PBO

TR

	Prosper	Spartan	Aramis
MFS	40.4 vs 18 mos	40.4 vs 16.2 mos	40.4 vs 18 mos
Time to new anti-neoplastic medication	39.6 vs 17.7 mos	-	-
PFS		40.5 vs 14.7 mos	36.8 vs 14.8 mos
Side effects	Falls, fracture, rash, seizure	Falls, rash fracture,hypertens-ion, hypothyroidism	Less falls, fractures

OVERALL SURVIVAL WITH MFS MEDICATIONS

- Darolutamide- In conjunction with androgen-deprivation therapy (ADT), darolutamide reduced the risk of death by 31% versus placebo (HR, 0.69; 95% CI, 0.53-0.88; *P* = .003) in patients with nmCRPC. At 3 years, the rates of OS were 83% with darolutamide versus 77% for placebo. The trial investigators noted that the effect of darolutamide on OS was statistically significant despite a high rate of patients in the placebo arm (55%) crossing over to the experimental-therapy arm
- Enzalutamide 288 of 933 patients (31%) in the enzalutamide group and 178 of 468 (38%) in the placebo group had died. Median overall survival was 67.0 months (95% confidence interval [CI], 64.0 to not reached) in the enzalutamide group and 56.3 months (95% CI, 54.4 to 63.0) in the placebo group (hazard ratio for death, 0.73; 95% CI, 0.61 to 0.89; P = 0.001).
- 52.0 months, 428 of 427 required OS events had occurred. Median treatment duration was 39.2 months with apalutamide and 11.5 months with placebo. Median OS was significantly longer with the addition of apalutamide, at 73.9 versus 59.9 months, with a hazard ratio of 0.784 (P = .016). In addition, apalutamide significantly lengthened time to cytotoxic chemotherapy, with a hazard ratio of 0.629 (P < .001)

ADT plus

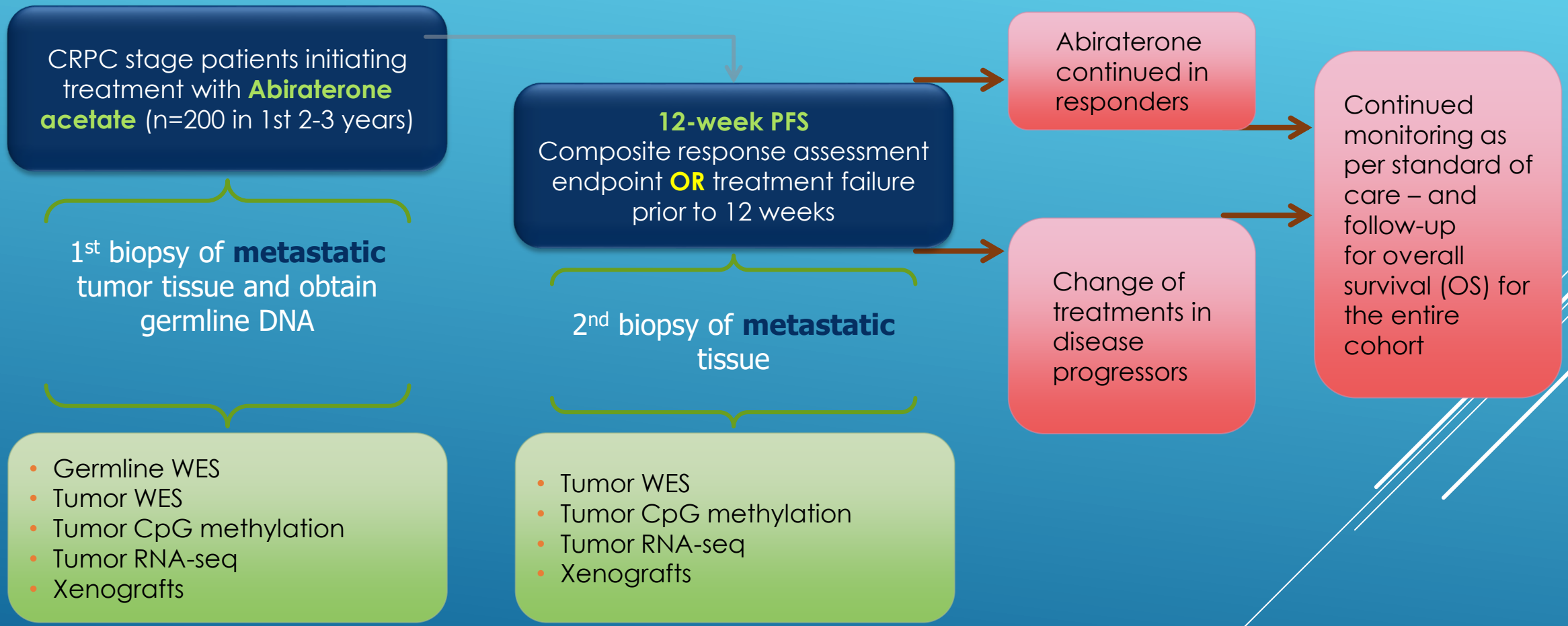
- Docetaxel
- Enzalutamide
- Apalutamide
- Abiraterone acetate and prednisone

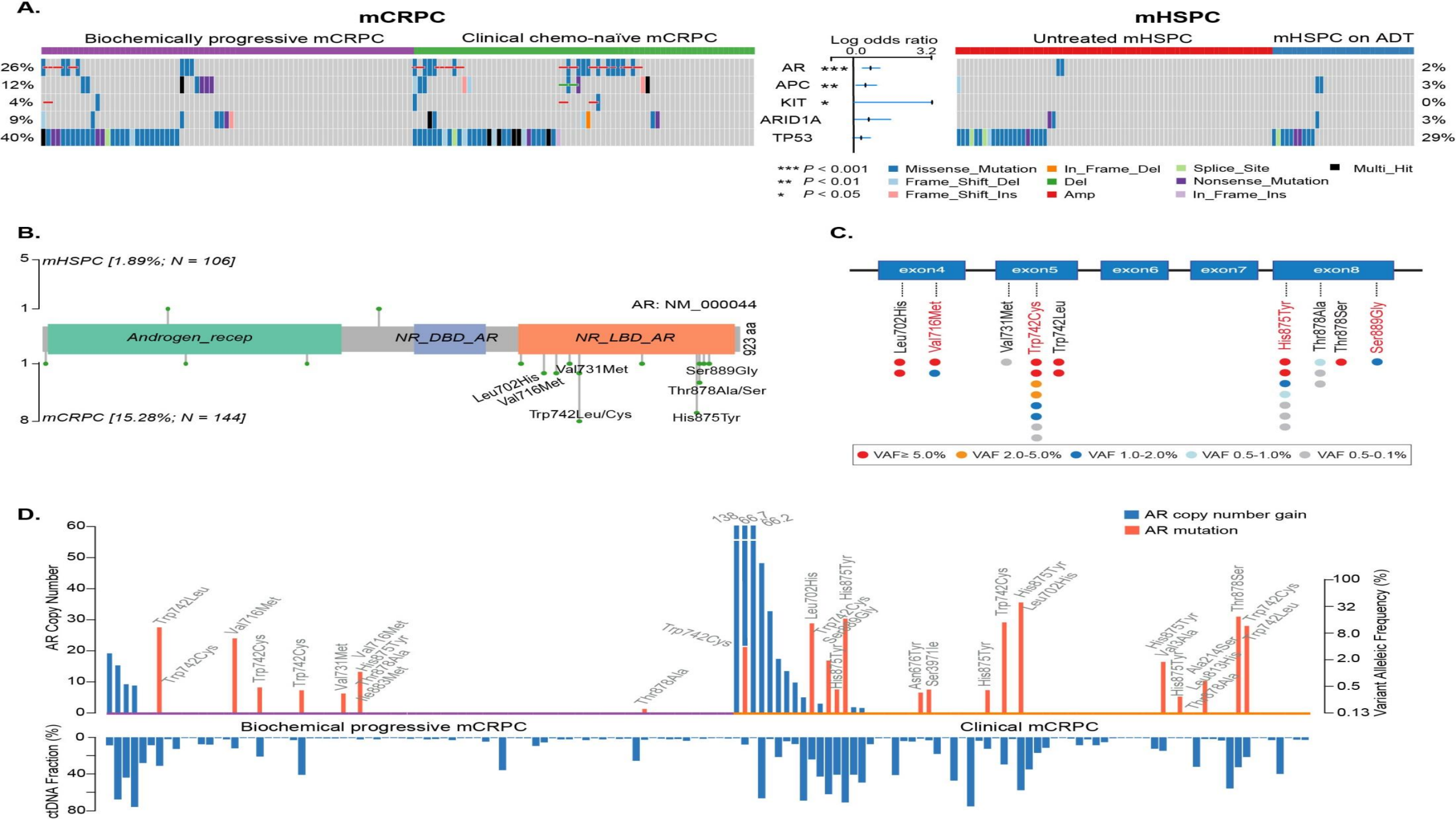
OPTIONS FOR METASTATIC HORMONE SENSITIVE DISEASE

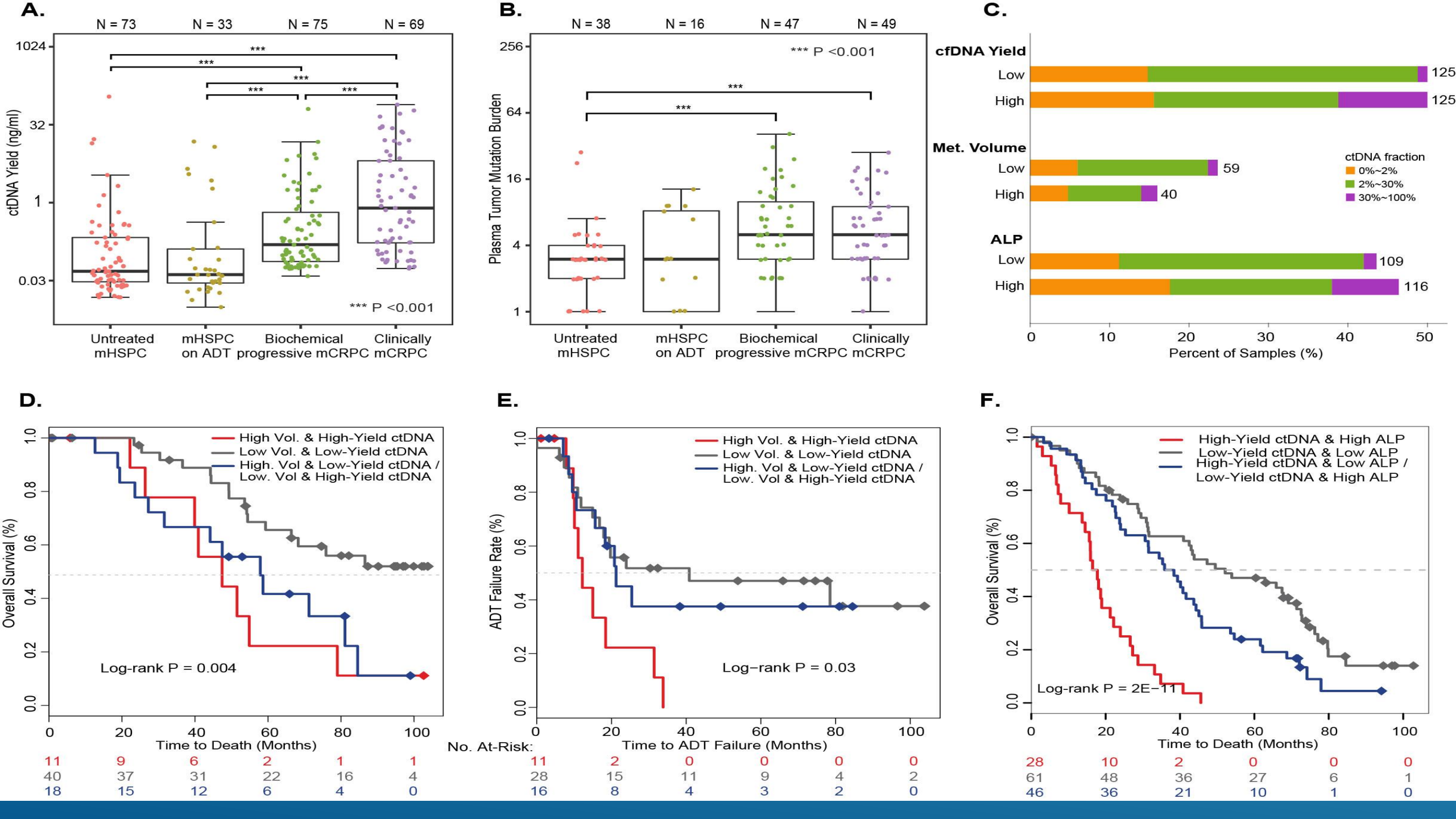
- Abiraterone and prednisone
- Enzalutamide
- Radium-223 for men with cancer that has spread to the bone
- Docetaxel and prednisone
- Sipuleucel-T for men who have few or no symptoms from the cancer
- Cabazitaxel and prednisone for men with prostate cancer that has worsened while receiving docetaxel

OPTIONS FOR CASTRATE RESISTANT PROSTATE CANCER

PROMOTE-1
ABIRATERONE ACETATE PHARMACOGENETICS
STUDY SCHEMA




A.
mCRPC
Biochemically progressive mCRPC
Clinical chemo-naïve mCRPC
mHSPC
Untreated mHSPC
mHSPC on ADT
Log odds ratio
0.0
3.2
AR
APC
KIT
ARID1A
TP53
26%
12%
4%
9%
40%
2%
3%
0%
3%
29%
*** P < 0.001
** P < 0.01
* P < 0.05
Missense_Mutation
Frame_Shift_Del
Frame_Shift_Ins
In_Frame_Del
Del
Amp
Splice_Site
Nonsense_Mutation
In_Frame_Ins
Multi_Hit
B.
mHSPC [1.89%; N = 106]
mCRPC [15.28%; N = 144]
AR: NM_000044
923 aa
Androgen_recep
NR_DBD_AR
NR_LBD_AR
Leu702His
Val716Met
Val731Met
Trp742Leu/Cys
Ser889Gly
Thr878Ala/Ser
His875Tyr
C.
exon4
exon5
exon6
exon7
exon8
Leu702His
Val716Met
Val731Met
Trp742Cys
Trp742Leu
His875Tyr
Thr878Ala
Thr878Ser
Ser889Gly
VAF≥ 5.0%
VAF 2.0-5.0%
VAF 1.0-2.0%
VAF 0.5-1.0%
VAF 0.5-0.1%
D.
AR copy number gain
AR mutation
AR Copy Number
Variant Alleleic Frequency (%)
Biochemical progressive mCRPC
Clinical mCRPC
ctDNA Fraction (%)


A.
N = 73
N = 33
N = 75
N = 69
1024
32
1
0.03
ctDNA Yield (ng/ml)
***
***
***
***
***
*** P <0.001
Untreated mHSPC
mHSPC on ADT
Biochemical progressive mCRPC
Clinically mCRPC
B.
N = 38
N = 16
N = 47
N = 49
256
64
16
4
1
Plasma Tumor Mutation Burden
*** P <0.001
***
***
Untreated mHSPC
mHSPC on ADT
Biochemical progressive mCRPC
Clinically mCRPC
C.
cfDNA Yield
Low
High
125
125
Met. Volume
Low
High
59
40
ALP
Low
High
109
116
ctDNA fraction
0%~2%
2%~30%
30%~100%
0
10
20
30
40
50
Percent of Samples (%)
D.
High Vol. & High-Yield ctDNA
Low Vol. & Low-Yield ctDNA
High. Vol & Low-Yield ctDNA / Low. Vol & High-Yield ctDNA
Overall Survival (%)
Log-rank P = 0.004
Time to Death (Months)
No. At-Risk:
11 9 6 2 1 1
40 37 31 22 16 4
18 15 12 6 4 0
E.
High Vol. & High-Yield ctDNA
Low Vol. & Low-Yield ctDNA
High. Vol & Low-Yield ctDNA / Low. Vol & High-Yield ctDNA
ADT Failure Rate (%)
Log−rank P = 0.03
Time to ADT Failure (Months)
11 2 0 0 0 0
28 15 11 9 4 2
16 8 4 3 2 0
F.
High-Yield ctDNA & High ALP
Low-Yield ctDNA & Low ALP
High-Yield ctDNA & Low ALP / Low-Yield ctDNA & High ALP
Overall Survival (%)
Log-rank P = 2E−11
Time to Death (Months)
28 10 2 0 0 0
61 48 36 27 6 1
46 36 21 10 1 0

multicenter trial randomizing (2:1) 256 patients to olaparib 300 mg twice daily and 131 patients to investigator's choice of enzalutamide or abiraterone acetate. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were divided into two cohorts based on their HRR gene mutation status. Patients with mutations in either *BRCA1, BRCA2*, or *ATM* were randomized in Cohort A (N=245); patients with mutations among 12 other genes involved in the HRR pathway were randomized in Cohort B (N=142); those with co-mutations (Cohort A gene and a Cohort B gene) were assigned to Cohort A

PROFOUND (NCT02987543)

RESULTS

- A statistically significant improvement was demonstrated for olaparib compared to investigator's choice in Cohort A for rPFS with a median of 7.4 months vs 3.6 months (HR 0.34; 95% CI: 0.25, 0.47; p<0.0001), for OS with a median of 19.1 months vs. 14.7 months (HR 0.69; 95% CI: 0.50, 0.97, p=0.0175) and for ORR 33% vs 2% (p<0.0001). A statistically significant improvement for olaparib compared to investigator's choice was also demonstrated for rPFS in Cohort A+B, with a median of 5.8 months vs. 3.5 months (HR 0.49; 95% CI: 0.38, 0.63; p<0.0001).

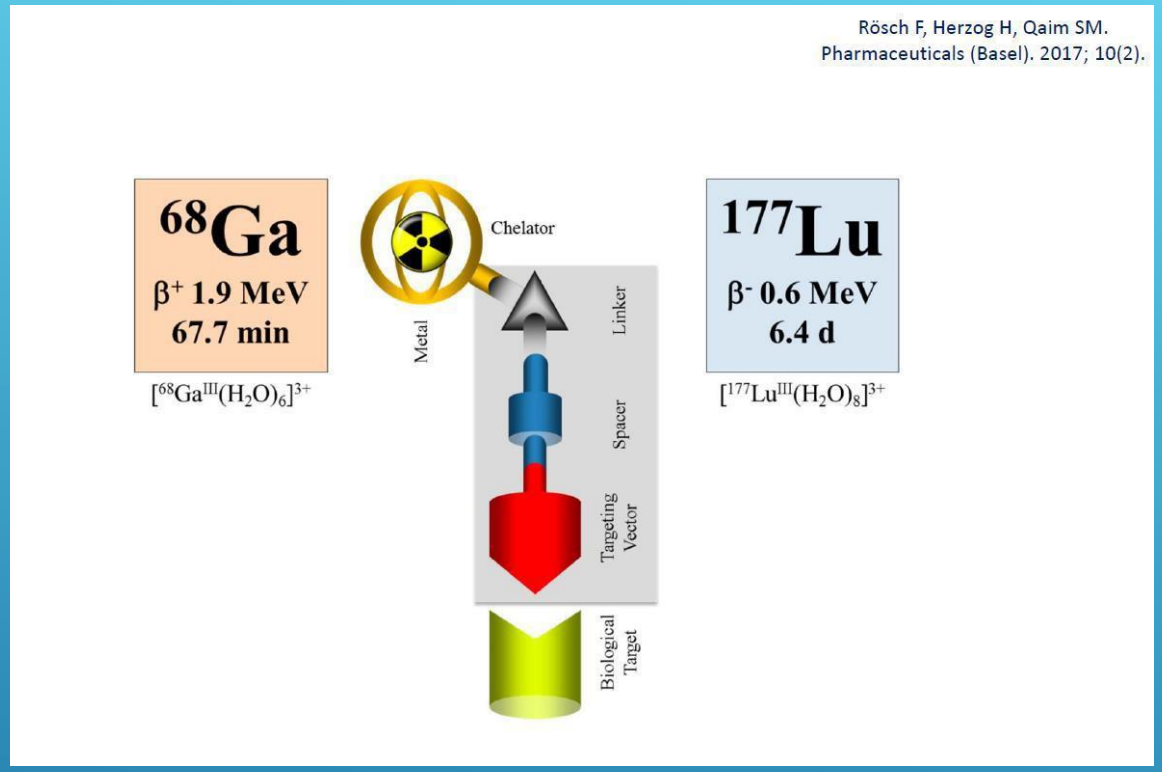
multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy.

TRITON2 (NCT02952534),

RESPONSE RATE

- Objective response rate (ORR) and duration of response (DOR) were assessed in 62 patients with measurable disease. The confirmed ORR was 44% (95% CI: 31, 57). Median DOR was not evaluable (NE; 95% CI: 6.4, NE). The range for the DOR was 1.7-24+ months. Fifteen of the 27 (56%) patients with confirmed objective responses had a DOR of ≥6 months.

RADIOLIGAND THERAPY



Advantages/ Indications:

- PET Imaging with 68Ga-PSMA ligand can present lesions suspicious for prostate cancer with excellent contrast and a high detection rate even when the level of prostate specific antigen is low
- PSMA expression allows the identification of benign and malignant prostatic epithelium and may be a potentially valuable marker in the treatment of patients with prostate cancer
- 68Ga-PSMA PET has promising potential for restaging in recurrence/ biochemical failure after definitive treatment of prostate cancer
- PSMA PET could be used as a marker of patient response to anti-androgen drugs

VISION TRIAL

- open-label trial included 831 patients (1179 initially screened) with progressive PSMA-positive mCRPC who received at least 1 novel androgen axis drug (eg, enzalutamide or abiraterone acetate and were previously treated with 1 to 2 taxane regimens

VISION RESULTS

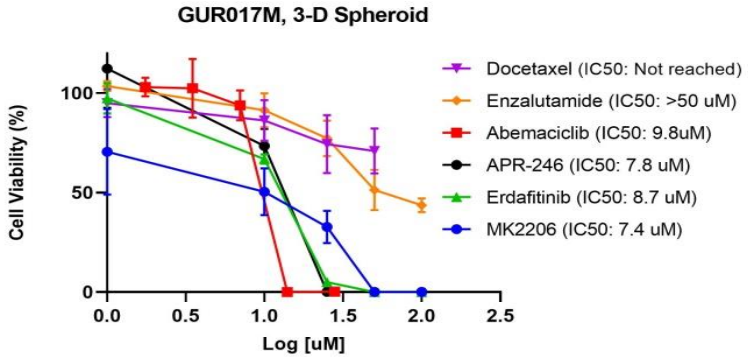
- Patients were randomized in a 2:1 ratio to LuPSMA (7.4 GBq every 6 weeks x 6 cycles; n = 551) plus SOC or SOC alone (n = 280)..
- The median OS was 15.3 months in the LuPSMA arm versus 11.3 months in the SOC alone arm, translating to a 38% reduction in the risk of death (HR, 0.62; 95% CI, 0.52-0.74; *P* <.001).The rPFS was 8.7 versus 3.4 months, respectively (HR, 0.40; 99.2% CI, 0.29-0.57; *P* <.001).
- There was also a statistically significant benefit favoring the LuPSMA arm for the key secondary endpoints of objective response rate (ORR), disease control rate (DCR), and time to first symptomatic skeletal event (SSE). The ORRs and DCRs were 29.8% versus 1.7% and 89.0% versus 66.7%, respectively. The median time to first SSE was 11.5 months in the LuPSMA group compared with 6.8 months in the control arm (HR, 0.50)

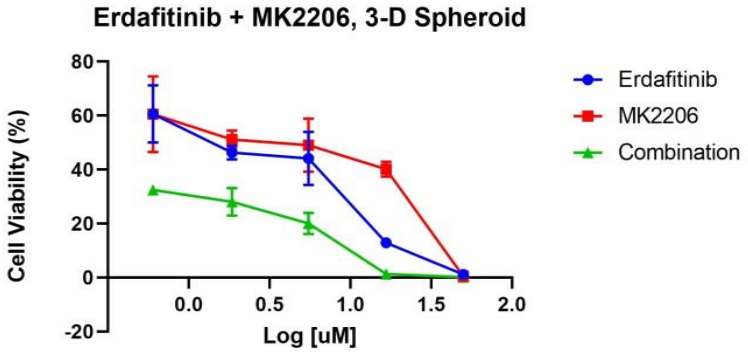
VISION TRIAL

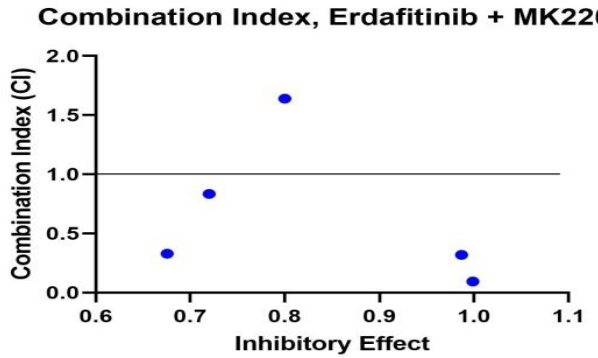
- *A 40% reduction in the risk of death was observed when 177Lu-PSMA-617A was added to standard of care therapy in patients with PSMA-positive metastatic castration-resistant prostate cancer.*
- The findings presented during 2021 American Society of Clinical Oncology Annual Meeting showed that at a median follow-up of 20.9 months, the addition of LuPSMA led to a 40% reduction in the risk of death and a 4-month improvement in median OS versus SOC alone (HR, 0.62). Adding the targeted radioligand therapy also led to a 5.3-month improvement in median radiographic progression-free survival (rPFS), translating to a 60% reduction in the risk of progression or death (HR, 0.40).

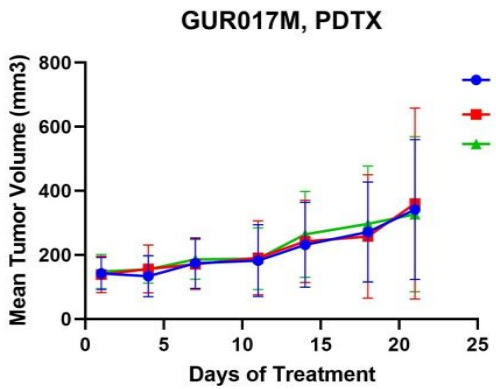
TOXICITY

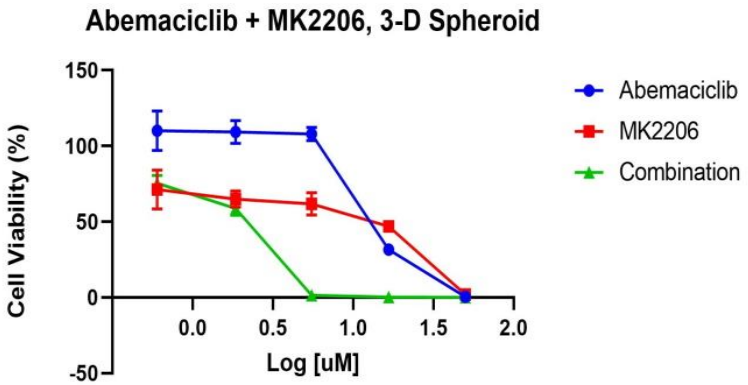
- The safety analysis included 529 patients in the LuPSMA cohort and 205 patients in the control group. The investigators considered LuPSMA treatment to be well tolerated. The most common adverse events (AEs) across all grades occurring in the LuPSMA arm were fatigue (49.1% vs 29.3% in the control arm), bone marrow suppression (47.4% vs 17.6%, respectively), dry mouth (39.3% vs 1%), nausea/vomiting (39.3% vs 17.1%), kidney effects (8.7% vs 5.9%), second primary malignancies (2.1% vs 1%), and intracranial bleeding (1.3% vs 1.5%).

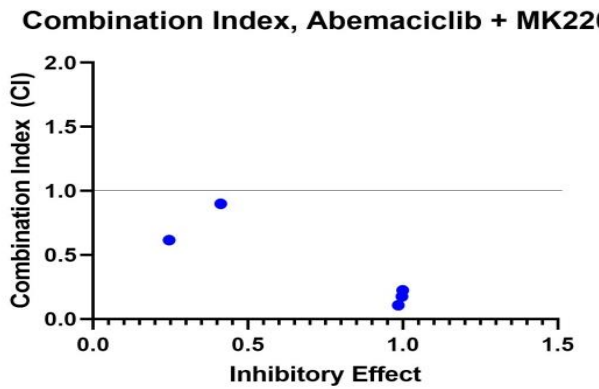

GUR017M, 3-D Spheroid
Cell Viability (%)
Log [uM]
Docetaxel (IC50: Not reached)
Enzalutamide (IC50: >50 uM)
Abemaciclib (IC50: 9.8uM)
APR-246 (IC50: 7.8 uM)
Erdafitinib (IC50: 8.7 uM)
MK2206 (IC50: 7.4 uM)

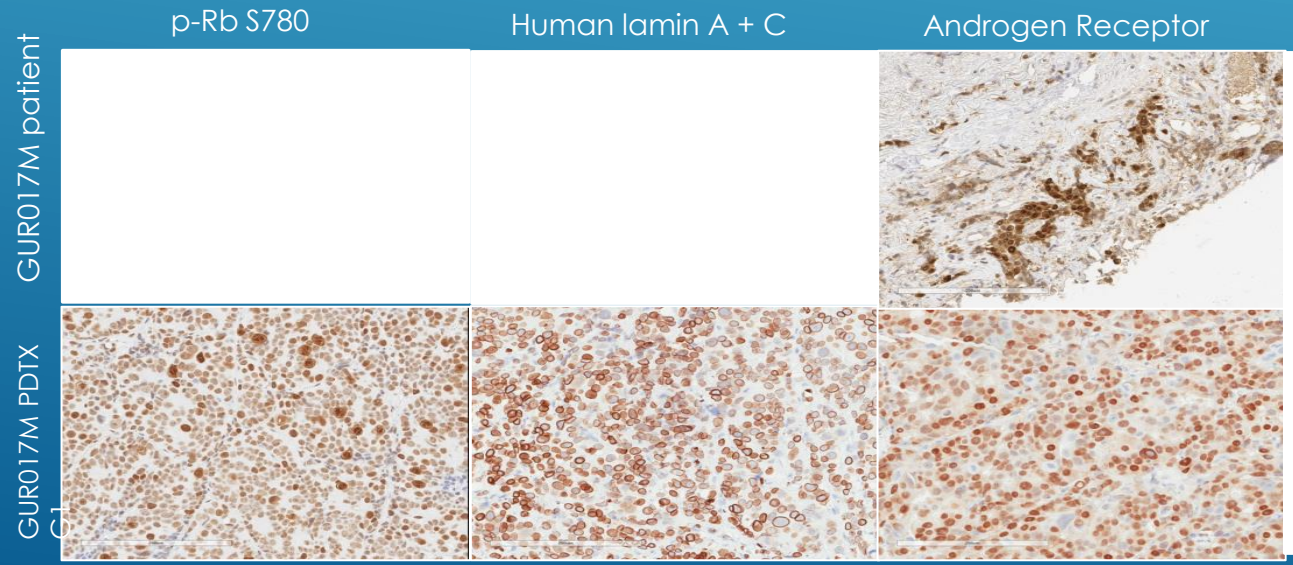

Erdafitinib + MK2206, 3-D Spheroid
Cell Viability (%)
Log [uM]
Erdafitinib
MK2206
Combination


Combination Index, Erdafitinib + MK2206
Combination Index (CI)
Inhibitory Effect


GUR017M, PDTX
Mean Tumor Volume (mm3)
Days of Treatment
Placebo
Enzalutamide (50 mg/kg)
Docetaxel (10 mg/kg)


Abemaciclib + MK2206, 3-D Spheroid
Cell Viability (%)
Log [uM]
Abemaciclib
MK2206
Combination


Combination Index, Abemaciclib + MK2206
Combination Index (CI)
Inhibitory Effect


p-Rb S780
Human lamin A + C
Androgen Receptor
p-AKT
H & E
GUR017M patient
GUR017M PDTX


MAYO BUILDING AND HOSPITAL
MAYO CLINIC


Thank
you